A possible functional organization of the corticostriatal input within the weakly-correlated striatal activity: a modeling study

Katsunori Kitano a, Toshio Aoyagi b,c, Tomoki Fukai a,c,*

a Department of Information-Communication Engineering, Tamagawa University, 6-1-1 Tamagawagakuen, Machida, Tokyo 194-8610, Japan
b Department of Applied Analysis and Complex Dynamical Systems, Kyoto University, Yoshidahonnachi, Sakyo, Kyoto 606-8501, Japan
c CREST, JST (Japan Science and Technology Corporation), Tokyo, Japan

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Abstract

Recently, it was reported in an in vivo study that pairs of the striatal projection neurons (medium-sized spiny neurons) of the basal ganglia show asynchronous spiking within weakly-correlated subthreshold depolarized states. In this computational study, we investigate a possible functional organization of corticostriatal inputs that accounts for the experimental observations within known anatomical and physiological constraints. In a pair of medium-sized spiny neurons, a small fraction of corticostriatal fibers is common to both neurons. To explain the weak correlations in sub- and supra-threshold activities of the neuron pair, we postulate that the two input channels, common or specific to the individual neurons, have distinct functional roles. The common input channel delivers random spike trains and is primarily responsible for the initiation and maintenance of the depolarized states. In contrast, the input through the neuron-specific channels elicit postsynaptic spikes by delivering intermittently-synchronized spikes. The results of this model were compared with those derived from a newly-performed analysis of the previous double-intracellular recording data. We show that the behavior of this model agrees qualitatively and quantitatively with that of the medium-sized spiny neurons observed in the experiments in a certain range of the coincident time window. © 2001 Elsevier Science Ireland Ltd & Japan Neuroscience Society. All rights reserved.

Keywords: Basal ganglia; Striatal spiny projection neurons; Synchrony; Asynchrony; Coincidence detection; Computational model

1. Introduction

The striatum is the entrance from the cerebral cortex to the basal ganglia which are heavily engaged in motor control. To understand the overall functions of the basal ganglia (Groves, 1983; Graybiel, 1995), it is of importance to clarify the functional framework of the striatal neural network. Because more than 90% of striatal neurons (Kemp and Powell, 1971; Parent and Hazrati, 1995) are projection neurons (medium-sized spiny neurons), which issue GABAergic recurrent axon collaterals (Bolam and Izzo, 1988; Pasik et al., 1988), the striatum has often been regarded as a competitive neural network (Plenz and Aertsen, 1996). In the competitive network of striatal projection neurons, only the most significant corticostriatal input will be selected for further processing by means of the mutual inhibition among the neurons. However, the results of electrophysiological experiments (Park et al., 1980; Rebec and Curtis, 1988; Kita, 1993; Jaeger et al., 1994; Koos and Tepper, 1999) do not support this view as strongly as those of anatomical studies. Hence the conventional view is currently challenged.

Recently, interesting data which give some insight into the cortical control of the striatal activity were reported in an in vivo double-intracellular recording study of medium-sized spiny neurons (Stern et al., 1997, 1998). The medium-sized spiny neurons typically exhibit distinct hyperpolarized (down) and depolarized (up) states (Wilson, 1995). The experimental results showed that the transitions between the two states are highly correlated in neighboring spiny-neuron pairs. This may indicate the presence of input common to each pair. Nevertheless, the subthreshold fluctuations in the membrane potentials as well as the action potentials being further studied.
within the ‘up’ states are only weakly correlated. In this paper, we explore a possible corticostriatal input organization which activates medium-sized spiny neurons in such a manner as consistent with these experimental findings.

Anatomically, a pair of medium-sized spiny neurons are innervated by two distinct types of corticostriatal fibers: one is common to the neuron pair and the other is specific to each neuron. In this model, we assume that the common input is primarily responsible for the initiation and maintenance of the ‘up’ states and comprises random spike trains. On the other hand, the neuron-specific input delivers intermittently-synchronized spikes which trigger postsynaptic action potentials. The coincident spikes to different neurons are assumed to be statistically uncorrelated. We studied how the degree of synchrony or asynchrony among the spiny neuron pairs within the ‘up’ state depends on various parameters which characterize the spatio-temporal pattern of synchronization, e.g. the width of the time window within which the coincident spikes occur, the ratio between the common and specific inputs, and so on. We also reanalyzed the data obtained in the previous double-intracellular recording study to derive the coherence among medium-sized spiny neurons within the ‘up’ state. The obtained results were compared with those of this model.

2. Method

2.1. Model

We used a compartmental model of medium-sized striatal spiny neurons (Wickens and Arbuthnott, 1993; Kotter and Wickens, 1995). Our model consists of two compartments, representing a soma and a dendrite (Fig. 1A). The somatic and dendritic compartments are modeled as cylinders. The somatic compartment contains a spike-generating sodium current $I_{Na}$, delayed rectifier current $I_K$ and a leak current, while the dendritic compartment has a delayed rectifier current and a leak current. The rate functions of these currents are given by those used in a model of hippocampal CA3 pyramidal neurons (Traub et al., 1991). In addition, both compartments involve an outward rectifier current $I_{OR}$ (Surmeier et al., 1988) and an inward rectifier current $I_{IR}$ (Uchiyama et al., 1989) with different densities.

The inward rectifier current is an anomalous potassium current that contributes to the resting membrane potential. The outward rectifier current consists of at least three different depolarization-activated potassium currents and contributes to the maintenance of the ‘up’ state at a few millivolts below threshold. We employed the following minimal model of Neisenbaum and Wilson (1995): $I_{IR} = g_{IR}(1 + \exp [(V + 105)/10])^{-1}(V - E_K)$ and $I_{OR} = g_{OR}\exp [(V + 60)/10] (1 + \exp [(V + 60)/10])^{-1}(V - E_K)$. The reversal potentials are given as $E_L = -70$ mV, $E_{Na} = -45$ mV and $E_K = -75$ mV. The maximal conductances are determined such that the model neuron can reproduce the electrophysiologically observed single-neuron behavior. The values of the parameters are listed in Table 1. From the values of the parameters, the membrane time constant and the conductance of the leak current can be calculated as 8 ms and 0.1 ms/cm², respectively.

A medium-sized spiny neuron receives a massive excitatory input from thousands of cortical pyramidal neurons (Parent and Hazrati, 1995; Wilson, 1995). However, it was found that medium-sized spiny neurons with totally overlapping dendritic volumes have only a small number of cortical axons in common and that cortical neurons with overlapping axons have few striatal target neurons in common (Kincaid et al.,...
Both common and neuron-specific cortical inputs project to the dendritic compartments of the model neurons (Parent and Hazrati, 1995). The same mean firing rate \(f \) (Hz) is assumed for both common and neuron-specific input fibers. Excitatory postsynaptic currents are described as
\[
I_{\text{syn}} = g_{\text{syn}}r(V - E_{\text{syn}}),
\]
where the rate variable \(r\) obeys the first-order kinetic equation
\[
dr/dt = zT(1 - r) - fr\]
(Destexhe et al., 1998). After the occurrence of every presynaptic spike, the relative amount of released transmitters \(T\) immediately takes the value 1 for 1 ms. For all other times it is 0.

We assume that the spikes arriving via the common and neuron-specific input fibers have different statistical properties and, consequently, different functional roles (Fig. 1B). The common input fibers deliver Poisson spike trains which are not intensive enough to elicit postsynaptic spikes. On the other hand, presynaptic spikes repeatedly exhibit transient synchronization among the neuron-specific input fibers. Coincident input spikes occur within the temporal width of \(\sigma\) [ms] and are powerful enough to trigger postsynaptic spikes. In each neuron-specific input, 30% of spikes belong to any of the coincident input events. As we shall see, with this probability of the occurrence of coincident spikes, the firing rate of model neurons is given within the experimentally-observed range for biologically reasonable values of \(f\). The synaptic conductance of corticostriatal fibers is adjusted within a physiologically realistic range such that both models may give almost the same firing rate for the same values of \(f\) and \(\sigma\).

In the present study, we do not include the feed-forward inhibition delivered by the striatal GABAergic interneurons (Calabresi et al., 1991; Koos and Tepper, 1999; Chergui et al., 2000). In a cortex-striatum-substantia nigra organotypic culture, the activity of the fast-spiking GABAergic interneurons was correlated with that of medium-sized spiny neurons (Plenz and Kitai, 1998). The inhibition from the interneurons is either depolarizing or hyperpolarizing depending on whether the ‘up’ state in a medium-sized spiny neuron is below or above the reversal potentials of the GABAergic input. Although the inhibition may have significant influences on the activity of the medium-sized spiny neurons within the ‘up’ state, more anatomical and electrophysiological data are necessary for incorporating the interneurons. It was suggested that the ‘up’ and ‘down’ transitions in the medium-sized spiny neurons reflect similar transitions in the corticostriatal neurons (Cowan and Wilson, 1994). We also do not attempt to model the cortical mechanism to generate the transitions.

We conducted extensive numerical simulations of both models and calculated the cross-correlations of the membrane-potential fluctuations and the spike cross-correlograms between the neuron pairs. During the measurement of the membrane cross-correlations, we

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>(g_{\text{Na}}) (mS/cm²)</td>
<td>100.0 (0.0)</td>
</tr>
<tr>
<td>(g_{\text{K(OR)}}) (mS/cm²)</td>
<td>30.0 (3.0)</td>
</tr>
<tr>
<td>(g_{\text{K(DR)}}) (mS/cm²)</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>(g_{\text{K(OR)}}) (mS/cm²)</td>
<td>1.0 (0.1)</td>
</tr>
<tr>
<td>(g_{\text{AMPA}}) (ms)</td>
<td>0.0 (0.7/0.35)</td>
</tr>
<tr>
<td>(g_{\text{AMPA}})</td>
<td>1.1</td>
</tr>
<tr>
<td>(\beta_{\text{AMPA}})</td>
<td>0.19</td>
</tr>
</tbody>
</table>

\(g_{\text{AMPA}}\) and \(\beta_{\text{AMPA}}\) are fixed to 0.7 ns in the (1:2)-model and 0.35 ns in the (2:1)-model (Kötter and Wickens, 1995).
applied a hyperpolarizing current to the model neurons to suppress spike generation, as in the double-intracellular recording study. Throughout this paper, the term ‘spike coincidence’ refers to the ratio of the central peak value (at zero time difference) of the spike cross-correlogram to that of the spike auto-correlogram. Similarly, the membrane coherence stands for the value of the membrane cross-correlation at zero time difference. The membrane cross-correlations were calculated according to the standard formula for continuous variables.

2.2. Experimental data analysis

Most of the experimental results necessary for the present theoretical studies have already appeared in the two papers by Stern et al. (1997, 1998). We analyzed their in vivo intracellular recording data of 14 pairs of medium-sized spiny neurons to obtain the cross-correlations of the membrane-potential fluctuations within the ‘up’ states. The data were recorded by those authors with the sampling rate of 4 kHz. The data were downsampled to 400 Hz for the present analyses. To study the cross-correlations only within the ‘up’ states, we clipped the intervals in which both neurons in the pairs simultaneously stay at the ‘up’ states without spiking out of the whole recording data. In the recording data, the duration of the clipped intervals varied in the range from 300 to 500 ms. We calculated the membrane cross-correlations between the activities of neuron pairs during these intervals to compare the results with those obtained by simulations of the present model.

3. Results

3.1. Single-cell behavior

The responses of the model neuron to depolarizing and hyperpolarizing injected currents are shown in Fig. 2A. Due to the inward rectification initiated by hyperpolarization, the amplitudes of the hyperpolarizing responses saturate at large current intensity. On the other hand, as the intensity of depolarizing current increases, the inward rectification is replaced by the outward rectification. Action potentials are generated during the current injection, if the membrane potential passes above a threshold (∼ −55 mV) lying slightly above the ‘up’ state.

Fig. 2B shows the I–V relationship obtained by this model. The resultant I–V relationship shows a good coincidence with that measured in in vitro studies (Jiang and North 1991; Neisenbaum and Wilson, 1995).

3.2. Coincidence detection by the striatal medium-sized spiny neurons

We show the results of simulations for the coincidence-detector corticostriatal network model. As mentioned previously, we are considering only such an ensemble of medium-sized spiny neurons as escape from the powerful feedforward inhibition by striatal interneurons. Since the medium-sized spiny neurons within the coactivated ensemble will be dynamically decoupled, it is sufficient to study the spiking behavior of a representative neuron pair. We investigate whether this model can reproduce the experimentally-observed ranges of firing rate, subthreshold membrane fluctuations and spike cross-correlations within the ‘up’ states. An example set of spike trains used in the present simulations of the (2:1)-model is shown in Fig. 3A.
The typical responses of a pair of model neurons to the above stimuli are shown in Fig. 3B. It is found that postsynaptic spikes are primarily elicited by the neuron-specific coincident presynaptic spikes. Most of the postsynaptic spikes occur asynchronously in the neuron pair, because the coincident spike input occurs at random times in the neuron-specific input channel of each neuron. However, some postsynaptic spikes are elicited occasionally by the summed effects of the random spikes in the neuron-specific and common inputs. Depending on which input channel provides a dominant contribution to the excitatory postsynaptic potentials (EPSPs), these postsynaptic spikes occur either synchronously or asynchronously. The spike cross-correlations are approximately given as $r/(1 + r)$, where $r$ stands for the ratio of synchronous postsynaptic spikes to asynchronous ones in number.

We emphasize that introducing common and neuron-specific random stimuli without the coincident spikes does not produce a sufficiently large variance of the membrane potential fluctuations within the ‘up’ states. In this case, the average value of the membrane coherence should be given as the ratio of the number of the common input fibers to the total number of active input fibers. Therefore, estimating the experimentally-observed average value at 0.2 (the average was taken over different recording sessions), we simulated the present model with 100 common and 400 neuron-specific input fibers (per neuron) for the case where both types of input deliver Poisson spike trains. Fig. 3C shows the average and variance of the membrane coherence obtained in repeated trials. It is noted that the variance was significantly smaller in the model than in the experiment. Also the spike cross-correlation ($<0.2$, not shown) was rather small compared with the experimental value. In general Poisson stimuli alone give rise to a small variance. The above results may indicate the presence of input which gives a stronger impact on the postsynaptic membrane fluctuations. We will not consider the case where both inputs are Poisson spike trains any longer.

Fig. 4 shows the average and variance of the membrane coherence obtained by simulations of the (2:1)- and (1:2)-models and also by the experimental data analysis. These results rejected the (2:1)-model with $\sigma \geq 20\text{ms}$ with the significance level $P < 0.01$. We can see that the results of the (2:1)-model most excellently agree with the experimentally obtained results if the coincident input spikes occur within the time window of 5 ms in each neuron-specific input channel. Similarly, the (1:2)-model with $\sigma \leq 10\text{ms}$ was rejected with $P < 0.01$. In the (1:2)-model, the best agreement was achieved at the coincidence window of about 30 ms.

To make a comparison between model and experiment in further detail, we calculated the cross-correlations of the membrane potential fluctuations within the ‘up’ states in the (2:1)-model with $\sigma = 5\text{ms}$, the (1:2)-model with $\sigma = 30\text{ms}$ and the experimental case. The typical results are presented by gray curves in Fig. 5. The experimental results show that the membrane cross-correlations vary in the temporal domain with a typical interval of 15–20 ms. This interval is considered to reflect the cell’s membrane time constant (8 ms in the present case), since the membrane time constant of 10 ms resulted in a longer interval of about 25 ms for the
same value of $\sigma$ (not shown). In some recording trials, the membrane cross-correlations show only much broader peaks (black curve in Fig. 5C). In our simulations, the (2:1)-model could reproduce all the varieties of the experimentally-observed behavior of the membrane cross-correlations. On the other hand, the (1:2)-model failed to reproduce the marked variations repeated with the short intervals of 15–20 ms, despite that the same membrane time constant was adopted in simulations. This is probably because in the (1:2)-model the typical time scale of the membrane fluctuations is given by $\sigma$, the coincidence window of synchronous inputs, which is much larger than the membrane time constant in this model.

We conducted extensive numerical simulations changing the values of $f$ and $\sigma$ in both (2:1)- and (1:2)-models. In Fig. 6, we show the obtained average firing rates and the spike cross-correlations as functions of $f$ and $\sigma$.

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Fig. 5. The cross-correlations of the membrane-potential fluctuations. The cross-correlations were calculated for the (2:1)-model with $\sigma = 5$ ms (A) and the (1:2)-model with $\sigma = 30$ ms (B). These values of $\sigma$ give the best agreement of the average membrane coherence with the experimental result (see Fig. 4). (C) The membrane cross-correlations were also calculated from the experimental data of the double-intracellular recording study. In both simulations and experiments, the behaviors of the cross-correlations in the temporal domain vary case by case. In some cases, the cross-correlations exhibit rapid variations within relatively-short intervals of 15–20 ms (gray patterns). In other cases, they exhibit only broad peaks (black curves). They can also exhibit the mixtures of these two patterns.

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Fig. 4. The values of the membrane coherence. These values were obtained by numerical simulations of the (2:1)-model (A) and the (1:2)-model (B) for various values of the coincidence time window $\sigma$. Filled and open circles designate the average values, while the error bars stand for the variance. The result of the experimental data analysis is same as that shown in Fig. 3C. It is displayed in both panels for comparison.
For a given value of $s$, the firing rate of the medium-sized spiny neuron models is an increasing function of $f$, and so is the spike cross-correlation. The latter result reflects the fact that the probability of having accidental coincident presynaptic spikes is monotonically increased with the increase in $f$. While the number of output spikes increases roughly proportionally to the value of $f$, the chance of coincidence increases roughly proportionally to the square of $f$. Therefore the ratio $r$, or the spike cross-correlation, should be increased as the value of $f$ is increased.

For a fixed value of $f$, the firing rate would be increased with the decrease in the value of $s$, if the coincident input spikes in a narrower time window could elicit a larger number of postsynaptic spikes. However, this increase can be clearly seen only when $s$ takes relatively small values ($< 15$ ms) in the (1:2)-model, namely, in the case where the effects of coincident spikes are rather strong. Thus, on an average, the same number of postsynaptic spikes were elicited by a coincident input in many cases of the present simulations. Also the spike cross-correlations show no strong dependence on the value of $s$ and take almost identical values in both models.

4. Discussion

In the present paper we constructed a two-compartmental model of striatal medium-sized spiny neurons and corticostriatal network models consisting of these neurons. In these networks, an arbitrary pair of medium-sized spiny neurons have two functionally-distinct cortical input channels, one common to the neuron pair and one specific to each neuron. Since the experimentally-observed firing of the neuron pairs was largely asynchronous, random, but not synchronous, spike trains were delivered through the common input.
channel. On the other hand, the intermittently-synchronous spikes were delivered through the neuron-specific input channels (Fig. 3A). Owing to the synchronization among spikes, the effects of the neuron-specific input channel on the sub- and suprathreshold postsynaptic activities were significantly enhanced compared with those of the common input.

We investigated whether and to what extent the network model could reproduce both weakly-correlated membrane fluctuations and largely asynchronous spike generation observed in vivo. The experimentally-obtained ranges of the firing rate and the spike coincidence are given as 13–28 Hz and ~0.3, respectively (Stern et al., 1997, 1998). Taking the resultant average membrane coherence (Fig. 4) into account, we may say that the results of simulations are in good agreement with the experimental results if \( f = 35–40 \text{ Hz} \) and \( \sigma \sim 5 \text{ ms} \) in the (2:1)-model, or if \( f = 35–40 \text{ Hz} \) and \( \sigma \sim 30 \text{ ms} \) in the (1:2)-model.

A closer inspection of the models’ behavior, however, indicated that the latter model is less likely. In the results of the experimental data analysis, the cross-correlations of the membrane potential fluctuations typically vary within the short time scale of 15–20 ms. This characteristic behavior of the membrane cross-correlations was not observed in the (1:2)-model. In contrast, the (2:1)-model did exhibit the characteristic behavior (Fig. 5). The time scale of the membrane coherence variations in general depends on the various time constants included in the models. Here the above difference between the two models arises mainly from the difference in the values of \( \sigma \), since other time constants were identical between both models. The results of simulations and the experimental data analysis indicated that the coincidence window of cortical spikes should be as small as 5–10 ms.

Many results of recent experiments on behaving animals reported that cortical neurons fire synchronously in task-related manners. The activities of many neurons in the frontal cortex of behaving monkeys are highly correlated in relation to behavioral events (Abeles et al., 1993; Vaadia et al., 1995). Since some neurons showed precisely-tuned relative times of firing, it was suggested that the information necessary for organizing behavior is represented by the ‘synfire reverberation’ in which cortical neurons are rapidly associated into a functional group by synchronization. Also neurons in the primary motor cortex of monkeys showed coincident spikes at the times of external events such as stimuli and movements or the times of animal’s expectancy of these events (Riehle et al., 1997). The results of these recording studies from behaving animals support that the striatum is innervated by coincident cortical spikes during behavior.

The occurrence of synchronous cortical activity was also suggested in in vitro experiments using cortical slices. Synchronous spike inputs applied to neocortical slices could reproduce the highly irregular firing of in vivo cortical neurons (Softky and Koch, 1993; Shadlen and Newsome, 1998), if synchronization occurs within a few tens of milliseconds with the average interval of about 100 ms (Stevens and Zador, 1998). This temporal pattern of coincident spikes resembles that employed for the neuron-specific input channels (the width of ~5–10 ms and the average interval of ~80 ms). Thus the results of the present model are consistent with those of the double-intracellular recording study within the known characteristics of the cortical activity.

In the present study, we have investigated the case where the common and neuron-specific inputs to each medium-sized spiny neuron play distinct roles in activating the neuron. As demonstrated in Fig. 3, a pair (in reality, an ensemble) of medium-sized spiny neurons may be raised simultaneously to the up states by the innervation through the common input channels. These neurons, however, do not fire unless the coincident spikes arrive at them through the neuron-specific input channels. In other words, the medium-sized spiny projection neurons in this model undergo two stages of the cortical control (Plenz et al., 1996). The role of common input may be a ‘preparatory’ input that keeps a set of medium-sized spiny neurons in the ‘up’ state so that they can respond to the coincident spikes through the specific input channel.

Lateral inhibition has long been regarded as a fundamental organizing principle of striatal function owing to the GABAergic recurrent axon collaterals of medium-sized spiny projection neurons. Modeling the basal ganglia with a hypothetical striatal competitive mechanism also allowed for the reproduction of some of their speculated functions in motor control, e.g. learning and execution of temporal sequence (Wickens and Arbuthnott, 1993; Contreras-Vidal and Stelmach, 1995; Beiser and Houk, 1998; Fukai, 1999). We briefly mention the possible influences of this lateral inhibition on the present network behavior.

During the measurement of the membrane potential fluctuations, the spiny neurons were hyperpolarized by an injected current in order to suppress action potentials in both experiments and simulations. Hence lateral inhibition had little effect on this measurement. Rather, the effect of (weak) lateral inhibition is expected to reduce the average firing rate and the spike cross-correlation. Both quantities exhibited similar behavior against the changes in input frequency \( f \) (Fig. 6). From this figure, we expect that our model gives the firing rate and spike cross-correlation consistent with the experimental ones at slightly higher values of \( f \) (than the previously mentioned values) in the presence of weak lateral inhibition. There are, however, several objections from electrophysiological (Jaeger et al., 1994; Koos and Tepper, 1999) and anatomical studies.
(Kaneko et al., 1993; Tokuno et al., 1996) to the functional significance of lateral inhibition. Although the results of this model do not reject the view that the striatum is a competitive neural network, coincidence detection is just sufficient for explaining the results of the double-intracellular recording study of medium-sized spiny neurons.

The striatum receives input from the thalamic nuclei (centromedian and parafascicular nuclei) as well as from the cortex. Recently, the direct thalamostriatal projections from the ventral anterior and ventral lateral thalamic nuclei, the major nuclei projecting to the frontal motor cortical areas, were also identified (McFarland and Haber, 2000). The influences of the thalamic input were not considered in this study due to the lack of sufficient data on the thalamostriatal input. Similarly, the influences of the striatal interneurons were not taken into account. These influences must be included in the future simulation studies of the striatal activity.

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