State-dependent alteration of dopamine and glutamate transmission in the prefrontal cortex by psychostimulants

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Abstract

In spite of accumulating evidence for dopaminergic contribution to cognitive functions, the mechanism how the cortical dopamine (DA) level is controlled is still obscure. To investigate the mechanisms of intracortical DA level control, this article investigates the dynamics of the prefronto-mesoprefrontal system under the influence of DA. The fundamental assumption of this model is closed-loop circuitry between the prefrontal cortex (PFC) and the midbrain DA nuclei. This study suggests that the system forms a regulator with peculiar characteristics. These characteristics would be responsible for differential responses to psychostimulants and may be critically relevant to negative symptoms and cognitive deficits in schizophrenia.

Keywords: Persistent activity; Pharmacology; Prefrontal cortex; Schizophrenia; Working memory

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1. Introduction

Dopamine (DA) has been suggested to play critical roles in cognitive functions [3]. In spite of accumulating evidence for dopaminergic contribution to cognitive functions, however, the mechanism how the cortical DA level is controlled is still obscure. Recently, Tanaka [16] showed computationally that changing in the DA level in the prefrontal cortex (PFC) can make the cortical circuit dynamics flexible enough to perform several different operations of spatial working memory. This is accomplished essentially by changing the ratio of the NMDA conductance to the non-NMDA conductance of PFC neurons due to the activation of DA D_1 receptors. The regulation of the DA level in the PFC would thus be critical to the control of cognitive functions.

During delay periods in working memory tasks, no external input is given. Then the brain processes *internally* the relevant cognitive information. In this 'internal mode', the intracortical DA level would be regulated by the cortical control of the activity of the midbrain DA neurons. Neuroanatomical studies suggest that the PFC and the midbrain DA nuclei form a closed-loop system [12,17]. In accordance with this notion, this laboratory has recently developed a closed-loop circuit model of the prefronto-mesoprefrontal system [18]. Using this model with some modifications, this article investigates how the extracellular DA level in the PFC is regulated in the 'internal mode'. The computer simulation shows that this system forms a 'regulator' for the regulation of the extracellular DA level in the PFC. The analysis, however, suggests that the dynamics of this regulator is somewhat peculiar. It has a stable hyperdopaminergic state but an unstable hypodopaminergic state. With this characteristic, the system is expected to respond to externally applied drugs in a complex manner. It is, therefore, interesting to see how psychostimulants (such as amphetamine, methamphetamine, cocaine, and methylphenidate) affect the synaptic transmission throughout the system.

2. Model

2.1. Circuitry of the model

In rats, the PFC projects to dopaminergic neurons in the ventral tegmental area (VTA) [13]. The dopaminergic neurons in the VTA, in turn, send axons to the PFC. The PFC-VTA, therefore, forms a closed-loop system. In monkeys as well, the PFC and the midbrain DA nuclei form a closed-loop system, but the anatomical connectivity with the dorsolateral PFC has not been well

established. The tracing studies by Williams and Goldman-Rakic [17] revealed that the DA neurons innervating the macaque PFC as a whole distribute across all three of the mesencephalic DA cell groups, A10, A9, and A8 (i.e., the VTA, substantia nigra, and the retrorubral area, respectively). Our model consists of the PFC and the midbrain DA nuclei. The latter is simplified to be a unit as a whole without discriminating a nucleus from the others.

2.2. Midbrain DA unit

The activity of the DA unit, u, depends on the feedback input from the PFC deep layer neurons, I_{PFC}:

$$\tau \frac{du}{dt} = I_{PFC} - u \tag{1}$$

where τ = 10 ms is the time constant of the DA unit. The DA level in the PFC is then given by

$$\tau_{DA} \frac{dy}{dt} = f_{DA}(u) - y, \qquad f_{DA}(u;u_0) = \frac{1}{1+\exp\left(-\frac{u-u_0}{0.05}\right)} \tag{2}$$

where τ_{DA} = 100 ms is the time constant of the DA release.

The action of psychostimulants is mimicked by changing the value of the parameter, u_0; decreasing in u_0 causes an increase in the extracellular DA level in the PFC. This is not a comprehensive description but an essential aspect of the actions of psychostimulants because they enhance the DA level by facilitating the release and inhibiting reuptake [4]. In the following, therefore, we call the drug that causes this action just 'the psychostimulant'.

The activation of the D_1 receptors follows the functional relationship:

$$z_{D1} = \alpha_{D1} f_R(y), \qquad f_R(y) = \frac{1}{1+\exp\left(-\frac{y-0.4}{0.1}\right)} \tag{3}$$

where z_{D1} is the degree of D_1 receptor activation and α_{D1} determines the strength of the response of the D_1 receptors (α_{D1} > 1 for receptor up-regulation or sensitization).

2.3. Prefrontal cortex

The PFC of this model contains 2160 pyramidal cells and 720 inhibitory interneurons. The dynamics of these neurons are described by the leaky integrate-and-fire model:

$$C\frac{dV_i}{dt} + I_{AMPA} + I_{NMDA} + I_{GABA_A} + I_{Nap} + I_{K(Ca)} + I_{leak} = 0 \tag{4}$$

where the transmembrane currents are given by

$$\begin{aligned}
I_{AMPA} &= \sum_j g_{AMPA,ji}(t - t_{ji})(V_i - E_{AMPA}) \\
I_{NMDA} &= \sum_j g_{NMDA,ji}(t - t_{ji})\, f_{Mg}(V_i)(V_i - E_{NMDA}) \\
I_{GABA_A} &= \sum_j g_{GABA_A,ji}(t - t_{ji})(V_i - E_{GABA_A}) \\
I_{Nap} &= g_{Nap}(V_i)(V_i - E_{Na}) \\
I_{K(Ca)} &= g_{K(Ca)}([Ca^{2+}]_i)(V_i - E_K) \\
I_{leak} &= g_{leak}(V_i - E_{leak})
\end{aligned} \tag{5}$$

The above currents are defined to be positive for outward flow. Here t_{ji} is the time at which an ion conductance of the postsynaptic neuron *i* starts to open by responding to the firing of the presynaptic neurons *j* ($t_{ji} = t_{sp,j} + \Delta t_{ji}$, where $t_{sp,j}$ is the time at which the presynaptic neuron *j* spikes and Δt_{ji} is the transmission and synaptic delay, which is chosen randomly from 2.0-10.0 ms). The conductance, $g_{s,ji}(t)$ (*s* = *AMPA*, *NMDA*, $GABA_A$), is described by a linear second-order system (15,16). The opening and closing time constants are (τ_1, τ_2) = (1.0, 5.0) [ms] for g_{AMPA} and g_{GABA_A} and (10.0, 100.0) [ms] for g_{NMDA}. The gating function of the NMDA current, f_{Mg} (V_i), represents the dependence of the current on the membrane potential, called the magnesium block. The persistent sodium current, I_{Nap}, is described here as a non-inactivating, voltage-dependent current. The potassium conductance, $g_{K(Ca)}$, is assumed to be proportional to the intracellular calcium concentration of neuron *i*, $[Ca^{2+}]_i$, whose dynamics is described by the impulse response of a first-order system (15,16). The leak conductance is g_{leak} = 25.0 nS for the pyramidal cells and 20.0 nS for the interneurons. The membrane capacitance is *C* = 0.5 nF for the pyramidal cells and 0.2 nF for the interneurons. The equilibrium potentials of the channels are: $E_{AMPA} = 0$ mV, $E_{NMDA} = 0$ mV, $E_{GABA_A} = -80$ mV, $E_{Na} = 50$ mV, $E_K = -95$ mV, $E_{leak} = -70$ mV. The ratio of the NMDA conductance to the AMPA

conductance is $g_{NMDA,\max}/g_{AMPA,\max}=0.05$ when $z_{D1}=0$. The ratio of the cross-directional inhibition to the isodirectional inhibition (14-16) is $g_{GABA_A(cross),\max}/g_{GABA_A(iso),\max}=0.12$.

The details and the circuitry of this model of the PFC are identical to [16] and the fundamental circuit properties for spatial working memory processing have been discussed in [14-15]. Dopaminergic modulation is also described in the same way with [16]. Unlike the previous model [16], however, the DA level in the PFC in this model is regulated autonomously because of the closed-loop circuitry (Fig. 1A). The effects of changing in the DA level on the conductance electrical properties are assumed here to be given by

$$g_s(V_i,t;z_{D1})=g_s(V_i,t;0)(1+\gamma_s\cdot z_{D1}),\quad s=\text{AMPA, NMDA, K(Ca), Leak} \tag{6}$$

$$E_{Na}(z_{D1})=E_{Na}(0)+\beta_E\cdot z_{D1} \tag{7}$$

where γ_s = -0.2 (for g_{AMPA}), +0.5 (for g_{NMDA}), -0.4 (for $g_{K(Ca)}$ and g_{leak} of the interneurons), and $\beta_E=-1.0$. The modulation of the leak conductance, described above, is assumed only for the interneurons [6].

/ Fig. 1 /

3. Results

3.1. Fundamental dynamics of the closed-loop regulator

When the DA level is low, the cortical circuit is less activated due to insufficient glutamate transmission [5,9]. An increase in the DA level enhances the activity of the cortical circuit in this regime. When the DA level is too high, however, the network activity of the PFC is suppressed by the excessive activation of the inhibitory interneurons in the cortex. This reduces the glutamatergic input to the DA neurons, and then reduces the intracortical DA release. The DA level in the cortex is thus regulated at the optimum level in normal condition. The dynamics is rather stable in the hyperdopaminergic state. When the DA level is slightly decreased from the optimum, on the other hand, insufficient feedback from the PFC to the midbrain decreases the DA release further, resulting in a hypodopaminergic state.

3.2. Influences of 'the psychostimulant'

The D_1 receptors were either up- or down-regulated beforehand in this series of simulation (Fig. 1B). After the starting of the simulation at t = 0 ms, the neurons in both the PFC and the midbrain DA nuclei raise their activities gradually to reach a steady state (t > 500 ms) (Figs. 2 and 3). This simulation shows that the up-regulation of the D_1 receptors generally decreases the DA release in the PFC. Then the PFC tends to become hypodopaminergic. In contrast, the down-regulation of the D_1 receptors generally increases the DA release in the PFC, which makes the PFC hyperdopaminergic. Local application of the psychostimulant into the PFC (whose action is mimicked by changing the value of u_0 from 0.2 to 0.1 for $t \geq 1000$ ms) changes the activities after t = 1000 ms. When the D_1 receptors were down-regulated (Fig. 2), the system was in a low-D_1 receptor activation and high-DA release state. The DA release increases greatly after the application of the psychostimulant. The firing rates of the pyramidal cells in the PFC, however, do not change significantly. As a result, the psychostimulant increases the DA release but not the glutamate release. When the D1 receptors were up-regulated (Fig. 3), the system was in a high-D_1 receptor activation and low-DA release state. The DA release does not change even after the application of the psychostimulant in this case. Instead, the glutamate release decreases significantly due to the decrease in the firing rates of the pyramidal cells in the PFC.

/ Fig. 2 / / Fig. 3 /

4. Discussion and Conclusion

Whether D_1 receptors are down-regulated or up-regulated in drug-free or drug-naive schizophrenic brains is in debate. The D_1 receptor availability was measured using SCH13390 [7,10] and NNC112 [1]. The results are surprisingly different: the D_1 receptor availability was increased [1], decreased [10], or unchanged [7]. This simulation suggests that the change in the release of DA and glutamate strongly depends on the state of the system. The mechanisms are explained as follows: When the D_1 receptors are down-regulated, the DA release in the PFC increases by increasing the glutamate transmission in the PFC. But the increase in the DA level in the PFC enhances the intracortical inhibition. Then the glutamate release is suppressed by inhibiting the pyramidal cells. Therefore, the activity of the PFC neurons slightly decreases and the net glutamate transmission does not increase. The up-regulated state is already hyper-activity of the D_1 receptors, in which intracortical inhibition is strong. Further increase in the glutamate

transmission by increasing the DA release yields very strong intracortical inhibition. The activity of the PFC is highly suppressed and net glutamate transmission decreases. This causes a decrease in the DA release, which cancels the increasing action of the psychostimulant or the DA releaser. Consequently, the DA release does not increase. It is remarkable that the application of the psychostimulant (at the level assumed in this simulation) decreases the glutamate level when the D_1 receptors are up-regulated. Note, however, that this simulation has assumed that the the 'psychostimulant' is applied only to the PFC. The interaction between the DA system and the glutamate system is to be studied also from a viewpoint of etiology of schizophrenia [2,8,11].

In conclusion, this study suggests that the PFC and the midbrain DA nuclei form a novel regulator with peculiar characteristics. This regulator would work in the 'internal mode' in which no external input is given. These characteristics may be critically relevant to negative symptoms and cognitive deficits in schizophrenia.

Acknowledgements

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References

[1] A. Abi-Dargham, O. Mawlawi, I. Lombardo, R. Gil, D. Martinez, Y. Huang, D.-R. Hwang, J. Keilp, L. Kochan, R.V. Heertum, J.M. Gorman, M. Laruelle, Prefrontal Dopamine D1 Receptors and Working Memory in Schizophrenia, J. Neurosci. 22 (2002) 3708-3719.

[2] B. Adams, B. Moghaddam, Corticolimbic dopamine neurotransmission is temporally dissociated from the cognitive and locomotor effects of phencyclidine, J. Neurosci. 15 (1998) 5545-5554.

[3] T.J., Brozoski, R.M. Brown, H.E. Rosvold, P.S. Goldman, Cognitive deficit caused by regional depletion of dopamine in preforntal cortex of rhesus monkey, Science 205 (1979) 929-932.

[4] R.S. Feldman, J.S. Meyer, L.F. Quenzer, Principles of neuropsychopharmacology, Sinauer, Sunderland, 1997.

[5] P.S. Goldman-Rakic, E.C. Muly III, G.V. Williams, D1 receptors in prefrontal cells and circuits, Brain Res. Rev. 31 (2000) 295-301.

[6] N. Gorelova, J.K. Seamans, C.R. Yang, Mechanisms of Dopamine Activation of Fast-Spiking Interneurons That Exert Inhibition in Rat Prefrontal Cortex, J. Neurophysiol. 88 (2002) 3150-3166.

[7] P. Karlsson, L. Farde, C. Halldin, G. Sedvall, PET Study of D1 Dopamine Receptor Binding in Neuroleptic-Naive Patients With Schizophrenia, Am. J. Psychiatry 159 (2002) 761-767.

[8] B. Moghaddam, Stress activation of glutamate neurotransmission in the prefrontal cortex: Implications for dopamine-associated psychiatric disorders, Biol. Psychiatry 51 (2002) 775-787.

[9] E.C. Muly, K. Szigeti, P.S. Goldman-Rakic, D1 receptor in interneurons of macaque prefrontal cortex: distribution and subcellular localization, J. Neurosci. 15 (1998) 10553-10565.

[10] Y. Okubo, T. Suhara, K. Suzuki, K. Kobayashi, O. Inoue, O. Terasaki, Y. Someya, T. Sassa, Y. Sudo, E. Matsushima, M. Iyo, Y. Tateno, M. Toru, Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET, Nature 385 (1997) 634-636.

[11] J.W. Olney, J.W. Newcomer, N.B. Farber, NMDA receptor hypofunction model of schizophrenia, J. Psychiatr. Res. 33 (1999) 523-533.

[12] S.R. Sesack, D.B. Carr, Selective prefrontal cortex inputs to dopamine cells: implications for schizophrenia,. Physiol. Behav. 77(4-5) (2002) 513-517.

[13] S.R. Sesack, V.M. Pickel, Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on

dopaminergic neurons in the ventral tegmental area, J. Comp. Neurol. 320 (1992) 145-160.

[14] S. Tanaka, Computational approaches to the architecture and operations of the prefrontal cortical circuit for working memory, Prog. Neuro-Psychopharm. & Biol. Psychiat. 25 (2001) 259-281.

[15] S. Tanaka, Multi-directional representation of spatial working memory in a model prefrontal cortical circuit, Neurocomputing 44-46 (2002) 1001-1008.

[16] S. Tanaka, Dopamine controls fundamental cognitive operations of multi-target spatial working memory, Neural Networks 15 (2002) 573-582.

[17] S.M. Williams, P.S. Goldman-Rakic, Widespread origin of the primate mesofrontal dopamine system, Cereb. Cortex 8 (1998) 321-345.

[18] K. Yamashita, S. Tanaka, Circuit properties of the cortico-mesocortical system, Neurocomputing 52-54 (2003) 969-975.

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Figure legends

Fig. 1. A: Fundamental architecture of this model, which is the closed-loop circuitry between the PFC and the midbrain DA nuclei. The cortex has three layers. Only the pyramidal cells in the deep layer send axons to the midbrain dopaminergic neurons. The dopaminergic neurons innervate the pyramidal cells and the interneurons in the PFC. **B:** Activation curves of the D_1 receptors in up-regulated (a: α_{D1} = 2.0) and normal or down-regulated (b: α_{D1} = 1.0) states.

Fig. 2. Dynamics of the model prefronto-mesoprefrontal system with down-regulated D_1 receptors in the PFC. The psychostimulant was applied at t = 1000 ms. **A:** DA neuron activity (dashed line), DA release (solid line), and D_1 receptor activation (dot-dashed line). **B:** Population average firing rate of the pyramidal cells in the superficial layer of the PFC (solid line) and glutamate release from the pyramidal cells in the deep layer of the PFC (dashed line). **C:** Population average firing rate of the pyramidal cells in the superficial layer of the PFC versus the DA release in the PFC. **D:** DA release in the PFC versus the glutamate release from the pyramidal cells in the deep layer of the PFC.

Fig. 3. Dynamics of the model prefronto-mesoprefrontal system with up-regulated D_1 receptors in the PFC. The psychostimulant was applied at t = 1000 ms. **A, B, C, D:** See the legend of Fig. 2.

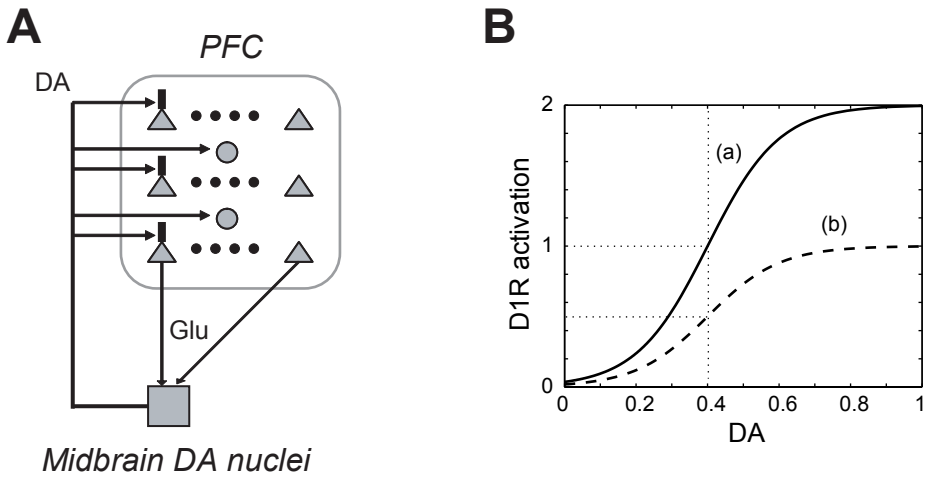
A
PFC
DA
Glu
Midbrain DA nuclei
B
D1R activation
DA
(a)
(b)
0
1
2
0
0.2
0.4
0.6
0.8
1

Fig. 1. Tanaka

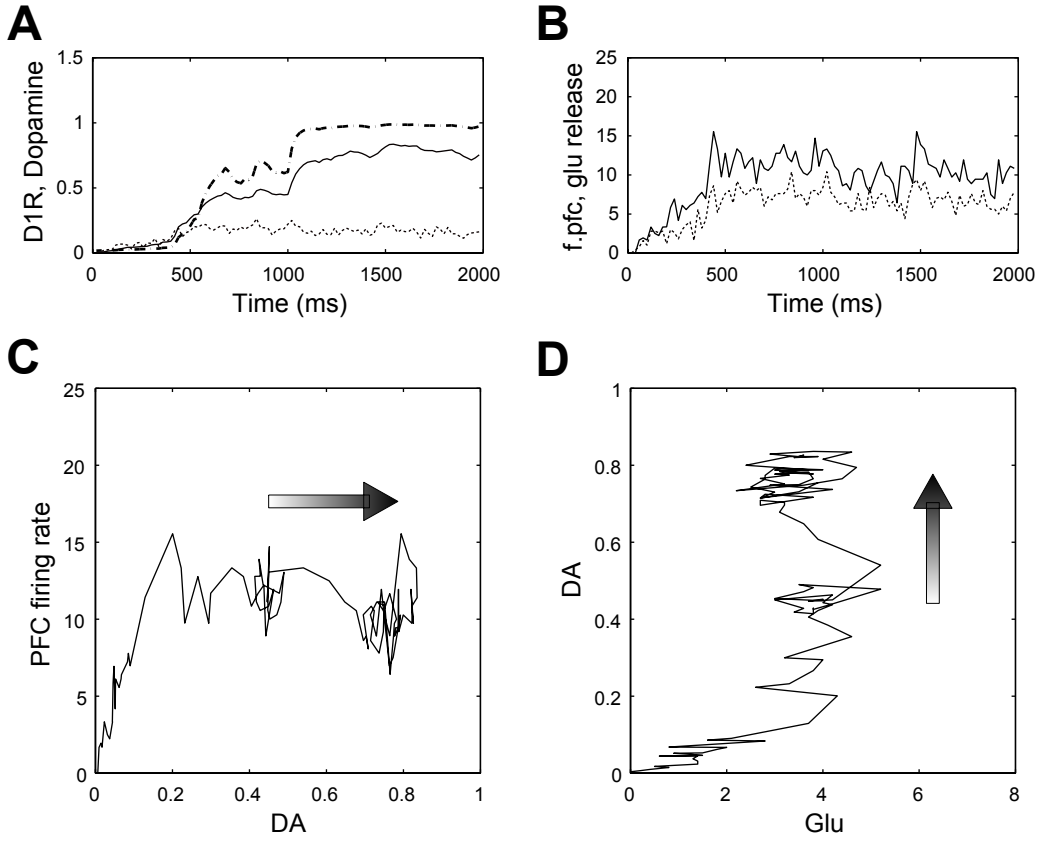
A
D1R, Dopamine
Time (ms)
B
f.pfc, glu release
Time (ms)
C
PFC firing rate
DA
D
DA
Glu

Fig. 2. Tanaka

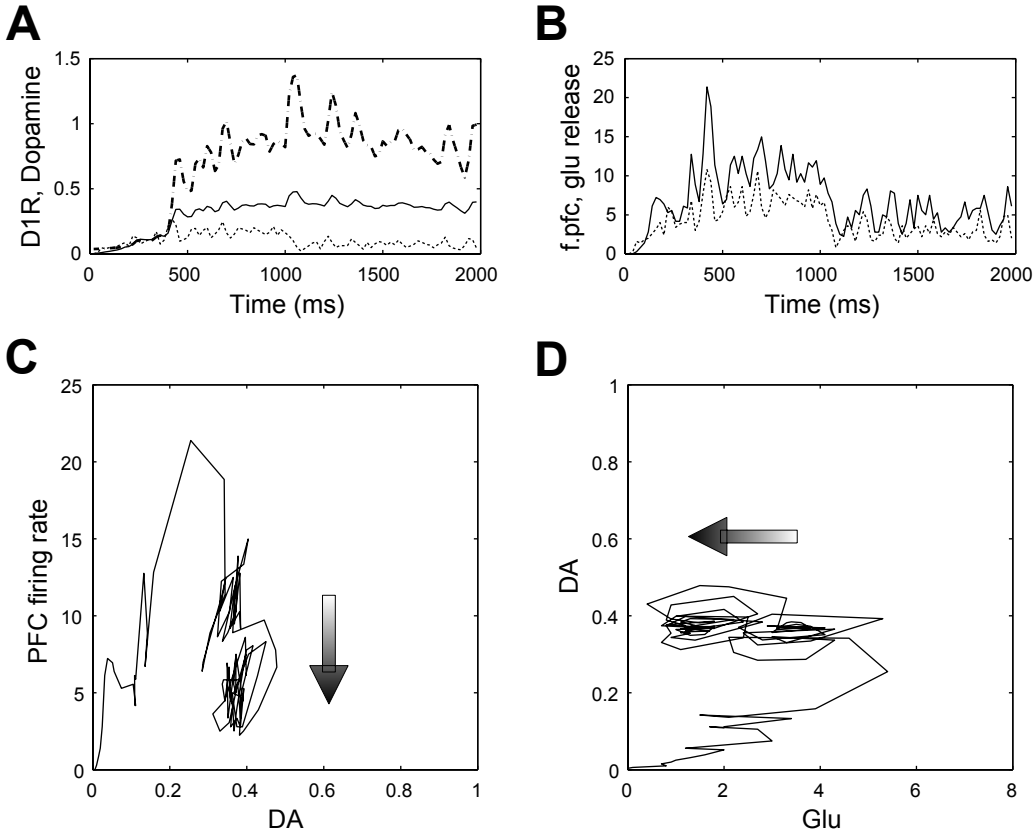
A
D1R, Dopamine
Time (ms)
B
f.pfc, glu release
Time (ms)
C
PFC firing rate
DA
D
DA
Glu

Fig. 3. Tanaka