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The role of short term depression for sustained neural activities in the prefrontal cortex: a simulation study

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Abstract—Neurons in the prefrontal cortex (PFC) of monkeys show mnemonic sustained activities during an oculomotor delayed response task. This sustained activity has been explained by computational studies which suggest that input balance of excitatory and inhibitory synapses could sustain neural activity. However, it is difficult for this balancing mechanism to sustain neural activity with robustness against a GABA_B current. In this study, we show that synaptic short term depression can play a role of the autonomous gain control of synaptic transmission for the sustained activities.

1. Introduction

An oculomotor delayed response task which requires a visuospatial memory has been used to investigate mnemonic substrata [1,2]. Neurons in the prefrontal cortex (PFC) of a monkey showed directional sustained activities in a delay period after a cue period [3–5]. There are many theoretical studies which deal with neural mechanisms for the sustained activities in the PFC. In these studies, the sustained activity is realized by a input balance between a moderate feedback inhibition and the self-activation of a recurrent excitatory circuit [6–9]. However, this balancing mechanism become unstable if GABA_B receptors, which are the major metabotropic inhibitory receptors in the PFC [10], are inroduced. The GABA_B receptors have a longer decay time constant than the AMPA and NMDA receptors [11], so that the excessive GABA_B current tends to prevent the sustained activity of excitatory neurons. Then it is important to clarify how the cortical neurons can show the stained activity robustly with a strong inhibitory input generated by the GABA_B receptors. The short term depression is thought to have a gain control ability [8,12,13]. In this study, we demonstrate how the gain control of the short term depression is carried out for the neural sustained activity in the PFC. We also show that the moderate depressing effect enables the neurons to sustain their activity.

2. Models

Network Model

The visuospatial cue signal is conveyed downstream from the visual cortex to the PFC through the postparietal cortical (PPC) [14]. The PFC and PPC network model is summarized as follows (Fig. 1): (1) excitatory neurons (200 [neuron]) in the PFC are activated by excitatory neurons (50 [neuron]) in the PPC. The probability that each neuron in the PPC is connected to one of excitatory neurons in the PFC is 0.5. (2) excitatory neurons in the PFC have recurrent connections, and interact with inhibitory neurons (50 [neuron]) in the PFC. The excitatory recurrent connection probability is 0.8. The connection probability from an excitatory to an inhibitory neurons in the PFC is 0.2, and that from an inhibitory to an excitatory neurons in the PFC is 0.8. Excitatory inputs are mediated by the AMPA and NMDA receptors while Inhibitory ones are mediated by the GABA_A and GABA_B receptors.

Neuron Model

While the Hodgkin-Huxley model [15] is called as "type II", cortical neurons are usually described by "type I", which involves a fast potassium current [16]. Indeed, numerous neurons including cortical pyramidal neurons are type I neuron [17]. In this study, the dynamics of membrane potential (V [mV]) is modeled as the following differential equation (type I):

$$C_m \frac{dV}{dt} = -\sum_x I_x, \tag{1}$$

where the suffix x indicates the current type ($x = Na, L, L, A, S$) and the currents ([μA/cm^2]) contain a fast sodium current $I_{Na} = \overline{g}_{Na} \cdot m^3 \cdot h \cdot (V - E_{Na})$, a delayed rectifier potassium current $I_K = \overline{g}_K \cdot n^4 \cdot (V - E_K)$, a leak current $I_L = \overline{g}_L \cdot (V - E_L)$, a fast transient potassium current $I_A = \overline{g}_A \cdot a^3 \cdot b \cdot (V - E_A)$, and a synaptic current I_S. Variables m, n, and a are activation factors, and n and b are inactivation factors. C_m is the membrane capacitance (1.0 [μF/cm^2]). Other parameter values we used are summarized in Table 1.

Synapse Model

The synaptic current I_S is the sum of the excitatory and inhibitory currents:

$$I_S = \frac{1}{A} \sum_y \overline{g}_y \cdot f_y \cdot (V - E_y), \tag{2}$$

where the suffix y indicates the type of receptors (AMPA, NMDA, GABA_A, or GABA_B), $\overline{g}_y$ indicates the maximum

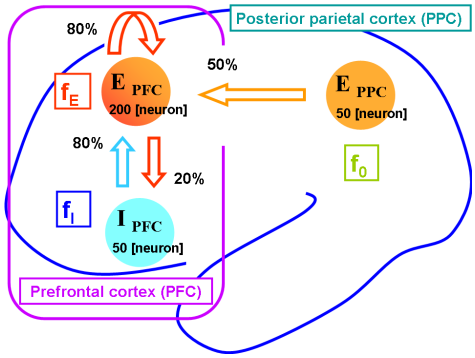

Figure 1: Schematic architecture of the model network. There are three neural assembly, excitatory neurons in the PFC (E_{PFC}) inhibitory ones in the PFC (I_{PFC}), and excitatory ones in the PPC (E_{PPC}). f_E, f_I, and f_0 represent spike frequencies of E_{PFC}, I_{PFC}, and E_{PPC}, respectively.

conductance, and A the surface area of a soma which is regarded as a sphere with the radius of 20 [μm]. The variable f_y is defined as the fraction of the receptors in the open state and described by the following equations:

$$f_y = f_{y,decay} - f_{y,rise} \quad (3)$$

$$\frac{d\, f_{y,decay}}{d\, t} = -\frac{f_{y,decay}}{\tau_{y,decay}} + S_e \cdot \delta(t - t_{AP}) \quad (4)$$

$$\frac{d\, f_{y,rise}}{d\, t} = -\frac{f_{y,rise}}{\tau_{y,rise}} + S_e \cdot \delta(t - t_{AP}), \quad (5)$$

where $f_{y,rise}$ and $f_{y,decay}$ correspond to the dynamics of the rising and decaying phases, respectively. t_{AP} denotes the occurrence time of the presynaptic action potential. The variable S_e represents the amount of the transmitter in an effective vesicle ($0 \leq S_e \leq 1$) and the other transmitters are in a recovered (S_r) or inactive (S_i) vesicle. The short term depression can be modeled as the dynamics of these vesicles which are expressed as the following equations [13]:

$$\frac{d\, S_e}{d\, t} = -\frac{S_e}{\tau_{inact}} + U \cdot S_r \cdot \delta(t - t_{AP}) \quad (6)$$

$$\frac{d\, S_r}{d\, t} = \frac{S_i}{\tau_{rec}} - U \cdot S_r \cdot \delta(t - t_{AP}) \quad (7)$$

$$S_i = 1 - S_r - S_e, \quad (8)$$

with the utilization ratio ($U = 0.6$) of S_r. The total of S_e, S_r, and S_i is normalized to 1. τ_{inact} and τ_{rec} are the time constants of inactivation (3 [ms]) and recovery, respectively. The other parameters are given in Table 1.

The time constant τ_{rec} controls the rate of vesicle recovery: the large value of τ_{rec} represents a strong depression of the synaptic efficacy. In the simulation, the time constant τ_{rec} is controlled by examining the sustained neural activities. For simplicity, only the synapses of excitatory recurrent connections and from excitatory neurons to inhibitory ones in the PFC are depressing synapses. Other

reversal potential	[mV]	conductance	[nS/cm^2]
E_{Na}	55	$\overline{g}_{Na}$	120
E_K	-72	$\overline{g}_K$	20
E_L	-17	$\overline{g}_L$	0.3
E_A	-75	$\overline{g}_A$	47.7
E_{AMPA}	0	$\overline{g}_{\mathrm{AMPA}}$	1
E_{NMDA}	0	$\overline{g}_{\mathrm{n}}$	0.4
E_{GABA_A}	-70	$\overline{g}_{\mathrm{GABA}_A}$	1.2
E_{GABA_B}	-95	$\overline{g}_{\mathrm{GABA}_B}$	0.1
time const.	[ms]	time const.	[ms]
$\tau_{\mathrm{AMPA}\,decay}$	2	$\tau_{\mathrm{AMPA}\,rise}$	0.19
$\tau_{\mathrm{NMDA}\,decay}$	80	$\tau_{\mathrm{NMDA}\,rise}$	0.67
$\tau_{\mathrm{GABA}_A\,decay}$	20	$\tau_{\mathrm{GABA}_A\,rise}$	0.21
$\tau_{\mathrm{GABA}_B\,decay}$	100	$\tau_{\mathrm{GABA}_B\,rise}$	2.70

Table 1: Parameters of the model neuron and synapse. The voltage-dependent NMDA conductance is modeled as $\overline{g}_{NMDA} = \overline{g}_n/\{1+0.33\cdot[Mg^{2+}]\cdot e^{-0.06\cdot V}\}$ [nS] ([Mg^{2+}] = 1 [mM]).

synapses are non-depressing synapses and S_e has a constant value (0.5). The latency from a presynaptic spike to a postsynaptic response also exists (5.0 [ms]).

3. Results

The simulation interval has two parts, the cue period (the first 500 [ms]) and the delay period (the subsequent 500 [ms]). In the cue period, excitatory neurons in the PFC receive input spikes from the PPC. The neurons in the PPC stochastically fire at the rate of 80 and 0 [Hz] during a cue and a delay period, respectively.

For analysis of the neural activity dynamics, we illustrates the time courses of the variables of the model and the corresponding phase plots (Fig. 2). In the phase plot, the arrows represent the schematic trajectory of population averaged firing rates of the PFC neurons during the cue period. The nullcline for the inhibitory neuron group in the PFC (circles) was defined as the set of frequencies in I_{PFC} (f_I) in the steady state when the various spike frequencies of E_{PFC} neurons (f_E) were applied. Similarly, the nullclines for the excitatory neurons during the cue (squares) and the delay (triangles) periods were defined as the sets of frequencies in E_{PFC} (f_E) in the steady state when the various spike frequencies of I_{PFC} (f_I) were applied.

The model network exhibits four types of firing patterns depending on the short term depression parameter τ_{rec} as shown in Fig. 2:

pattern 1

As mentioned above, $GABA_B$ current has so large inhibitory effect that it is difficult for the excitatory neurons to sustain their activity. To demonstrate this, the effect of the short term depression in the model is weakened by setting τ_{rec} to a very small value (10 [ms]). Such a too weak

depression shows a long term and large periodical wave during the cue period and cannot sustain the neural activity during the delay period. This long and large wave is caused by the strong feedback inhibition after the excessive excitatory recurrent current. From the point of view of the vesicle state, both of the variables S_r and S_i extremely fluctuate during the cue period. When entering the delay period, all the neurons are inactivated by the long term inhibition generated by the $GABA_B$ receptors, and then cannot start to fire again.

In the phase plane, the trajectory of the excitatory and inhibitory firing rates shows a limit cycle along about the nullclines during the cue period (Fig. 2e). This limit cycle passes the origin (0,0). However, if once the activity state (f_I,f_E) reaches the origin (0,0) during the delay period, it cannot escape from the origin because of no driving force ($f_0 = 0$). This implies that sustained activity disappears.

pattern 2

If the effect of the short term depression is strengthened ($\tau_{rec} = 40$ [ms]), the excitatory and inhibitory neurons in the PFC succeed to show the sustained activity during the delay period (Fig. 2b). This seems to be difficult to understand because the synaptic depression decreases excitatory currents so that the activities of the excitatory neurons is weakened. However, the process of the vesicle recovery becomes slow down due to the short term depression. Consequently, comparing with the excitatory high firing rate, it is hard for the inhibitory neurons to fire because of a small S_r value. In the phase plane (Fig. 2f), the trajectory of the activity state (f_I,f_E) rapidly approaches the crossing point of the nullclines.

pattern 3

If the effect of the short term depression is more strengthened ($\tau_{rec} = 90$ [ms]), only the excitatory neurons in the PFC succeed to show the sustained activity during the delay period (Fig. 2c) because of the similar mechanism to *pattern 2*. In other words, excitatory neurons can sustain their activities without balance between activation and inhibition. The crossing point of the nullclines of the delay period (circles and triangles) is close to the x axis (Fig. 2g). In this case, the slow vesicle recovery regulates the excitatory activity.

pattern 4

If the short term depression is too strong (τ_{rec}=130 [ms]), the sustained activity doesn't appear during the delay period (Fig. 2 d) from lack of available vesicles. In this case, the crossing point of the nullclines of the delay period is equal to the origin (Fig. 2 h). This indicates that the sustained activity is impossible.

4. Discussion

In this study, we showed that the moderate short term depression can realize the sustained activities of the excitatory neurons. This sustained activity also appears in the other network sizes (400 excitatory and 100 inhibitory neurons, or 100 excitatory and 25 inhibitory neurons in the PFC, not shown). The short term depression could change effective excitatory currents adapting to the excitatory firing rate, and then prevent the excitatory neurons from receiving a strong excitatory and inhibitory feedback. Due to this autonomous balancing mechanism, we suggest that the short term depression should be one basis of the sustained firing activities. The functional role of the inhibitory feedback is thought as the lateral inhibition for signal selection [10, 18, 19].

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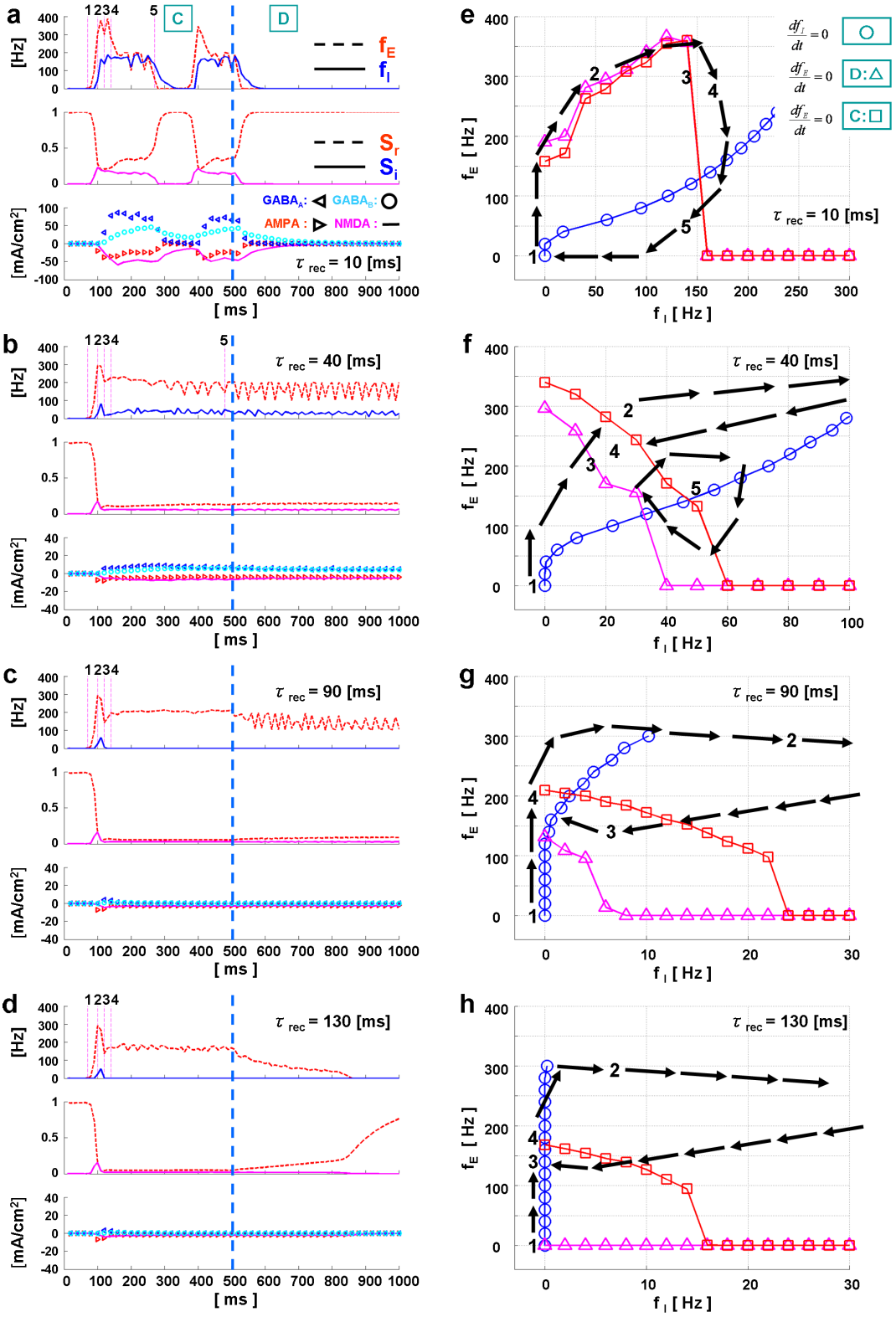

Figure 2: Responses of the PFC neurons with various τ_{rec} values. τ_{rec} is 10, 40, 90, and 130 [ms] from the top. In each figure of the left column (**a**–**d**), population average of firing rates (*top*), the average of S_r and S_i of excitatory neurons (*middle*), and synaptic currents (*bottom*) are shown. The right column (**e**–**h**) displays the phase plots of the firing rates of the left figures, showing nullclines (see text) and the schematic trajectories. The frequencies at the timing which are labeled with the integers 1–4 or 5 in the left figures correspond to the points labeled with the same integers.