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SIMULATION OF THE CAPACITY AND PRECISION OF WORKING MEMORY IN THE HYPODOPAMINERGIC STATE: RELEVANCE TO SCHIZOPHRENIA

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Abstract—Working memory (WM) impairment has received attention as a behavioral characteristic of schizophrenia. Neurobiological studies have led to the hypothesis that a deficit in dopamine transmission through D1 receptors in the prefrontal cortex (PFC) is associated with WM impairment in schizophrenia. However, empirical approaches that aim to clarify the nature of the impairment and its underlying mechanism are difficult to enact, especially in unmedicated patients. By contrast, computational approaches using biologically plausible models have formed a powerful theoretical framework for the study of WM impairment in schizophrenia. This article attempts to directly connect neurobiological findings to the neuropsychological behaviors present in patients with schizophrenia. Using a biologically plausible prefrontal cortical circuit model, we simulated sustained activity during a simultaneous, multitarget WM task. We subsequently analyzed how dopaminergic modulation via D1 receptor activation alters the capacity and precision of WM and investigated the underlying mechanism. Hypodopaminergic modulation resulted in imprecision and a reduced capacity in WM primarily due to decreased *N*-methyl-D-aspartate (NMDA) conductance. Increasing NMDA conductance ameliorated both impairments. These results account for the mechanism that underlies WM impairments in schizophrenia and provide a theoretical basis for combination therapy with antipsychotic drugs and drugs that enhance NMDA receptor function, which is expected to be effective for the treatment of WM impairments in these patients.

Key words: schizophrenia, computational, *N*-methyl-D-aspartate, dopamine, persistent activity, prefrontal cortex.

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Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; CR, calretinin; $GABA_A$, gamma-aminobutyric acid type-A; K(Ca), calcium-dependent potassium; Nap, persistent sodium; NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex; PV, parvalbumin; SD, standard deviation; sp/s, spikes per second; WM, Working memory.

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INTRODUCTION

Schizophrenia is characterized by a broad range of cognitive deficits (Gold, 2004; Bowie and Harvey, 2005). Impairments in working memory (WM) have received attention as a core cognitive deficit in the illness (Goldman-Rakic, 1994; Lee and Park, 2005), and the reduction in WM capacity is particularly robust (Goldman-Rakic, 1994; Barch, 2005; Lee and Park, 2005; Gold et al., 2010). Whether the precision of WM is decreased in schizophrenia is also an important issue (Spitzer, 1993; Gold et al., 2010; Hahn et al., 2012; Mayer and Park, 2012). Some studies have suggested the imprecision of WM (Spitzer, 1993; Mayer and Park, 2012). For example, Mayer and Park (2012) identified a decrease in WM precision and an increase in the amount of false memory (i.e., an incorrect memory with confidence) in schizophrenia patients and suggested that the WM imprecision could primarily be attributed to the increase in false memory. By contrast, Gold et al. (2010) demonstrated that the WM precision of patients did not differ from normal controls. Thus, the precision of WM in schizophrenia remains controversial. The measurement of the processes mediated by the complex WM system has limitations (Hahn et al., 2012; Mayer and Park, 2012), and the relationship between the capacity and precision of WM remains unclear (Roggeman et al., 2014).

Dopamine D1 receptors are more abundant than D2 receptors in the prefrontal cortex (PFC) (Hall et al., 1994). Nonhuman experimental studies have provided data regarding the relationship between WM performance and dopamine receptors in the PFC (Sawaguchi et al., 1990; Sawaguchi and Goldman-Rakic, 1994; Williams and Goldman-Rakic, 1995; Murphy et al., 1996; Arnsten, 1998). These studies have suggested that the effect of dopamine on WM performance is mediated by D1 rather than D2 receptors. Based on an experiment that used an oculomotor delayed-response task, Goldman-Rakic et al. (2000) suggested that there is an optimum range of D1 receptor activation in the PFC for WM performance and described it as an inverted-U-shaped curve. Low D1 receptor activation by iontophoretic application of D1 receptor antagonists significantly decreased the delay-period activity of pyramidal cells in the PFC of monkeys that performed WM tasks (Sawaguchi et al., 1990; Sawaguchi, 1997). Chronic D2 receptor antagonism in neuroleptic therapy causes the down-regulation of D1 receptors in the PFC and severe impairments in WM in monkeys, which are reversed by short-term

coadministration of a selective full D1 agonist (Lidow et al., 1997; Castner et al., 2000). In patients with schizophrenia, many studies have suggested that reduced prefrontal dopamine activity plays a critical role in WM impairment (Weinberger et al., 1988, 2001; Kahn et al., 1994; Egan et al., 2001; Akil et al., 2003; Winterer and Weinberger, 2004). Low cerebrospinal fluid concentrations of homovanillic acid, a parameter that reflects low dopamine activity in the PFC, are associated with poor WM performance in schizophrenia (Weinberger et al., 1988; Kahn et al., 1994). Moreover, genetic studies suggest that the valine allele of catechol-O-methyltransferase, which is the high-activity allele of an enzyme involved in dopamine metabolism, may increase the risk for schizophrenia and may be related to reduced WM performance in patients (Egan et al., 2001; Weinberger et al., 2001; Akil et al., 2003). Together, these neurobiological studies, which include nonhuman experimental studies, have led to the hypothesis that a deficit in dopamine transmission mediated by D1 receptors in the PFC of patients with schizophrenia is associated with WM impairment.

A computational modeling approach based on a biologically plausible scenario can help to overcome the limitations of experimental research regarding WM performance (Durstewitz et al., 2000; Brunel and Wang, 2001; Tanaka, 2002a,b, 2006; Loh et al., 2007a,b; Rolls et al., 2008). Durstewitz et al. (2000) demonstrated that D1 receptor activation enhanced the robustness of PFC neuron persistent activity against distractors within the delay period in a WM task model. Brunel and Wang (2001) simulated an optimal range of D1 modulation for the occurrence of persistent PFC neuronal activity during a WM delay period. In addition to these studies that have focused on the mechanism by which D1 receptor activation affects the persistent activity of PFC neurons, some computational studies have explored the network properties that contribute to the capacity and precision of WM. Tanaka (2002a) suggested that WM capacity varies with the ratio of *N*-methyl-D-aspartate (NMDA) conductance to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) conductance in PFC neurons because of D1 receptor activation. Using a neural network model in which excitatory neurons are divided into two selective pools, Loh et al. (2007a,b) demonstrated that the high-activity state in each pool randomly switches according to decreased NMDA conductance, which is a result of reduced D1 receptor activation. Roggeman et al. (2014) demonstrated the trade-off between WM capacity and precision using a model with two modules.

Although the computational modeling approaches previously described have contributed to a theoretical framework of WM impairment in schizophrenia, little is known about direct connections between neurobiological findings and the neuropsychological behaviors that comprise WM impairment in schizophrenia. Therefore, this study aims to simulate the reduced capacity and imprecision in a WM task with the condition of a deficit in dopamine transmission through D1 receptors in the PFC. We use a prefrontal cortical circuit model and simulated delay-period activities in a simultaneous multi-target delayed-response task. Our model is composed of neurons equipped with the biophysical properties of NMDA receptors, AMPA receptors, and ion channels. Each neuron can be modulated by different degrees of D1 receptor activation. Thus, this simulation enables us to investigate the mechanism that causes the reduced capacity and imprecision in WM in schizophrenia and provides pharmacological implications.

EXPERIMENTAL PROCEDURES

Neuron model

The neurons (pyramidal cells and interneurons) are described here in a single compartment, leaky integrate-and-fire model and have NMDA, AMPA, gamma-aminobutyric acid type-A ($GABA_A$), persistent sodium (Nap), calcium-dependent potassium (K(Ca)), and leak channels:

$$C\frac{dV_i}{dt} + I_{\mathrm{AMPA}} + I_{\mathrm{NMDA}} + I_{\mathrm{GABA_A}} + I_{\mathrm{Na_P}} + I_{\mathrm{K(Ca)}} + I_{\mathrm{leak}} + I_{\mathrm{cue},i} + I_{\mathrm{NS}} = 0 \tag{1}$$

where V_i is the membrane potential of the neuron, the membrane capacitance is $C = 0.5$ nF for pyramidal cells and 0.2 nF for interneurons, and the transmembrane currents are given as follows:

$$I_{\mathrm{AMPA}} = \sum_j g_{\mathrm{AMPA},ji}(t)(V_i - E_{\mathrm{AMPA}}) \tag{2}$$

$$I_{\mathrm{NMDA}} = \sum_j g_{\mathrm{NMDA},ji}(t) f_{\mathrm{Mg}}(V_i)(V_i - E_{\mathrm{NMDA}}) \tag{3}$$

$$I_{\mathrm{GABA_A}} = \sum_j g_{\mathrm{GABA_A},ji}(t)(V_i - E_{\mathrm{GABA_A}}) \tag{4}$$

$$I_{\mathrm{Nap}} = g_{\mathrm{Nap}}(V_i)(V_i - E_{\mathrm{Nap}}) \tag{5}$$

$$I_{\mathrm{K(Ca)}} = g_{\mathrm{K(Ca)}}([\mathrm{Ca}^{2+}]_i)(V_i - E_{\mathrm{K(Ca)}}) \tag{6}$$

$$I_{\mathrm{leak}} = g_{\mathrm{leak}}(V_i - E_{\mathrm{leak}}) \tag{7}$$

The term $I_{\mathrm{cue},i}$ represents the cue-signal input for the corresponding pyramidal cell, and I_{NS} is the random nonsignal input that controls the spontaneous firing rates of pyramidal cells and interneurons. The equilibrium potentials of the channels are as follows: $E_{\mathrm{AMPA}} = 0$ mV, $E_{\mathrm{NMDA}} = 0$ mV, $E_{\mathrm{GABA_A}} = -80$ mV, $E_{\mathrm{Nap}} = 50$ mV, $E_{\mathrm{K(Ca)}} = -95$ mV, and $E_{\mathrm{leak}} = -70$ mV. The conductances, $g_{s,ji}(t)$ (s = AMPA, NMDA, $GABA_A$), are described by the linear second-order system:

$$\frac{d^2 g_{s,ji}(t)}{dt^2} + \left(\frac{1}{\tau_1} + \frac{1}{\tau_2}\right)\frac{dg_{s,ji}(t)}{dt} + \frac{1}{\tau_1\tau_2} g_{s,ji}(t) = \left(\frac{1}{\tau_1} + \frac{1}{\tau_2}\right) J(t) \tag{8}$$

where $J(t) = v_{ji} g_{s,ji,\max}\delta(t - t_{ji})$, $v_{ji} = w_{ji}/\Delta t$, w_{ji} describes the strength of the connection from neuron j to neuron i, Δt is the integration time step (0.1 ms), and $\delta(t)$ is the Dirac delta function. Here, t_{ji} is the time at which an ion conductance of the postsynaptic neuron i begins to open by responding to the firing of the presynaptic neuron j ($t_{ji} = t_{\mathrm{sp},j} + \Delta t_{ji}$, where $t_{\mathrm{sp},j}$ is the time at which the