DOPAMINERGIC CONTROL OF WORKING MEMORY AND ITS RELEVANCE TO SCHIZOPHRENIA: A CIRCUIT DYNAMICS PERSPECTIVE

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Abstract—This article argues how dopamine controls working memory and how the dysregulation of the dopaminergic system is related to schizophrenia. In the dorsolateral prefrontal cortex, which is the principal part of the working memory system, recurrent excitation is subtly balanced with intracortical inhibition. A potent controller of the dorsolateral prefrontal cortical circuit is the mesocortical dopaminergic system. To understand the characteristics of the dopaminergic control of working memory, the stability of the circuit dynamics under the influence of dopamine has been studied. Recent computational studies suggest that the hyperdopaminergic state is usually stable but the hypodopaminergic state tends to be unstable. The stability also depends on the efficacy of the glutamatergic transmission in the corticoencephalic projections to dopamine neurons. When this cortical feedback is hypogluta-matergic, the circuit of the dorsolateral prefrontal cortex tends to be unstable, such that a slight increase in dopamine releasability causes a catastrophic jump of the dorsolateral prefrontal cortex activity from a low to a high level. This may account for the seemingly paradoxical overactivation of the dorsolateral prefrontal cortex observed in schizophrenic patients. Given that dopamine transmission is abnormal in the brains of patients with schizophrenia and working memory deficit is a core dysfunction in schizophrenia, the concept of circuit stability would be useful not only for understanding the mechanisms of working memory processing but for developing therapeutic strategies to enhance cognitive functions in schizophrenia.

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Abbreviations: DA, dopamine; DLPFC, dorsolateral prefrontal cortex; FS, fast-spiking; HVA, high-voltage-activated; NFS, non-fast-spiking; PFC, prefrontal cortex.

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Working memory is not a unitary system but consists of subsystems (Baddeley, 1986, 2003). Numerous functional imaging studies have suggested that performing working memory tasks activates several different areas of the cortex, including the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate area, and the posterior parietal cortex (PPC) (for example: Fletcher and Henson, 2001; Jonides et al., 1998; Leung et al., 2002; Sakai et al., 2002). This network may include the attentional control system (Awh and Jonides, 2001; Awh et al., 2000; Chafee and Goldman-Rakic, 1998, 2000; de Fockert et al., 2001; Courtney et al., 1998; Curtis and D’Esposito, 2003; Kastner and Ungerleider, 2000; Stedron et al., 2005; Tanaka, 2003). Some of the areas that are activated by the performance of working memory tasks are, however, different for different tasks, suggesting that they are primarily related to task-specific processing or modalities the tasks employ. In contrast, the DLPFC is commonly activated by all kinds of working memory tasks, and is therefore considered to be involved in a working memory process that is common across tasks, such as maintenance of working memory. However, further specification of working memory processes is not straightforward. So far, neuroimaging studies have suggested that the DLPFC plays a central role in the maintenance and manipulation of working memory (Curtis and D’Esposito, 2003; D’Esposito et al., 1999, 2000; Leung et al., 2002; Owen et al., 1996; Rowe et al., 2000; Smith and Jonides, 1999). Executive functions would require cooperation of subprocesses (Funahashi, 2001; Perrett and Lang, 1999) and would be mediated by a large cortical–subcortical network (Elliott, 2003; Royall et al., 2002). Still, it would be the case that the DLPFC plays a central role also in those functions (for reviews: Carpenter et al., 2000; Funahashi, 2001; Fuster, 2000; Robbins, 1996; Smith and Jonides, 1999; Tanji and Hoshi, 2001).

Since the pioneering works (Fuster and Alexander, 1971; Kubota and Niki, 1971), neuroanatomical, neurophysiological and neurocomputational studies have been elucidating the machinery of the DLPFC for working memory (for reviews: Castner et al., 2004; Constantinidis and Wang, 2004; Durstewitz et al., 2000b; Funahashi, 2001; Fuster, 2000, 2001; Goldman-Rakic, 1987, 1995, 1996; Goldman-Rakic et al., 2000; Tanaka, 2001; Ungerleider, 1998; Wang, 2001). With anatomical basis (Goldman-Rakic, 1987; Gonzalez-Burgos et al., 2000; Melchitzky and Lewis, 2003; Melchitzky et al., 1998, 2001), it has been suggested that recurrent excitation or mutual excitation between pyramidal neurons having similar preferences of memory fields plays a primary role in the maintenance of working memory. However, computational model networks with recurrent excitation easily go runaway, showing epileptiform activity of all the neurons in the network without coding any meaningful information. A number of computational studies have suggested that stable activity of neurons in a cortical circuit is attained on a subtle balance...
between the recurrent excitation and intracortical inhibition (Amit and Brunel, 1997; Amit and Mongillo, 2003; Brunel, 2003; Brunel and Wang, 2001; Compte et al., 2000; Durstewitz et al., 2000b; Fellous and Sejnowski, 2003; Latham and Nirenberg, 2004; Tanaka 1999, 2001; Wang, 1999, 2001). The intracortical inhibition would have different roles in working memory, being consistent with the existence of a wide variety of subtypes of inhibitory interneurons in the cortex (Cauli et al., 1997; Gupta et al., 2000; Kawaguchi, 1993, 1995; Kawaguchi and Kubota, 1993, 1996, 1997; Krimer and Goldman-Rakic, 2001; Miles, 2000; Somogyi et al., 1998; Tamas et al., 1998). In the visuospatial working memory, roles of two types of the intracortical inhibition, the iso- and cross-directional inhibition, have been studied (Rao et al., 1999, 2000; Tanaka, 1999, 2000, 2001, 2002a). Their studies suggested that a primary role of the isodirectional inhibition is to restrict or tune memory fields, while the cross-directional inhibition contributes to the suppression of background activity (Rao et al., 1999, 2000; Tanaka, 1999, 2000, 2001). This notion becomes clearer when neurons represent spatial working memory with multiple targets (Tanaka, 2002a). In this case, the cross-directional inhibition would play an important role in controlling the competition between targets by mediating mutual inhibition. Thus established scarcely stable representation of working memory is subject to modulation by neuromodulators.

Catecholaminergic modulation of working memory activity has been studied neurophysiologically using the delayed-response task paradigm (Arnsten, 1998; Sawaguchi, 1991; Sawaguchi and Goldman-Rakic 1991, 1994; Sawaguchi et al., 1990a,b, 1994; Williams and Goldman-Rakic, 1995). Local injection of selective dopamine (DA) D1 receptor antagonists into the DLPFC in monkeys impaired spatial working memory but had no effect on performance in the control task requiring visually guided saccades, indicating that sensory and motor functions were unaltered (Sawaguchi and Goldman-Rakic, 1991, 1994). In contrast, stimulation of D1 receptors in aged monkeys enhanced spatial working memory (Castner and Goldman-Rakic, 2004). This suggests that D1 receptors play a selective role in spatial working memory of the primate. In accordance with this, computational studies have illustrated how dopaminergic modulation by D1 receptor activation changes the circuit dynamics for working memory of their models (Brunel and Wang, 2001; Dreher and Burmood, 2002; Dreher et al., 2002; Durstewitz et al., 1999, 2000a; Tanaka, 2002a,b, 2005; Yamashita and Tanaka, 2002, 2003, 2005). Here, circuit dynamics are dynamic circuit properties that emerge synergistically from interacting neuronal dynamics. In contrast, the dopaminergic modulation that was incorporated into their models is at an individual neuron level. These studies, therefore, filled a gap between the circuit dynamics and the neuronal dynamics. The first part of this article argues that D1 receptor activation changes the circuit dynamics so that it can alter the representation of working memory. We propose that, by controlling D1 receptor activation, the system can differently represent spatial working memory with multiple target locations. The closed-loop, prefronto–mesoprefrontal system would control DA release in the DLPFC. In this system, while the well-known inverted-U shape characteristic of dopaminergic modulation comes from a circuit property of the DLPFC, the actual operating point on the inverted-U curve for working memory processing is determined by the activity of the cortico-mesocortical system. Both the DA releasability in the DLPFC and the efficacy of the cortico-comesencephalic glutamatergic transmission would play critical roles in controlling the activity of the cortico-mesocortical system. We argue, secondly, how changes in these parameters affect the circuit dynamics for working memory.

Working memory research benefits from schizophrenia research. In fact, the impairment of working memory and other cognitive functions is one of the major symptoms of schizophrenia (Fleming et al., 1995, 1997; Goldman-Rakic, 1994; Gooding and Tallent, 2004; Park and Holzman, 1992, 1993), and the study of working memory in the context of schizophrenia could provide insights into its mechanisms. In the history of the research and treatment of schizophrenia, tremendous effort has been devoted to understanding the relationship between the symptoms of schizophrenia and neurotransmitters/neuromodulators, such as DA, serotonin, and glutamate. This is reasonable because typical antipsychotics, such as haloperidol, are DA D2 receptor antagonists, and many atypical antipsychotics are highly selective for DA and serotonin receptors. The brains of schizophrenic patients are in a hypodopaminergic state in the cortex, especially in the prefrontal cortex (PFC), and a hyperdopaminergic state in the striatum (Abi-Dargham, 2004; Abi-Dargham and Moore, 2003; Abi-Dargham et al., 1998, 2000, 2002; Breier et al., 1997; Davis et al., 1991; Franklin et al., 2003; Goldman-Rakic et al., 2004; Kahn and Davis, 2000; Kegeles et al., 2000; Koh et al., 2003; Laruelle, 2003; Laruelle and Abi-Dargham, 2003; Laruelle et al., 1999, 2003; Manoach, 2003; Seeman and Kapur, 2000; Suhara et al., 2002). N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine and ketamine, induce schizophrenia-like symptoms in healthy subjects (Ballal et al., 2001, 2003; Bunney et al., 2000; Halberstadt, 1995; Jentsch and Roth, 1999; Jentsch et al., 1997, 1999, 2000; Krystal et al., 2003; Le Pen et al., 2003; Noda et al., 2000; Olney and Farber, 1995a,b; Tsai and Coyle, 2002). These facts suggest that abnormal transmission of DA, serotonin, and glutamate is critically related to the symptoms of schizophrenia.

The brains of patients with schizophrenia exhibit inconsistent lower or higher activation of the DLPFC when they perform working memory tasks (Andreasen et al., 1992; Callicott et al., 2000, 2003a,b; Carter et al., 1998; Manoach, 2003; Meyer-Lindenberg et al., 2001, 2002; Paulman et al., 1990; Weinberger and Berman, 1998), and this activity is associated with the impairment of cognitive functions including working memory, which are commonly seen in schizophrenia (Elvevag and Goldberg, 2000; Goldberg and Green, 2000, 2002; Goldberg et al., 2003; Gooding and Tallent, 2004; Kuperberg and Heckers, 2000; Lewis, 2004; Weinberger and Gallhofer, 1997; Winterer and Weinberger,
However, the mechanisms of such inconsistent activation of the DLPFC in schizophrenia are largely unknown. A theoretical analysis with the basic prefronto-mesoprefrontal circuit model recently attempted to account for this kind of activation of the DLPFC in schizophrenia (Tanaka et al., 2005). It suggests that, when the efficacy of the glutamatergic transmission in the corticomesencephalic projections to midbrain DA neurons is low, the circuit of the DLPFC tends to be unstable, such that a slight increase in DA releasability causes a catastrophic jump of the DLPFC activity from a low to a high level. The third and last part of this article will argue how this may be related to the inconsistent activation of the DLPFC in the brains of the patients with schizophrenia.

**DOPAMINERGIC CONTROL OF WORKING MEMORY**

**Dopaminergic modulatory systems**

There are four dopaminergic pathways existing in the brain, the mesocortical system, the mesolimbic system, the nigrostriatal system, and the tuberoinfundibular system, each of which has activity with a unique set of physiological and psychological effects (Stahl, 2000). In the following, we focus on the issues of working memory representation and its modulation by DA. The system we consider is, therefore, the DLPFC circuit for working memory representation and the mesocortical dopaminergic system that is supposed to modulate working memory activity in the DLPFC.

**Dopaminergic modulation in the circuit**

Since the pioneering work of Brozoski et al. (1979), the critical involvement of DA in cognitive functions has been suggested by many investigations. It is, however, only recently that the circuit mechanisms by which DA controls or modulates cognitive functions have been coming to light through neuroanatomical and neurophysiological findings (Gao and Goldman-Rakic, 2003; Gao et al., 2001, 2003; Gonzalez-Islas and Hablitz, 2001, 2003; Le Moal, 2000; Seamans and Yang, 2004; Seamans et al., 2001b; Yang et al., 1999). These studies have disclosed several aspects of complicated actions of DA in the circuit. Some of them have suggested that dopaminergic modulation in the cortical circuit is not homogeneous but rather circuit specific. For example, Goldman-Rakic and coworkers (Gao and Goldman-Rakic, 2003; Gao et al., 2001, 2003) have found that DA depressed inhibitory transmission from fast-spiking (FS) interneurons to pyramidal neurons but enhanced inhibitory transmission from non-fast-spiking (NFS) interneurons to pyramidal neurons. Because FS neurons form synaptic contacts on perisomatic domains while NFS neurons synapse on peridendritic domains, this implicates circuit-dependent dopaminergic modulation of intracortical inhibition (Gao et al., 2001, 2003). This circuit perspective would be particularly important for the understanding of dopaminergic mechanisms of working memory and other cognitive functions.

**Modulation of working memory activity via D1 receptors**

Electrophysiological recordings from the brains of behaving monkeys showed alterations of working memory performance by the local application of D1 receptor antagonists in the DLPFC (Sawaguchi, 2001; Sawaguchi and Goldman-Rakic, 1991, 1994). By combining iontophoretic analysis of DA receptors with single-cell recording in monkey during working memory performance, Williams and Goldman-Rakic (1995) suggested, for the first time, that D1 receptors selectively modulate the memory fields of DLPFC neurons. Goldman-Rakic and coworkers (Goldman-Rakic et al., 2000; Muly et al., 1998) proposed a hypothesis that accounts for the cellular mechanisms of the modulation of memory fields by D1 receptors. In this hypothesis, D1 receptor activation causes a change in the balance between the excitation and the inhibition in the DLPFC circuit, which changes the firing rates of the DLPFC neurons during the delay period. Their experimental result suggests that stimulation of D1 receptors in the DLPFC modulates working memory with an inverted-U shape profile (Desimone, 1995; Goldman-Rakic et al., 2000; Williams and Goldman-Rakic, 1995). Currently, this profile of dopaminergic modulation is widely known, but it actually has dual interpretations. One is physiological, in which the average firing rate during the delay period is modulated by DA with this profile. The other is behavioral, in which working memory performance also shows the inverted-U shape modulation by DA (Arnsten, 1997; Cai and Arnsten, 1997; Honey and Bullmore, 2004; Mattay et al., 2000; Zahr et al., 1997). Both seem to have grounds, but they are not identical. At least at present, there is no evidence that the relationship between the activity level in the delay period and working memory performance is monotonic.

The inverted-U shape modulation of the activity of DLPFC neurons has been reproduced in computational studies (Brunel and Wang, 2001; Tanaka, 2002b; Yamashita and Tanaka, 2002, 2003, 2005). Brunel and Wang (2001) used a leaky integrate-and-fire neuron model with NMDA, AMPA, and GABA A channels as well as the leak channel. In their model, DA was assumed to change the values of NMDA, AMPA, and GABA A channels. Among these parameters, the NMDA conductance is the most critical for the generation of the inverted-U shape characteristic. Both the pyramidal neurons and the interneurons in their model have NMDA conductances whose dependences on D1 receptor activation are given by sigmoidal curves with the same height. The essential point of the generation of the inverted-U shape characteristic is that the sigmoidal curve for the interneurons is rightward shifted, so that the NMDA conductance of the interneurons increases even in the high D1 receptor activation region. Consequently, the GABAergic inhibition becomes relatively stronger when D1 receptors are highly activated. Tanaka and Yamashita (Tanaka, 2002b; Yamashita and Tanaka, 2003) also showed computationally the inverted-U shape characteristic of dopaminergic modulation. They used a leaky integrate-and-fire neuron model with NMDA, AMPA,
GABA<sub>α</sub>, persistent sodium, calcium-dependent potassium, and the leak channels. Their models assumed that D1 receptor stimulation increases NMDA conductance and persistent sodium currents (by leftward shifting the current-voltage curve) and decreases AMPA and calcium-dependent potassium conductances, in accordance with experimental results (Chen et al., 2004; Gao et al., 2001; Gorelova and Yang, 2000; Gorelova et al., 2002; Pedarzani and Storm, 1995; Seamans et al., 2001a,b; Zhou and Hablitz, 1999) and the previous computational model of dopaminergic modulation (Durstewitz et al., 2000a). By taking into account the hypothesis that D1 receptor activation effectively increases glutamatergic input acting on NMDA receptors of pyramidal neurons when the extracellular DA concentration is low but further activation of D1 receptors increases that of interneurons (Muly et al., 1998), Tanaka and Yamashita (Tanaka, 2002b; Yamashita and Tanaka, 2003) assumed a greater increase of the NMDA conductance of the interneurons in the hyperdopaminergic region compared with that of the pyramidal neurons. The studies of both groups thus suggest that the decrease of the activity of DLPFC neurons in the hyperdopaminergic region of the inverted-U shape profile is due to stronger GABAergic inhibition over the circuit while the increase of the activity in the hypodopaminergic region is due to an increase in glutamatergic transmission via NMDA receptors. The maximum activation of DLPFC neurons is in between them.

D1 receptor stimulation has another important characteristic: it increases the robustness of working memory representation (Durstewitz and Seamans, 2002; Durstewitz et al., 1999, 2000a). The robustness was examined by adding a distractor to the circuit in the delay period to observe if the target pattern activity was disrupted. Robustness against distractors increases with D1 receptor activation. The neuron model used by Durstewitz et al. (2000a) is a Hodgkin-Huxley type with sodium, persistent sodium, high-voltage-activated (HVA) calcium, delayed rectifier potassium, slowly inactivating potassium, fast BK calcium- and voltage-activated (HVA) calcium, delayed rectifier potassium, Hodgkin-Huxley type with sodium, persistent sodium, high-voltage-dependent C-type potassium, NMDA, AMPA, and GABA<sub>α</sub> channels on the pyramidal neurons and sodium and delayed rectifier potassium, NMDA, AMPA, and GABA<sub>α</sub> channels on the GABAergic interneurons. This model assumed that D1 receptor activation modulates persistent sodium, slowly inactivating potassium, HVA calcium, NMDA, AMPA, and GABA<sub>α</sub> currents. The simulation showed that the robustness depended more strongly on NMDA conductance than AMPA and GABA<sub>α</sub> conductances.

Operational control hypothesis

The role of DA in working memory might not be restricted to merely increasing the robustness of the working memory representation of a single target location. Computer simulation of spatial working memory with multiple targets further suggests that DA can have an active role in working memory processing (Tanaka 2002a,b). These simulations used a leaky integrate-and-fire neuron model for DLPFC neurons; AMPA, NMDA, calcium-dependent potassium channel, persistent sodium channel, and leak conductances were assumed to depend on D1 receptor activation. The task in the simulation was based on the oculomotor delayed-response task (Funahashi et al., 1989) but multiple target locations were cued simultaneously or sequentially. When simultaneously cued, increasing the NMDA conductance tends to allow acceptance of increasing numbers of targets to be represented as working memory (Tanaka, 2002a). With two sequentially cued targets of spatial working memory, the simulation further showed that changes in D1 receptor activation in the DLPFC could change the storage strategy of the DLPFC (Tanaka, 2002b). When the D1 receptor activation is low, the circuit replaces the first target by the second target (Fig. 1A). With an intermediate level of D1 receptor activation, the circuit accepts both targets. That is, it stores two targets after receiving the second cue (Fig. 1B). When D1 receptor activation is high, the circuit rejects the second target, maintaining only the first target as working memory even after receiving the cue for the second target (Fig. 1C). Note that the NMDA/AMPA conductance ratio is increasing from Fig. 1A to Fig. 1C. In this situation, NMDA receptors play a critical role, again. As noted in the last subsection, D1 receptor stimulation increases the robustness of working memory representation primarily by increasing the NMDA conductance. The robustness of the representation of the first target thus increases with D1 receptor activation in this simulation. Therefore, the representation of the first target with lowest robustness is easily replaced by the second target (Fig. 1A). In contrast, the representation of the first target with highest robustness persists even after receiving the second cue (Fig. 1C). The response to the second cue is only transient because the cross-directional inhibition from the robust first target representation is so strong that it suppresses the activity to represent the second target. In the intermediate case (Fig. 1B), the representation of the first target is not replaced but coexists with the second target. In this case, the robustness of the representation of the first target is strong enough to maintain the representation but still weak so that the cross-directional inhibition does not eliminate the second target. The circuit thus responds differently to the same second cue by changing D1 receptor activation. Most cognitive operations are obviously more complex than these. The simulated operations shown in Fig. 1 are, as they were, fundamental cognitive operations. Still, this model suggests an interesting feature of dopaminergic modulation of cognitive functions of the brain: DA can control fundamental cognitive operations by changing the D1 receptor activation (the “operational control hypothesis”).

The gating hypothesis of DA proposes that a phasic dopaminergic signal controls the gating of afferent information into the DLPFC to allow it, when necessary, to establish a new representation in the DLPFC (Braver and Cohen, 2000; Cohen et al., 2002; Montague et al., 2004; O’Reilly et al., 1999). The operational control hypothesis proposes a similar but different function of DA. It would, therefore, be interesting to see the differences between the gating hypothesis of DA and the operational control hypothesis. First of all, the former is a procedure for updating
the representation. On the other hand, the essential feature of the latter is that DA can alter the circuit dynamics qualitatively so that it represents working memory differently depending on how much the D1 receptors are activated. This is a kind of selective processes for working memory loading. Second, the gating hypothesis requires an external input to gate (Moody et al., 1998), while the operational control hypothesis does not. The gating function may be mediated by a thalamocortical circuit or, more widely, a prefronto–striato–pallido–thalamo–prefrontal network (Kalivas et al., 2001; Tanibuchi and Goldman-Rakic, 2003, 2005; Watanabe and Funahashi, 2004a,b), as suggested by connectionist model studies (Braver and Cohen, 2000; Braver et al., 1999; Cohen et al., 2002; Frank et al., 2001). The phasic activity of DA neurons in the ventral tegmental area and substantia nigra (Hollerman et al., 1998; Schultz, 1998; Waelti et al., 2001) may be related to the gating function (Braver and Cohen, 2000; Cohen et al., 2002; Montague et al., 2004; O’Reilly et al., 1999). In contrast, the DA function in the operational control hypothesis is based on the tonic action of DA on DLPFC neurons. Midbrain DA neurons exhibit both phasic and tonic modes of activity, and these modes could contribute to different aspects of working memory. Therefore, the operational control hypothesis proposes a new function of DA rather than an alternative to the gating function. That DA has a role in working memory that depends on the tonic DA action is supported by recent microdialysis monitoring of the DA release in the medial PFC of rats performing a delayed-response task, suggesting that the accuracy of performance depends on the magnitude of the DA release (Phillips et al., 2004). Interestingly, the DA release for accurate performance was not dependent on the presence of reward. Moreover, the new function would not be merely to increase robustness of working memory representation because, if this were the case, it would be incompatible with a decrease in DA efflux during the delay period. Rather, it is more likely to be related to an operation of working memory during the test phase as well as the training phase. Further argument on this issue requires additional experimental and theoretical studies.

Contribution of D2 receptors

Some functional imaging studies have suggested the involvement of D2 receptors in working memory (Kimberg et al., 2001; Luciana et al., 1992; Luciana and Collins, 1997; Mehta et al., 2001, 2004), but other studies have not replicated these results (Kimberg et al., 1997, 2001; Muller et al., 1998). From these imaging studies, however, it is still uncertain which aspect of working memory processing depends on D2 receptors. Recently, how D1 and D2 agonism differentially influences executive functions has been assessed at the behavioral level (Roesch-Ely et al., 2005). They used pergolide (a mixed D1/D2 agonist) and bromocriptine (a selective D2 agonist) for healthy humans performing Stroop tasks and delayed response tasks. The results were that only bromocriptine showed decreased interference in the Stroop tasks and that neither agonist had any effect on the delayed response tasks. They argued that D2 agonism facilitated the switching from reading to color naming. This interpretation is consistent with
the suggestion made by Seamans and Yang (2004) that the predominance of D2 modulation provides a net reduction in inhibition. McDowell et al. (1998) suggested, in functional imaging, that bromocriptine improved executive functions but had no effect on the maintenance of working memory without significant executive demands. Taken together, it seems that the role of D2 receptors is more relevant to executive functions than to the maintenance of working memory.

In the cortex, DA D2 receptors are relatively scarce (Lidow and Goldman-Rakic 1994; Lidow et al., 1989), yet they have a role in working memory processing. Recently, by the iontophoretic application of a D2 agonist and an antagonist, Wang et al. (2004a) suggested that D2 receptors contribute only to response-related activity and have little effect on delay-period activity of spatial working memory in the DLPFC of monkeys. Their interpretation of this result is that the response-related activity is corollary discharge, informing the DLPFC that a motor command has been completed, which is modulated by D2 receptors. This idea has led us to construct a model to reproduce their result (Ebi et al., 2005). The model of the cortical circuit has two populations (Population D and Population S); the excitatory and inhibitory neurons in Population D have D1 receptors, while those in Population S have D2 receptors (Fig. 2). The neurons in Population D receive cue inputs and maintain the information as working memory. The neurons in Population S receive response-related signal as an efference copy (Wang et al., 2004a). There would be overlapping of both the neuronal distribution across the populations and the distributions of D1 and D2 receptors over the populations in the cortex. This dichotomy in the model is just for clarifying the roles of D1 and D2 receptors. Note, however, that this is consistent with their conclusion that "neurons with saccade-related activity either have a high density of postsynaptic D2 receptors or receive an external input from neurons that do, whereas cells expressing memory-related persistent activation are preferentially modulated by D1 receptors" (Wang et al., 2004a). One of the interesting features in this study is that, in spite of generally inhibitory actions of D2 receptors on neuronal activity and GABAergic actions, the synergistic result of D2 receptor activation is the facilitation of the transient response-period activity (Fig. 2). This is a kind of disinhibition due to D2 receptor stimulation. The neurons of Population S do not exhibit the cue-related or delay-period activity, as shown in the figure. In contrast, the neurons of Population D exhibit delay-period activity. However, D2 receptor stimulation does not affect the delay-period activity, in accordance with their result (Wang et al., 2004a). Moreover, though the neurophysiological data in Fig. 2 show that D2 receptor activation also seems to affect the cue-period activity to some extent, the activities of the neurons they examined that exhibited cue-related activity were not affected by the D2 receptor agonist or antagonist (Wang et al., 2004a). These results suggest that D1 and D2 receptors have different roles in working memory processing in the DLPFC.

Further dissociation of the roles of D1 and D2 receptors in working memory along with anatomical studies would provide knowledge about the circuit-specific mechanisms of working memory processing. This would enable receptor type- and circuit-specific models of working memory. In psychiatry, intensive efforts to develop cognitive enhancers are currently being made (for example: Barch, 2004; Farah et al., 2004). Such models may be useful to develop means for process-specific enhancement of cognitive functions.

**STABILITY OF THE PREFRONTO–MESOPREFRONTAL SYSTEM**

**Open-loop and closed-loop controls of DA release in the PFC**

The operational control hypothesis, argued in the last section, requires the regulation of the extracellular DA level in the DLPFC. Midbrain DA neurons can release DA phasically and tonically under various regulating mechanisms (Dreher and Burnod, 2002; Dreher et al., 2002; Fiorillo et al., 2003; Grace, 1991, 1995, 2000; Schultz, 1998, 2001, 2002). Phasic activity of DA neurons, which is supposed to be triggered by an input from outside the mesocortical system, would be able to increase the extracellular DA concentration in the DLPFC rapidly. The released DA is removed by reuptake. In the mesocortical system, this mode of DA control, the open-loop control, may play a role in loading or updating of working memory. In the maintenance of working memory, however, the reciprocal connectivity between the DLPFC and the midbrain DA nuclei (Sesack and Carr, 2002; Tzschenkte, 2001; Williams and Goldman-Rakic, 1998) would enable another mode of DA control, the closed-loop control. In this mode of control, the corticomesencephalic projections to the DA neurons would modulate tonic activity of the DA neurons. Recent computational studies suggest that this closed-loop system forms a "regulator" of DA release in the DLPFC (Tanaka, 2005; Yamashita and Tanaka, 2003). This is in accord with the multiple regulatory system view in the mesolimbic system: "burst firing induces massive synaptic DA release, which is rapidly removed by reuptake before escaping the synaptic cleft, whereas increased population activity modulates tonic extrasynaptic DA levels that are less influenced by reuptake" (Floresco et al., 2003). It is, therefore, likely that the brain uses different control modes for different processes of working memory.

**Stability analysis of the prefronto–mesoprefrontal system**

The dynamics of the prefronto–mesoprefrontal system have been analyzed further. The basic architecture of the model is shown in Fig. 3. The model consists of the DLPFC and the midbrain DA nuclei. It has been anatomically and physiologically confirmed in rodents that mesocortical DA neurons send axons to the cortex and receive feedback projections from the cortex (Sesack and Carr, 2002; Sesack et al., 2003; Tzschenkte, 2001). In primates, the DA afferents originate from a widespread continuum of
neurons in the substantia nigra, ventral tegmental area (VTA), and the retrorubral area (Williams and Goldman-Rakic, 1998). The present computational model deals with the population of the mesocortical DA neurons as a unit. The activity of this unit determines the DA release in the DLPFC, which then modulates the activity of the DLPFC neurons by D1 receptor activation. The activity of the DLPFC feeds back to the DA unit. Beside this cortical feedback, this unit receives phasic and tonic inputs, which generate the phasic and tonic activities of the DA unit, respectively. The phasic input triggers the DA release in the DLPFC. In the simulation, it is usually strong enough to increase the DA release in the DLPFC rapidly. In contrast, the tonic input to the DA unit is utilized just for biasing the activity of the DA unit and is rather weak or often vanishing. In the cortex, the cue input triggers the sustained activity of

Fig. 2. Effects of D2 receptor activation on the saccade-related activity of DLPFC neurons. (A) The model has two populations of neurons, each of which is related to delay-period activity (PD and ND) or saccade-related activity (PS and NS). P denotes pyramidal neurons and N denotes GABAergic interneurons. (B) Time courses of the activity of PS for various levels of D2 receptor stimulation. The colored lines in the figure are the time courses of the neuronal activity recorded from monkey DLPFC for low (green), intermediate (blue), and high (red) D2 receptor stimulation (Wang et al., 2004a). The three-dimensional surface plot shows the result of the computer simulation of the model.
the DLPFC, respectively, where the state variables, \( z \), \( \tilde{n} \), \( \tilde{p} \), and \( \tilde{n} \) denote the activity of the pyramidal neurons in the DLPFC, the activity of the GABAergic interneurons in the DLPFC, the activity of the DA neurons in the midbrain, and the DA release in the DLPFC, respectively.\[ z = z_{\text{max}} f(y_d(t)) \] is the level of D1 receptor activation and its effects on the signal transduction pathways (Duman and Nestler, 2000; Greengard, 2001) (we simply call this “D1 receptor activation” in the following), \( z_{\text{max}} \) is the sensitivity of the D1 receptors, and

\[
f(x) = \begin{cases} 
\tanh(0.15x) & x \geq 0 \\
0 & x < 0 
\end{cases}
\]

The pyramidal neurons in the DLPFC receive a transient cue input, \( I_{\text{cue}}(t) \), during 100 ms in the beginning of the simulation, which triggers circuit dynamics. The DA neurons receive phasic (\( I_{\text{phasic}}(t) \)) and tonic (\( I_{\text{tonic}}(t) \)) inputs from outside the circuit (Fig. 3). The phasic input is synchronized with the cue input to the DLPFC. In this model, the D1 receptor activation is assumed to change \( \tilde{W}_{dp}, \tilde{W}_{pn}, \) and \( \tilde{y}_d \) as \( \tilde{W}_{dp} = W_{dp}(0.12z + 0.68), \tilde{W}_{pn} = W_{pn}(0.12z + 0.68), \) and \( \tilde{y}_d = \gamma_{\text{d}}(0.24z + 0.26) \) as \( \gamma_{\text{d}} = 0.27, W_{nn} = 0 \) (for simplicity in this simulation), \( W_{pd} = 0.023, W_{dy} = 0.30 \).

From the above set of equations, one obtains the equilibrium state of the system as a fixed point in the state space. Fig. 4 shows the fixed points and the trajectories showing the state transition to the fixed points. The fixed points of this system in the \( f(x_p) - z \) space (i.e. the space of the firing rate of the pyramidal neurons of the DLPFC and the D1 receptor activation) are obtained by the intersections of the \( x_p \) nullcline and the \( y_d \) nullcline. The fixed points indicated by small circles in the figure are stable, while those by small triangles are unstable. The origin is always a stable fixed point, and another stable fixed point emerges in Fig. 4A, B, C, and F. The gray curves show trajectories of the state transition to a stable fixed point. The locations of the fixed points depend on two important circuit parameters, which are the synaptic weights \( W_{dy} \) and \( W_{pd} \). The synaptic weight \( W_{dy} \) denotes the DA releasability from the axon terminals of the mesocortical projections in the DLPFC. The amount of DA released in the DLPFC changes with this parameter even when the activity of the DA neuron is unchanged. The synaptic weight \( W_{pd} \) denotes the efficacy of glutamatergic transmission in the...
corticomesencephalic projections. Though there could be several mechanisms to change this efficacy, we regard this as an independent parameter without specifying the mechanism in this model. When the efficacy of glutamatergic transmission is low and the DA releasability is not high (Fig. 4D and E), the origin is the only stable fixed point because there is no intersection of the $x_p$ nullcline and the $y_d$ nullcline. When the system has two stable fixed points (Fig. 4F), an unstable fixed point exists between the two. From this positional relationship of these fixed points, it can be stated that the hyperdopaminergic state is generally stable while the hypodopaminergic state tends to be unstable. These results suggest a model of the activity of the DLPFC under normal and abnormal conditions. In the remaining part of this article, we will discuss how it is related to schizophrenia.

RELEVANCE TO SCHIZOPHRENIA

Unstable activation of the PFC

Schizophrenia is a complex syndrome and the etiology is not likely to be attributable to a single cause. Nevertheless, there could be critical factors that account for some aspects of the symptoms. From a circuit dynamics perspective, the failure of the regulation of the prefronto-mesoprefrontal dopaminergic system would be one of them. This is consistent with the hypothesis that the PFC is hypodopaminergic in schizophrenia (Davis et al., 1991; Kahn and Davis, 2000), which is supported by receptor imaging studies (Abi-Dargham et al., 2002; Guo et al., 2003; Okubo et al., 1997). In functional imaging studies, on the other hand, the DLPFC in schizophrenia has originally been reported to be hypoactive when performing a working memory task (Andreasen et al., 1992; Carter et al., 1998; Meyer-Lindenberg et al., 2002; Paulman et al., 1990; Ramsey et al., 2002; Weinberger and Berman, 1998). This task-related hypofrontality has been repeatedly observed in many studies (Berman, 2002). Later, however, functional imaging studies reported exaggerated activation of the DLPFC for working memory performance compared with normal subjects (Callicott et al., 2000, 2003a,b; Manoach, 2003; Manoach et al., 1999, 2000; Weinberger et al., 2001). The relationship between the activation of the DLPFC and the performance of working memory tasks, therefore, seems to be complicated (see also: Honey et al., 2002; Perlstein et al., 2001, 2003).

Fig. 4. Portraits on the $f(x_p)$–z plane of the model prefronto-mesoprefrontal system with high (A–C) and low (D–F) efficacy of corticomesencephalic glutamatergic transmission. Here, $f(x_p)$ denotes the activity of the pyramidal neurons and z is the D1 receptor activation level. Multiple fixed points are obtained as the intersections between $x_p$ and $y_d$ nullclines. Among these intersections, circles and triangles represent stable and unstable fixed points, respectively. The unstable fixed point is the hyperbolic fixed point or the saddle point of the system. The dynamics of this model near the fixed points are determined by linearizing the model equations around their fixed points and estimating the associated eigenvalues. An increase in the DA releasability influences the location of the fixed points except for the origin. The DA releasability and the glutamatergic transmission efficacy are indicated by the % values relative to 0.30 and 0.023, respectively.
In the following, we apply the model from the previous section to see how the activity of the DLPFC changes with the DA releasability and the efficacy of the glutamatergic transmission in the corticomesencephalic projections. Fig. 5 shows the dependences of the DLPFC activity and the DA release or the D1 receptor activation (both are identical in this simulation because the sensitivity of the D1 receptors, $z_{\text{max}}$ in the model, is fixed) on the DA releasability in high and low corticomesencephalic glutamatergic transmission cases. There is a pair of a stable branch (the blue curve in the figure) and an unstable branch (the red dashed curve in the figure) as well as another stable branch on the horizontal axis. In the hyperglutamatergic condition (Fig. 5A and B), the stable fixed point (the light blue dot) shows a relatively low firing rate of the DLPFC neurons with a high D1 receptor activation. Further increase in the DA releasability decreases the firing rate of the pyramidal cells in the DLPFC but the D1 receptor activation itself does not change very much. In the hypoglutamatergic condition (Fig. 5C and D), there is no stable fixed point other than zero for both the activity of the pyramidal cell and the D1 receptor activation when the DA release is less than 180%. That is, low or moderate DA releasability does not lead to activation of the DLPFC. A slight increase in the DA releasability causes a catastrophic jump of the activity to a high level, and only the states with high DA releasability provoke activation of the DLPFC (Fig. 5C). Yet, the D1 receptor activation level remains fairly low (Fig. 5D). When the DA releasability is at 300% in the hypoglutamatergic case, the DLPFC activity is much higher than that in the hyperglutamatergic case, while the D1 receptor activation level is lower than that in the hyperglutamatergic case. The distinguishing feature in this case is that the unstable region (indicated by a red shadow in Fig. 5C) is enlarged. When the DLPFC is activated moderately, therefore, the activity goes to either a high level or the zero level (the two light blue dots in the figure). That is, the unstable dynamics of the circuit makes the activation of the DLPFC highly susceptible to the input.

The transition of the DLPFC state from a hypoactive state to a hyperactive state is abrupt or catastrophic under the hypoglutamatergic condition. This catastrophic transition occurs by increasing the releasability of DA in the DLPFC. An increase in the DA releasability may be associated with subjective effort to improve performance at working memory tasks. Callicott et al. (2000) showed that a subgroup of patients with schizophrenia who performed an n-back task relatively normally had increased DLPFC activation compared with normal controls, while patients who performed poorly failed to activate the DLPFC. The above computational results show both the exaggerated activation and the inactivation of the DLPFC, which have been observed in patients with schizophrenia (Callicott et al., 2000, 2003a,b; Manoach, 2003; Manoach et al., 1999, 2000). Moreover, the above result suggesting that this

![Diagram](https://i.imgur.com/3Q5Q5Q.png)

**Fig. 5.** Bifurcation diagram of the activity of the pyramidal cells in the DLPFC (A and C) and the D1 receptor activation (B and D). The efficacy of corticomesencephalic glutamatergic transmission is fixed at 200% (A and B) or 30% (C and D) relative to 0.023 (100%). The blue solid line indicates the stable branch of the bifurcation. The red dashed line indicates the unstable branch of the bifurcation. The vertical green dashed line shows a catastrophic jump of the state. The horizontal axis is the DA releasability relative to 0.30 (100%).
occurs when the corticomesencephalic glutamatergic transmission is weak is compatible with the hypoglutamatergic hypothesis of schizophrenia (Aghajanian and Marek, 2000; Carlsson et al., 2001, 2004; Goff and Coyle, 2001; Halberstadt, 1995; Jentsch and Roth, 1999; Kim et al., 1980; Krystal et al., 2003; Laruelle et al., 2003; Meador-Woodruff and Healy, 2000; Meador-Woodruff and Kleinman, 2002; Moghaddam, 2003; Olney and Farber, 1995; Tsai and Coyle, 2002). Taken together, this study proposes that the activation of the DLPFC for working memory performance under normal and abnormal conditions (as in schizophrenia) can be accounted for, at least in part, by the dynamics of the prefronto–mesoprefrontal system, which is produced by the synergistic actions of DA, glutamate, and GABA. This synergism, being restricted by the circuitry of the system, changes with the circuit parameters. In this study, those parameters are the DA releasability and the efficacy of the glutamatergic transmission in the corticomesencephalic projections to the midbrain DA neurons. Both have been key in the research of schizophrenia.

**DA releaser**

The response to DA releasers, such as amphetamine and cocaine, would also provide important information on the intrinsic dynamics of the prefronto-mesoprefrontal dopaminergic control system. There is a tremendous amount of research on these psychostimulants both in humans and animals (for reviews: Barch, 2004; Elliott and Bevenridge, 2005; Fone and Nutt, 2005; Goldman-Rakic et al., 2004; Pierce and Kalivas, 1997; Seeman and Madras, 1998; Santoro, 1998; Steketee, 2003; White and Kalivas, 1998). A computational trial to simulate the response to a DA releaser was made recently using the prefronto–mesoprefrontal closed-circuit model described in the last section (Tanaka, 2005). In this simulation, the effect of a DA releaser is taken into account by shifting the activity-release curve of DA. This study addressed how the neuronal activities of both the DLPFC and the midbrain DA unit, the DA release in the DLPFC, and the DA-glutamate interaction changed when the sensitivity of the D1 receptors of DLPFC neurons (\(z_{\text{max}}\)) changed.

A DA releaser was applied into the DLPFC in the simulation, which increased the DA release at the terminals in the DLPFC without a direct change in the activity of the DA neurons in the midbrain. The activity of the DA neurons is modulated indirectly via the feedback input from the DLPFC. Apparently, the DA release is not determined only by the DA system. The change in the DA concentration modulates the glutamatergic as well as GABAergic transmission in the DLPFC circuit. Fig. 6 depicts some results of the simulation (Tanaka, 2005). With hyposensitive or normal D1 receptors, the DA releaser increases the DA release in the DLPFC (Fig. 6C and E). This does not always occur. With hypersensitive D1 receptors, the DA releaser does not increase the DA level in the DLPFC (Fig. 6G and I). In this case, the administration of the DA releaser makes the DLPFC hyperdopaminergic, which suppresses the activity of the DLPFC neurons (Fig. 6H). Then, the glutamatergic transmission decreases (Fig. 6J). This cancels out the increase of DA release by the DA releaser, maintaining the net DA release in the DLPFC unchanged (Fig. 6G).

The DA-glutamate interaction is one of the key features to an understanding of the circuit mechanisms for cognitive functions. Given that the DA–glutamate interaction would occur at many sites of the system (Del Arco and Mora, 2005; Morari et al., 1998; Sesack et al., 2003; Tseng and O'Donnell, 2003, 2004; West et al., 2003), however, more comprehensive studies would be necessary. This issue would also be critical in the research of schizophrenia to consolidate the DA hypothesis and the glutamate hypothesis.

**DISCUSSION**

This article has proposed that the mesocortical dopaminergic system can control working memory. The fundamental assumption is closed-loop or feedback control of dopaminergic modulation based on the closed-loop circuitry of the prefronto–mesoprefrontal system. In this control scheme, working memory activity of the DLPFC, which is subject to dopaminergic modulation, can control the activity of midbrain DA neurons. The computer simulation with this model suggests that this system works as a regulator of DA release. We argued that this control scheme would be particularly suitable for the regulation of neuronal activity during delay periods in working memory tasks without explicit input. The closed-loop circuitry has both anatomical and physiological grounds in rodents (Sesack and Carr, 2002; Sesack et al., 2003; Tzschentke, 2001). The importance of the closed-loop circuitry, in this context, lies in the intrinsic nature of the system as a regulator of DA release in the DLPFC (Tanaka, 2005; Yamashita and Tanaka, 2003). In this model, therefore, dysregulation of the control of dopaminergic modulation is largely responsible for working memory impairment.

Critical parameters that govern the dynamics of the prefronto–mesoprefrontal system are the DA releasability in the DLPFC and the efficacy of the corticomesencephalic glutamatergic transmission from the DLPFC to the midbrain DA neurons. A system dynamics analysis of the prefronto–mesoprefrontal system revealed that a hypoglutamatergic condition enlarges an unstable region so that a slight increase in the DA releasability in the DLPFC causes a catastrophic jump from a hypofrontal state to a hyperfrontal state. The activation level of this hyperfrontal state is higher than the activation level with a normal glutamatergic condition. We argued that this might account for the increased activation of the DLPFC during working memory performance in some patients with schizophrenia. At present, however, it is uncertain how this kind of activation of the DLPFC is related to the impairment of working memory. Patients with schizophrenia show an overall deficit of working memory and executive functions, which are often greater than those of patients with frontal lobe lesions (Pantelis et al., 1997). Robbins and coworkers (Pantelis et al., 1997; Robbins, 1990) suggested that cognitive deficits
Fig. 6. Dynamics of the model prefronto–mesoprefrontal system with hyposensitive and hypersensitive D1 receptors in the PFC. (A) The architecture of the model. (B) The sensitivity curves of the effect of D1 receptor activation. (a) The hyposensitive case ($z_{max}=1.0$) (C–F). (b) The hypersensitive case ($z_{max}=2.0$) (G–J). (C, G) Time courses of the DA neuron activity (blue), DA release (green), and D1 receptor effect (red). The DA releaser was applied at $t=1000$ ms. (D, H) Population average firing rate of the pyramidal cells in the superficial layer of the PFC (dark blue) and glutamate release from the pyramidal cells in the deep layer of the PFC (magenta). (E, I) Population average firing rate of the pyramidal cells in the superficial layer of the PFC versus the DA release in the PFC. (F, J) DA release in the PFC versus the glutamate release from the pyramidal cells in the deep layer of the PFC.
in patients with schizophrenia would be caused more generally by the dysfunction of the frontostriatal system. Moreover, abnormalities of the DLPPFC in schizophrenia may reflect a compromised neural strategy for handling cognitive information by the DLPPFC (Callicott et al., 2003). These issues are to be studied further.

The basic idea underlying the arguments in this article is compatible with the disconnection hypothesis proposed for the mechanistic description of schizophrenic brains by Friston (1998, 2005). This perspective is no doubt important, given that cognitive information processing is produced by the integration of mutually connected regions. However, this hypothesis does not specify how dynamics change as a consequence of the alteration in connectivity. On the other hand, many computational studies with biophysical modeling have addressed the circuit dynamics for the maintenance of working memory (Amit and Brunel, 1997; Amit and Mongillo, 2003; Brunel, 2003; Compte et al., 2000; Durstewitz and Seamans, 2002; Durstewitz et al., 1999, 2000a,b; Fellous and Sejnowski, 2003; Tanaka, 1999, 2000, 2001, 2002a,b; Wang, 1999, 2001; Wang et al., 2004b; Yamashita and Tanaka, 2002, 2003, 2005). So far, however, they have not addressed the dynamics of a larger network for either the maintenance or other processes of working memory with a few exceptions of preliminary studies (Miyashita et al., 2003; Tabuchi and Tanaka, 2003; Tanaka, 2003). The circuit presented in this article is a part of a large network that mediates working memory processes and other cognitive functions. Yet, this article has shown how the connectivity (i.e. the DA releasability and the efficacy of the corticomencesphalergic glutamatergic transmission in this case) alters the circuit dynamics. This approach should be extended to assess the whole working memory system. In such a system, not only DA but other neuromodulators including norepinephrine and serotonin would also play significant roles. To elucidate the mechanisms of neuromodulatory effect in such a huge and complex system, a strategic approach that integrates the circuit dynamics perspective and the connectivity perspective would be necessary.

CONCLUSION

In summary, based on the simulation of circuit dynamics being modulated by DA, we have first proposed the operational control hypothesis of working memory processing. Second, the analysis of the prefronto–mesoprefrontal closed-loop system, a regulator for the DA release in the DLPPFC, has illustrated how the operating point on the inverted-U shape curve of dopaminergic modulation is determined dynamically. It is interesting to note that there exists a pair of stable and unstable fixed points on the inverted-U curve and that the unstable fixed point is always to the left of the stable fixed point. The distance between these fixed points influences the dynamics. When they are located closely to each other, the dynamics tend to be vulnerable. This occurs when the cortical feedback is hypoglutamatergic. This concept has been applied to account for inconsistent lower or higher activation of the DLPPFC in the brains of patients with schizophrenia. In the circuit dynamics perspective, such kind of activation of the DLPPFC in schizophrenia can be attributable, at least partly but essentially, to the dysregulation of the prefronto–mesoprefrontal dopaminergic control system. This should be tested by collaborative works of functional imaging studies and computational studies.

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