Spontaneous Subthreshold Membrane Potential Fluctuations and Action Potential Variability of Rat Corticostriatal and Striatal Neurons In Vivo

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Stern, Edward A., Anthony E. Kincaid, and Charles J. Wilson. Spontaneous subthreshold membrane potential fluctuations and action potential variability of rat corticostriatal and striatal neurons in vivo. J. Neurophysiol. 77: 1697–1715, 1997. We measured the timing of spontaneous membrane potential fluctuations and action potentials of medial and lateral agranular corticostriatal and striatal neurons with the use of in vivo intracellular recordings in urethane-anesthetized rats. All neurons showed spontaneous subthreshold membrane potential shifts from 7 to 32 mV in amplitude, fluctuating between a hyperpolarized down state and depolarized up state. Action potentials arose only during the up state. The membrane potential state transitions showed a weak periodicity with a peak frequency near 1 Hz. The peak of the frequency spectra was broad in all neurons, indicating that the membrane potential fluctuations were not dominated by a single periodic function. At frequencies >1 Hz, the log of magnitude decreased linearly with the log of frequency in all neurons. No serial dependence was found for up and down state durations, or for the time between successive up or down state transitions, showing that the up and down state transitions are not due to superimposition of noisy inputs onto a single frequency. Monte Carlo simulations of stochastic synaptic inputs to a uniform finite cylinder showed that the Fourier spectra obtained for corticostriatal and striatal neurons are inconsistent with a Poisson-like synaptic input, demonstrating that the up state is not due to an increase in the strength of an unpatterned synaptic input. Frequency components arising from state transitions were separated from those arising from the smaller membrane potential fluctuations within each state. A larger proportion of the total signal was represented by the fluctuations within states, especially in the up state, than was predicted by the simulations. The individual state spectra did not correspond to those of random synaptic inputs, but reproduced the spectra of the up and down state transitions. This suggests that the process causing the state transitions and the process responsible for synaptic input may be the same. A high-frequency periodic component in the up states was found in the majority of the corticostriatal cells in the sample. The average size of the component was not different between neurons injected with QX-314 and control neurons. The high-frequency component was not seen in any of our sample of striatal cells. Corticostriatal and striatal neurons’ coefficients of variation of interspike intervals ranged from 1.0 to 1.9. When interspike intervals including a down state were subtracted from the calculation, the coefficient of variation ranged from 0.4 to 1.1, indicating that a substantial proportion of spike interval variance was due to the subthreshold membrane potential fluctuations.

INTRODUCTION

The firing patterns of striatal projection neurons are usually considered to be a reflection of convergent patterned input arising from the cortex by way of the corticostriatal cells. Recent studies indicate that striatal neurons and corticostriatal neurons show qualitatively similar patterns of spontaneous subthreshold membrane potential fluctuations and similar firing patterns in vivo (Cowan and Wilson 1994; Wilson 1993). These studies have shown that both corticostriatal cells and the spiny projection neurons of the striatum (which receive most corticostriatal inputs) exhibit shifts of membrane potential between two preferred values. Both preferred membrane potentials are subthreshold, that is, the average membrane potential is below spike threshold both when the cell is at the more depolarized level (which we have called the up state) and when it is hyperpolarized (the down state). However, noisy fluctuations in the up state can trigger action potentials in either cell type (Cowan and Wilson 1994; Wilson 1993; Wilson and Kawaguchi 1996), and thus the firing patterns of corticostriatal neurons and striatal neurons are largely shaped by the membrane potential shifts. Therefore it has been suggested that the membrane potential shifts of striatal neurons occur in the way they do mainly because they reflect the firing (and the membrane potential shifts) of the cortical cells that provide much of their excitatory input (Wilson 1993). Although this conclusion is qualitatively consistent with the existing data, a quantitative comparison is required to determine which aspects of the patterns of membrane potential fluctuations in corticostriatal neurons are faithfully communicated to the striatal cells.

Membrane potential shifts like those observed in corticostriatal neurons have been described for cortical pyramidal cells in general, and have been described as a low-frequency oscillation characteristic of the anesthetized or sleeping animal (e.g., Steriade et al. 1993). Simultaneous intracellular recording of single cortical cells and of cortical field potentials indicates that in urethan-anesthetized animals, cells in large areas of the cerebral cortex undergo these shifts of membrane potential synchronously (Amzica and Steriade 1995; Steriade et al. 1993). Because each striatal cell is innervated by many corticostriatal neurons, and the membrane potential changes of each corticostriatal neuron are not well represented in the spike train of any one of these cells, some degree of coherence in the membrane potential shifts of corticostriatal neurons converging on a striatal neuron is expected for the cortical membrane potential waveform to be imposed on the striatal cell.

Even if, as suggested above, the membrane potential shifts of striatal neurons are imposed by cortical input, it is not necessary that they be statistically identical to those of the cortical cells. For example, if the corticostriatal neurons were under the influence of a periodic low-frequency oscillator, deviations from periodicity observed in individual neurons might not be shared among all the cortical neurons converg-
ing onto a striatal cell. In this case the membrane potential shifts of the striatal cell would be expected to show a higher degree of periodicity (defined as the proportion of total energy accounted for by a single periodic component) than any of the cortical cells providing its input. Similarly, some corticostriatal neurons show subthreshold high-frequency (30–45 Hz) membrane potential oscillations, which may act synchronously across the population of cortical neurons, and thus could structure the input to striatal neurons. Thus, by examining the frequency content and strength of periodicity of membrane potential fluctuations in projection neurons of the cerebral cortex, and in neurons of one of their major subcortical target structures, we intended to determine which temporal features of the ongoing pattern of cortical activity are communicated to neurons at the next level.

In the experiments described here, we analyzed data from a sample of identified striatal spiny neurons, and another of identified corticostriatal cells, recorded separately but under identical anesthetic and other experimental conditions. The temporal patterns of membrane potential shifts in these two cell samples were compared with determine whether those of the corticostriatal neurons could account for those of the striatal cells, assuming that the input to the striatal cells was a spike-frequency encoded representation of the membrane potential of the corticostriatal cells. Thus, we analyzed the frequency content and deviations from periodicity in the membrane potential fluctuations of corticostriatal and striatal neurons, to determine whether the low-frequency periodic signals are preferentially transmitted over the corticostriatal link (i.e., if the deviations from periodicity seen in corticostriatal neurons are a kind of noise that is averaged out by the striatal cell) or whether the deviations from periodicity seen in cortical neurons are faithfully represented in the striatal cells’ membrane potentials (and so could also be synchronous across large populations of corticostriatal neurons). We analyzed the occurrence of high-frequency oscillations in the membrane potential of corticostriatal cells and in striatal cells to determine whether corticostriatal neurons’ firing reflects that oscillation, and whether it is synchronous enough across the set of cortical cells converging in the striatum to be detected in the membrane potential of the striatal neurons.

METHODS

The experiments were performed on 22 male Sprague-Dawley or Long-Evans rats weighing 189–436 g, initially anesthetized with urethane (1.25 g/kg ip) and given hourly supplemental injections of ketamine-xylazine (30 and 7 mg/kg im, respectively). The animals’ temperatures were maintained at 37°C. The animals were placed in a stereotaxic instrument and the skull exposed with a single incision. The cisterna magna was opened to drain the cerebrospinal fluid. All animals continued to breathe without artificial respiration, and rats were suspended by a clamp at the base of the tail to minimize movements of the brain due to breathing. Small (1 mm) burr holes were drilled in the skull to allow insertion of stimulating electrodes. Bipolar stimulating electrodes were pairs of 000 insect pins insulated to 0.5 mm of their tips and separated by 0.5 mm, fixed in place with the use of dental cement. Stimulation electrode placement for contralateral neostriatum was 9.5 mm anteroposterior, 3.0 mm mediolateral, 4.5 mm dorsoventral. Stimuli for orthodromic and antidromic activation were 0.1-ms square wave pulses 30–1,000 μA in amplitude. For insertion of the recording electrodes, a large opening was made in the skull over the frontal pole of the cortex, or over the head of the ipsilateral neostriatum. Recording electrodes were glass micropipettes filled with 3–5% biocytin (Sigma) dissolved in 1 M potassium acetate, and, in some cases, 25 mM QU-314 (Astra) to block sodium action potentials. Electrode resistances ranged from 30 to 100 MΩ. After insertion of recording electrodes, the exposed cortex was covered with a low-melting-point paraffin wax to reduce pulsation movements.

Recordings were made with the use of an active bridge amplifier, filtered, and digitized at a minimum rate of ~4 kHz. Neurons were stained by passing 1.5-nA depolarizing pulses 300 ms in duration every 600 ms for 10–60 min. At the end of the experiment the animals were given a lethal dose of Nembutal or urethan intraperitoneally and were perfused intracardially with isotonic buffered saline followed by 400 ml 4% formaldehyde in 0.15 M sodium phosphate buffer (pH 7.2–7.6). Intact brains were removed and postfixed in cold phosphate-buffered formaldehyde.

The brains were trimmed and cut on a vibratome in 50-μm parasagittal sections. Sections containing labeled neurons or processes were processed for biocytin with the use of the method of Takahashi (1974). The equation governing the inward rectifier was

\[ g_{IR} = \frac{g_{IR_{max}}}{1 + e^{t/V_h}}. \]

Outward rectification was represented as a time- and voltage-dependent, nonactivating potassium conductance with the use of the Hodgkin and Huxley (1952) formalism. The conductance of the outwardly rectifying conductance \( g_k \) was calculated as

\[ g_k = g_{K_{max}} \times n^\alpha. \]

The activation variable \( n \) was determined by forward and backward rate constants \( a \) and \( b \), calculated as follows (with all constants in V)

\[ \frac{dn}{dt} = -(\alpha + \beta) \times n + \alpha \]

\[ \alpha = \frac{10.0}{\tau_{max} \times (V - V_s - 0.049)} \times \frac{1}{1 - e^{-[(V - V_s - 0.049)/0.01]}} \]

\[ \beta = \frac{0.17}{\tau_{max} \times e^{-[(V - V_s - 0.01)/0.01]}} \]

Integration was performed with the use of the Gear method with a maximum time step of 0.1 ms. Synaptic conductances were represented as conductance changes with an exponential rise and decay, with time constants of 0.1 and 2.5 ms, respectively. The synaptic reversal potential was set to 0 mV, and the peak synaptic conductance was 0.1 nS. The half activation voltage for the inwardly rectifying potassium conductance was set to ~100 mV. It activated with hyperpolarization. The potassium equilibrium potential was ~90 mV. The slope factor \( V_i \) for the inward rectifier was
10 mV. The equations for the outwardly rectifying conductance as above resulted in an effective slope factor of activation of 8 nA
when plotted as an activation curve and fit with a Boltzmann func-
tion. The half activation voltage for the outwardly rectifying potas-
sium conductance was set to −40 mV. The maximal conductance
of both potassium conductances was 2 mS/cm². The maximal time
constant of activation of the outwardly rectifying conductance
(τ_{max}) was 5 ms. Leak conductance was 0.04 mS/cm², and the leak
current reversed at the potassium equilibrium potential. Membrane
capacitance was set at 1 μF/cm² and intracellular resistivity at 200
Ω·cm.

RESULTS

Twelve corticostriatal and 12 neostriatal neurons were
compared in this study. In an additional six corticostriatal
neurons QX-314 was injected intracellularly through the re-
cording electrode. Identification of neostriatal spiny projec-
tion neurons was based on morphological classification of
the neurons after intracellular staining. Identification of the
corticostriatal neurons was based either on antidromic ac-
tivation from contralateral neostriatum (n = 6), or on intracel-
lar staining and tracing of the axon to termination in the
ipsilateral neostriatum (n = 9), or both (n = 3). All cortico-
striatal neurons used in the study were located in the medial
or lateral agranular cortex. All neurons in the sample had
membrane potentials (measured in the down state) more
negative than −50 mV and action potentials with ≈10 mV
of overshoot. The membrane potential was corrected for tip
potential with the use of the extracellular potential recorded
immediately after withdrawal from the cell.

Two-state nature of membrane potential fluctuations

All neostriatal spiny neurons and corticostriatal neurons
showed spontaneous shifts of the membrane potential. Figure
1 shows intracellular records of the membrane potential of
a corticostriatal neuron and a neostriatal neuron. The mem-
brane potentials at each time point are presented as frequency
histograms at right. These will be called all-points histo-
grams, by analogy to those used in analyzing data from
single-channel recordings. The histograms from both neostri-
atal and corticostriatal neurons showed clear bimodality,
suggesting that they might be approximated by the sum of Steriade 1995; Steriade et al. 1993 ) , and that the mechanism
of both potassium conductances, by analogy to those used in analyzing data from coworkers have shown that a slow oscillation in the 0.1-
to 1.0-Hz frequency range exists in the cortex of urethan-
ated and corticostriatal neurons showed clear bimodality, anesthetized cats ( Amzica and Steriade 1995; Contreras and
results were stationary. The spectra, after subtraction of the DC
components, are shown in Fig. 2, A and B, for a corticostria-
tal and a neostriatal projection neuron. A broad, large peak

Are up and down state transitions periodic?

From inspection of the raw data (e.g., Fig. 1), it was
evident that the membrane potential transitions were to some
extent periodic, with a frequency near 1 Hz. Steriade and
coworkers have shown that a slow oscillation in the 0.1-
to 1.0-Hz frequency range exists in the cortex of urethan-
anesthetized cats (Amzica and Steriade 1995; Contreras and
Steriade 1995; Steriade et al. 1993 ) , and that the mechanism
of the oscillation was due to disfacilitation of cortical synap-
tic input. We tested for periodicities in the spontaneous activ-
ity of corticostriatal and neostriatal membrane potential by
performing Fourier analyses on the membrane potential data.
The traces were downsamped to 200 Hz, and discrete Fou-
rier transforms were performed with the use of rectangular
windowing on one to three 20- to 60-s data segments from
each of the 12 neostriatal and 12 corticostriatal neurons.

Traces without action potentials were used for these analy-

ses. For some neurons it was necessary to hyperpolarize the cells by 1–5 mV to prevent action potentials. The average
magnitude spectrum over all traces was calculated by averag-
ing the spectra of the individual segments. None of the indi-
vidual spectra differed substantially from the averages, indi-
cating that the magnitude spectra of the membrane potentials
were stationary. The spectra, after subtraction of the DC
components, are shown in Fig. 2, A and B, for a corticostria-
tal and a neostriatal projection neuron. A broad, large peak
FIG. 1. Spontaneous fluctuations of the membrane potential of corticostriatal and striatal neurons. **Left**: 6.4 s of spontaneous recordings from a corticostriatal and striatal neuron. These were digitized at 4 kHz. Membrane potentials of the up and down states are labeled at the right ends of the traces. **Right**: all-points histograms showing the amount of time spent at any given membrane potentials for the recordings shown at left. Histograms do not include the action potentials.

was evident in the spectra between 0.1 and 5 Hz, with a maximum at 1 Hz. The width of this peak indicated that despite the obvious influence of a periodicity near 1 Hz, the spontaneous shifts in membrane potential could not be considered to be due to the influence of a single oscillatory process.

Because the spontaneous membrane potential transitions were only approximately described by periodic functions, we analyzed the timing of state transitions as a stochastic process. Transitions to the up and down states were detected with the use of the following thresholding procedure. All-points histograms were constructed for each neuron. The minimum value (separation) point in the histogram between states was calculated, and one half the distance between that point and the modal value of the up or down state was taken as the transition point to that state. The time of transition to an up state was thus defined as the time at which the membrane potential attained a voltage halfway between the best separation value and the modal value of the up state. With the use of this procedure, the duration of each up state and down state was measured and dwell time histograms were constructed. Figure 2, C and D, shows examples of dwell time histograms for a representative corticostriatal and neostriatal neuron, measured over 2 min of continuous recording. These differ from the all points histogram in that they do not measure total time in each state, but the durations of individual episodes in each state. The mean dwell time of the up state for corticostriatal and neostriatal neurons was

**TABLE 1. Statistics of spontaneous membrane potential shifts in corticostriatal and striatal neurons**

<table>
<thead>
<tr>
<th></th>
<th>Corticostriatal Neurons</th>
<th>Striatal Neurons</th>
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<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Range</strong></td>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td>$V_m$ of up state</td>
<td>$-48.82 \pm 5.26$ mV (4.48 mV)</td>
<td>$-39.13$ to $-60.62$ mV</td>
</tr>
<tr>
<td>$V_m$ of down state</td>
<td>$-63.37 \pm 4.75$ mV (1.84 mV)</td>
<td>$-53.14$ to $-72.32$ mV</td>
</tr>
<tr>
<td>Up-down $V_m$</td>
<td>$14.55 \pm 4.20$ mV (2.92 mV)</td>
<td>$6.80$ to $22.00$ mV</td>
</tr>
<tr>
<td>Duration of up state</td>
<td>$508.29 \pm 128.24$ ms (331.10 ms)</td>
<td>$40.0$ to $1,712.50$ ms</td>
</tr>
<tr>
<td>Duration of down state</td>
<td>$282.91 \pm 39.41$ ms (134.52 ms)</td>
<td>$48.25$ to $1,125.00$ ms</td>
</tr>
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Values of means ± SD are calculated between averaged values for each neuron; values in parentheses are averages of the SDs within each neuron. Range is the minimal and maximal value of each measure. $V_m$, membrane potential.
FIG. 2. Fourier spectra and dwell times of spontaneous membrane potential fluctuations of corticostriatal and striatal neurons show broad peaks reflecting both periodicity and deviations from periodicity. A and B: 2 separate continuous 60-s segments of recordings from each cell were digitized at 4 kHz and downsampled to 200 Hz. Discrete Fourier transforms were performed on the downsampled records, and the averages of the 2 Fourier spectra up to 50 Hz are shown. C: durations of the individual up and down states of the corticostriatal neuron shown in A. D: durations of the individual up and down states of the striatal neuron shown in B.

508.29 and 422.57 ms, respectively, whereas the mean times for down states were 282.91 ms for corticostriatal neurons and 313.01 ms for neostriatal neurons. For each neuron, the distribution of dwell times could be approximated by Gaussian distributions (with the use of the Kolmogorov-Smirnov test for goodness of fit). No significant differences were found between the means of the distributions of the down state durations ($t = 1.78; \text{df} = 22; \text{not significant}$) or the up state durations ($t = 1.80; \text{df} = 22; \text{not significant}$) of the two cell types. The dwell time in each state varied considerably within neurons. In contrast to the variances of membrane potential of the individual states (measured from the all-points histogram), the within-cell variance for dwell times exceeded the between-cell variance of state durations for both cell types. The up state durations of corticostriatal cells were more variable than those of neostriatal neurons. Thus a test for homogeneity of variances between the up state durations of both cell types revealed a significant differ-
FIG. 3. No serial dependence was found for successive corticostriatal or striatal membrane potential state durations. Up state durations plotted as a function of the durations of the preceding down state in continuous recordings taken from a single corticostriatal and a single striatal neuron. A: corticostriatal neuron return map. B: striatal neuron return map. In all cases, the slope and correlation did not differ significantly from 0, showing independence of successive state durations.

ence between cell types (df = 11:11; F = 2.84; P < 0.05), whereas a comparison of the variance of down state durations between cell types showed no significant difference (df = 11:11; F = 0.87; not significant). The distributions of up state durations for each cell type were positively skewed, because of the presence of some very long up states. The skew was more prevalent in the distributions of the corticostriatal up states. The long up state durations were present in most cells of our sample, and were the principal cause of the greater variability of the up state durations in corticostriatal neurons.

Like the frequency spectra, the dwell time histograms were broader than expected if the up and down state transitions were dominated by a strong periodic signal. They were consistent with the presence of a very noisy 1-Hz rhythmicity in the membrane potentials state transitions. The difference in the variance of dwell times for up and down states could be attributed to differences in the noise process, or in the responses of the two cell types to noisy inputs. If the variance in dwell times were due to superimposition of nonperiodic pertubations (noise) on a 1-Hz periodic oscillation, a serial dependence of dwell times would be expected. In that case, short up states would tend to be followed by long down states, because these represent half periods of the oscillator and deviations from a constant period would be due to uncorrelated superimposed noise. If the source of the 1-Hz periodicity were intrinsically noisy, no serial dependence of up and down state dwell times would be expected. A similar test is possible for the time between up state (or down state) transitions, which represents the full period of the oscillation.

To test for serial dependence in the patterns of spontaneous membrane potential shifts, the durations of up states were represented relative to the previous down state durations. Examples of serial correlograms for up and down state dwell time are shown in Fig. 3 for 30 sequential state transitions in the same neostriatal neuron and corticostriatal neuron used in Fig. 2. The successive events are connected by lines. For all cells, as in the example in Fig. 3, A and B, the duration of an up state was independent of the duration of the immediately preceding down state. The same result was found when measuring down state durations as a function of the duration of the previous up states (not shown).

We used the serial correlation test for renewal processes to test independence of successive intervals (Cox 1962; Cox and Lewis 1966). In no cell could we reject the null hypothesis of randomly ordered intervals.

Because the apportionment of time between up and down state in a single cycle of the slow oscillation might be governed by different influences than those that determine the period of the oscillation, we also examined the durations between successive up state transitions. The first-order time-interval histograms of the durations of the intervals between up state transitions for a single corticostriatal and neostriatal neuron are shown in Fig. 4. The mean time between transitions did not differ between neostriatal and corticostriatal neurons, being 752.5 ms for neostriatal and 816.8 ms for corticostriatal cells (df = 22; t = 1.01; not significant). The variances were significantly larger for the corticostriatal neurons (df = 11:11; F = 2.85; P < 0.05). The distributions did not differ significantly from Gaussians.

As a test for an effect of recent history of transitions (not simply the previous interval) on the time between up state transitions, we calculated autocorrelation histograms for transitions to the up state. This analysis displays the probability of an up state transition as a function of time since a previous up state transition. An example is shown in Fig. 4 for representative corticostriatal and neostriatal neurons. Figure 4A shows the first-order interval histograms for up state transitions in the two neurons, and Fig. 4B shows the autocorrelation functions for the same data set. Two autocorrelations are shown superimposed in each figure. The black lines are the histograms expected if there were no order
Corticostriatal and striatal up state transitions are not order dependent. A: 1st-order interval histograms of durations between successive up state transitions for individual corticostriatal and striatal neurons. Lines and symbols: autocorrelations calculated from the raw data. Black line: autocorrelation calculated by recursively convolving the 1st-order interval histograms (shown in A). Deviations in the right side of each histogram do not exceed the 95% confidence intervals for the histogram (see text), indicating that the up state transitions can be classified as renewal processes.

Nature of the membrane potential fluctuations within the up and down states

One approach to understanding the generation of membrane potential fluctuations in both striatal and corticostriatal neurons is to separate the components responsible for the state transitions and those responsible for the higher-frequency fluctuations that accompany both states. The simplest model of this type is one in which the cells are considered to be subjected to a synaptic barrage that episodically becomes stronger and weaker, but is otherwise unpatterned. In this model the only difference between the up and down states is the mean rate of the random synaptic input. Models such as this, which separate the process responsible for state transitions from that responsible for the rest of the components of membrane potential fluctuation, generally predict that the spectral content of the membrane potential waveform would be altered if the state transitions were removed from consideration. To examine the expected frequency content of membrane potential fluctuations under these conditions, a series of computer simulations was performed with the use of synaptic input to a uniform finite cylinder, 1 μm diam and 500 μm long. To generate clear up and down states at realistic membrane potentials, representations of potassium channels activating in the down state (inward rectification) and in the...
up state (outward rectification) were included, in addition to the voltage-insensitive potassium (leak) conductance of the membrane. These were included to approximate the arrangement of ion channels that are present in the membrane of the striatal projection neuron, and that have been shown to emphasize and regulate the up and down states of that cell (Nisenbaum and Wilson 1995; Wilson and Kawaguchi 1996). The cylinder was used instead of an isopotential membrane patch because previous studies have shown profound effects of potassium currents on synaptic transmission due to alteration of dendritic electrotonic structure (Wilson 1993, 1995). Figure 5 shows the spectrum for 5 s of a Monte Carlo simulation of stochastic synaptic excitation distributed uniformly along the 10 compartments making up the cylindrical dendrite, and recorded at one end. Synaptic inputs had rising time constants of 0.1 ms and decay time constants of 2.5 ms, with a maximum synaptic conductance of 0.1 nS. Background synaptic input had a density of 60 synapses per second, whereas an additional 1,250 per second synaptic excitation was gated by two Gaussian probability distribution functions, calculated by fitting Gaussians to the dwell time histograms of the up and down states of striatal spiny neurons described above. Passive membrane resistivity was 25,000 Ω·cm²; membrane capacitance was 1 μF/cm²; cytoplasmic resistivity was 200 Ω·cm. Thus the passive time constant of the membrane was 25 ms, and the passive length constant was 559 μm. Inward rectification had a half activation voltage of −100 mV, a voltage sensitivity of 12 mV, and a maximal conductance of 2 mS/cm². Outward rectification was nonactivating, and had a half activation voltage of −40 mV, a voltage sensitivity of 8 mV, and a maximal conductance of 2 mS/cm². The inward rectification was instantaneous, whereas the time constant of the outward rectification was as described in Wilson (1995) with a maximal time constant of 5 ms. All three nonsynaptic conductances had reversal potentials at −90 mV, whereas the synaptic currents reversed at 0 mV. As shown in Fig. 5A, such simulations produced both episodes of increased synaptic activation corresponding to up states with the same temporal patterns seen in striatal and corticostriatal neurons, and also a lesser level of synaptic activation during the down states, which occurred as a spillover of synaptic activation into the interval between up states. The stochastic gating signal governing the rate of synaptic excitation is shown in Fig. 5B, scaled to correspond to the up and down state mean membrane potentials in Fig. 5A. This represents a pure state transition signal, independent of the statistical characteristics of the synaptic excitation in either state. The magnitude spectra of both the simulated membrane potential and the state transitions alone were calculated with the use of the discrete Fourier transform, and the results are plotted in Fig. 5, C and D. The magnitude spectra were plotted on a log/log scale. Comparison of Fig. 5, C and D, shows that the up and down state transitions dominate the spectrum of the membrane potential fluctuations, and can account for the overall shape of the spectrum of both striatal and cortical neurons (compare with spectra in Fig. 6). The frequency composition of the synaptic input within the up and down states was extracted in two ways. In the first, illustrated in Fig. 5E, the spectrum due to state transitions alone was subtracted from that of the membrane potential. The resulting spectrum did not contain the peak near 1 Hz, but resembled that of a simple resistance-capacitance (RC) filter with a time constant between 8 and 16 ms, being flat over a wide range of low frequencies and rolling off between 10 and 20 Hz to become nearly linear with frequency above the cutoff frequency. This apparent time constant was not attributable to the dynamics of the synaptic conductance (2.5 ms) but represents an effective membrane time constant. This was confirmed with the use of the second method for extracting the frequency composition of the signal in the up and down states, which was to extract the activity in the two states. In the computer simulation, this was achieved by running the entire 5-s episode in the up or down state. The results of these simulations are shown in Fig. 5F. These spectra, corresponding to the membrane potential fluctuations in the up and down states, respectively, resemble that shown in E, but with different cutoff frequencies. In the up state, the cutoff frequency is between 5 and 10 Hz, corresponding to a time constant between 10 and 30 ms, whereas in the down state the cutoff frequency was near 50 Hz, suggesting a time constant near 3 ms. These corresponded closely to the effective membrane time constants measured in the simulations by passing a small hyperpolarizing current step. In simulations varying the dynamics of the synaptic conductance and the strength of the voltage-dependent potassium conductances, the shifts in the spectra were shown to correspond to voltage-dependent shifts in effective membrane time constant caused by the relative contributions of the passive and voltage-dependent conductances at the membrane potential of the up and down states.

In the computer simulation described above, the spectral composition of the up and down state transitions differed substantially from that of the membrane potential within states, because these arose from fundamentally different processes. The up and down state transitions were generated by a doubly stochastic point process based on the up and down state dwell time distributions and the independence of the transitions (as indicated in Figs. 2 and 3). The fluctuation of membrane potential within states was effectively Poisson shot noise filtered by the membrane time constant at the voltage corresponding to each state. To test this simple model, the spectra for cortical and striatal neurons (excluding the DC component) were plotted on a log/log scale, as shown in Fig. 6 (Vₘ). These spectra showed large low-frequency components that grew in magnitude gradually from 0.1 Hz to 1 Hz, and fell more rapidly at >1 Hz. A line was fit to the negative slope in the range from 1 to 50 Hz for each neuron. The slopes of this portion of the spectra for corticostral neurons ranged between −0.81 and −1.09, with a mean of −0.96 ± 0.10 (SD). The slopes of the spectra of neostriatal neurons ranged between −0.87 and −1.18, with a mean of −1.03 ± 0.09 (SD). No significant differences of the slope were found between corticostral and neostriatal neurons, or between these slopes and −1.0. Thus the frequency range at >1 Hz consisted of a linear decrease in magnitude with frequency (power linear with the square of frequency). This result was similar to that observed in the computer simulations, and by analogy should be largely due to the state transitions themselves.

To separate frequency components arising from the state transitions and those arising from the membrane potential
FIG. 5. Monte Carlo simulation of striatal and corticostriatal membrane potential fluctuations assuming Poisson synaptic excitation whose density increases and decreases to create up and down states. Synaptic inputs had rising time constants of 0.1 ms and decay time constants of 2.5 ms, with a maximum synaptic conductance of 0.1 nS. Synaptic inputs were distributed uniformly along a cable with a diameter of 1 μm and a length of 500 μm, represented as 10 equal compartments. Membrane potential was recorded from 1 end of the cable. Background synaptic input had a density of 60 synapses/s, whereas an additional 1,250 synapse/s synaptic excitation was gated with the use of the dwell time histograms for striatal neurons. The resulting membrane potential fluctuations are illustrated in A. B state transitions used to gate the synaptic excitation rate, scaled to match the mean membrane potential achieved in the simulation. C and D: corresponding magnitude frequency spectra. The nonperiodic nature of the state transitions was adequate to create both the peak near 1 Hz, and the linear spectra above 1 Hz, shown in D. The spectrum of the synaptic input in the up and down states was separated from that created by the state transitions in 2 ways, illustrated in E and F. In E, the spectrum in D was subtracted from that in C. This resulted in a flat spectrum extending above 10 Hz, with a cutoff frequency between 10 and 20 Hz (1). In additional simulations, the state transitions were omitted, and the synaptic excitation was maintained for 5 s at the level characteristic of the up state or that of the down state. The spectra for these simulations are shown in F. The down state spectrum had a much higher cutoff frequency, because of the low input resistance imposed by the inward rectifier at rest. The cutoff frequency in the up state was higher (between 5 and 10 Hz), but did not approach the 1 Hz peak seen in C and D.
noise within each state, we employed the same two approaches that were useful in analyzing the computer simulations. These are illustrated in Fig. 6, along with representative results from one striatal and one corticostriatal neuron. In the first method, a waveform was synthesized consisting of noise-free up and down states adjusted to occur at the same time as those in the membrane potential record of each cell (as determined with the use of the threshold method described previously). The frequency spectra of these waveforms were computed and plotted on the same scale, and are labeled Transitions in Fig. 6. The difference between the spectrum of the raw data and that of the transitions provided one estimate of the spectrum of fluctuations within the up and down states. In the second approach, segments of data consisting purely of up or down state were extracted from the original recordings. These were also obtained with the use of the threshold as described above, except that segments of data immediately after and before the transitions were excluded by eye so that frequency components associated with the transitions would not be present in either sample. Episodes of up or down state membrane potential varied in duration, so the individual spectra from these data segments did not all cover the entire frequency range. Individual spectra for segments of up and down state data are labeled Individual States in Fig. 6. These individual state magnitude spectra were averaged, with each contributing to the average over its own frequency range, yielding spectra for the up state and down state data for each neuron. These are labeled mean Up state and mean Down state in Fig. 6. No significant differences were found between the average slopes of the up and down spectra of either corticostriatal or striatal neurons. Likewise, the average slopes of the curves for either the up or down states did not differ significantly between corticostriatal and striatal neurons. Magnitude spectra were computed for data samples taken with the same electrode immediately after withdrawal from the cell to determine the spectrum of the instrumentation noise. These are labeled extracellular trace in Fig. 6 ($V_{Na}$).

For both corticostriatal and neostratal neurons, the spectra in the up state had 7–12 times the overall magnitude of that in the down state. This is consistent with the larger SD of membrane potentials seen in the up state (Fig. 1), and is also consistent with the results from computer simulations. Unlike the results of the computer simulation, however, the spectra of up and down state transitions were not comparable in magnitude, but a much larger proportion of the total signal was represented by the fluctuations within states, and particularly in the up state. This difference in the magnitude of fluctuations in the up and down states was not due to a voltage-dependent process, because artificial depolarization or hyperpolarization of the membrane did not produce a similar change in membrane potential variance (not shown). Also unlike the simple model, the frequency spectrum of the membrane potential fluctuations within states (calculated with the use of both the difference spectrum and the spectrum of individual states) did not correspond to that of RC filtered white noise, but rather reproduced the more complex spectrum of the up and down state transitions. This result is inconsistent with the simple model of membrane potential state transitions reflecting changes in mean rate of an unpatterned synaptic barrage. It suggests instead that the process giving rise to the pattern of up and down state transitions and that responsible for synaptic input within a state share the same spectral structure, and may even be identical.

**High-frequency periodic component in the up state of corticostriatal neurons**

In the examples shown above, there were no peaks in the magnitude spectra at $>1$ Hz. However, in 8 of 12 corticostriatal neurons tested, a significant peak in the noise was seen at $\sim 40$ Hz. This peak was not seen in any of our sample of neostratal neurons. The high-frequency component had a constant frequency when present, although the frequency varied between neurons (range: 30–42 Hz, median $= 37$ Hz). Significance of the peak was tested by the height of the peak compared with the 95% confidence intervals of the noise of the Fourier spectrum (Abeles 1982). The Fourier spectrum was smoothed with the use of a five-point Gaussian smoothing function. The deviation of our spectra from the smoothed spectrum provided the distribution from which the 95% confidence intervals were calculated. Figure 7A shows an example of an intracellular recording from one of these neurons. An expanded trace of the membrane potential during the up state is shown in Fig. 7B. The arrows emphasize peaks at 37 Hz, both with and without spikes. The first-order spike interval histogram is shown in Fig. 7C, with clear peaks at multiples of 27 ms. Although these peaks do not account for all of the spikes, a significant proportion of the spikes falls into these bins. The magnitude spectrum of the recording in Fig. 7A is shown in Fig. 7D, and is plotted on a log/log scale in Fig. 7E. This component represents only a small portion of the total energy of the recording. Most of the energy in the spectrum is represented by the state transitions and other low-frequency peaks, as in the examples in Fig. 6. Figure 7F shows the Fourier spectra of up and down states analyzed separately, as in Fig. 6. Figure 7G shows the spectra of the individual states plotted on a log/log scale. The spectra in Fig. 7, D and F, are noisier than those in Fig. 6 because of averaging over fewer data segments. The 40-

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**Fig. 6.** Contributions of 2-state activity and synaptic fluctuations to the frequency spectra of the membrane potential of corticostriatal and striatal neurons. Recordings 20–60 s in duration of membrane potential of corticostriatal and striatal neurons were downsampled to 200 Hz. Discrete Fourier transforms were performed on 20-s samples of the membrane potential, and the Fourier spectra were averaged over the samples. **Top right:** Mean voltage of the up and down states for each neuron was calculated, and transition times were used to generate a waveform corresponding to the state transitions. The magnitude spectrum of this waveform is shown at top right and is labeled Transitions. **Bottom left:** Spectra of extracted samples of up and down state recordings. Individual spectra are superimposed, with the black lines representing up states and the gray lines representing down states. **Bottom right:** Gray lines are the differences between the frequency spectrum of the membrane potential and that of the transitions alone. Black lines represent the mean of up and down spectra at left.
Hz peak was present only in the up state, and was much more apparent in the up state than in the spectrum of the entire trace. The 40-Hz peak was also present in cells that had been injected with QX-314 (4 of 6), indicating that this component was not dependent on voltage-dependent Na\(^+\) currents. The average size and frequency of the high-frequency component did not differ significantly between neurons injected with QX-314 and control corticostriatal neurons.

Firing patterns of corticostriatal and neostriatal neurons

Because action potentials arise only while the neurons are in the up state, shifts in membrane potential should account for some of the variance in spike trains. To assess the firing of corticostriatal and striatal cells in our intracellular recordings, we measured the mean and SD of the interspike interval distributions for each neuron, and calculated the coefficient of variation (CV = SD/mean). Figure 8 shows the interspike interval histograms for a 60-s continuous recording from a corticostriatal cell and an 80-s continuous recording from a neostriatal cell. It was usually necessary to take longer recordings from neostriatal neuron because of their lower firing rates. As shown in Fig. 8, the interspike interval histograms of both corticostriatal neurons and striatal spiny cells were weighted heavily toward short intervals, but had long tails due to the presence of a few very long intervals. In many cells, as in the striatal cell in Fig. 8, the distribution was clearly bimodal, as expected from a cell firing in an episodic or bursty fashion. The long intervals in all cases were comparable with the mean dwell time of the down state. Interspike intervals were sorted according to their relation to the membrane potential shifts as either intervals spanning down states or as intervals contained within an up state. For the example shown in Fig. 8, the median of all the interspike intervals of the corticostriatal cell was 27.8 ms, whereas that for the striatal spiny cell was 60.7. After subtraction of the down state intervals, the median of the corticostriatal interval histogram was 25.0 ms, whereas the median of the striatal histogram was 37.8 ms. For the entire sample, corticostriatal neuron median interval spike intervals ranged from 24.8 to 145.6 ms, whereas those of the striatal neurons ranged from 42.5 to 184.0 ms. Subtraction of the intervals spanning transitions to the down state greatly reduced the variance of intervals in all cells of both types. For corticostriatal neurons, median interspike intervals within the up state ranged from 20.0 to 47.3 ms, whereas those of the striatal neurons ranged from 35.0 to 72.5 ms. This difference suggests that a large proportion of the variance of interspike intervals in both cell types was due to the up and down state transitions.

To further characterize the degree to which spike times were due to the membrane potential shifts, we calculated the CV of spike intervals. This gives a firing-rate-independent measurement of spike train variability. A random spike train would be expected to give a CV of 1, whereas a perfectly regular pacemaker neuron would have a CV value of 0. An irregularly bursting neuron would have a CV >1.0. For the example shown in Fig. 8, the mean interspike interval was 89.7 ± 160.0 (SD) ms for the corticostriatal cell and 324 ± 509.7 ms for the striatal cell. This gives CV values of 1.79 for the corticostriatal neuron and 1.57 for the striatal neuron. CVs for all corticostriatal neurons ranged from 1.02 to 1.89 (mean = 1.45), and those of the striatal neurons ranged from 1.1 to 1.72 (mean = 1.39). However, when making the same calculation without including the intervals spanning state transitions, the means ± SD for the time interval histograms shown in Fig. 8 were 39.7 ± 42.0 ms for the corticostriatal cell and 57.0 ± 55.2 ms for the striatal cell, yielding CVs of 1.06 for the corticostriatal neuron and 0.97 for the striatal neuron. After the subtraction of the down state intervals, the ranges of the CVs were 0.44–1.10 (mean = 0.84) for corticostriatal neurons, and 0.66–1.03 (mean = 0.79) for striatal neurons.

With the exception of the regular firing seen in corticostriatal neurons exhibiting subthreshold high-frequency oscillations described previously, there was no evident pattern to the firing of neurons during the up state. Although neurons fired in a regular-spiking manner when depolarized by injected current while in the down state (not shown), no spontaneous regular-spiking behavior was seen in the neurons in our sample. Thus, although all of these cells were regular-spiking cells in the sense used for in vitro recordings (McCormick et al. 1985), none of them fired rhythmically during the up state. The average firing rate did not show any tendency to change as a function of time in the up state in either corticostriatal or striatal neurons, nor did they show any order dependence in firing. These were assessed with the use of a serial correlation of spike times in the up state. Examples of serial correlations are shown in Fig. 9, top. In these, each interspike interval is plotted against the previous interval. Long intervals along each axis represent the intervals between up states. Firing within an up state is represented as a cluster of short intervals near the origin. This cluster, which is shown for each cell at higher scale in Fig. 9, bottom, is symmetrically placed between the axes, indicat-
ing that there was no tendency for the cells to speed up or slow down during an up state. It also showed no internal structure, suggesting no order dependence of spike times during the up state.

**DISCUSSION**

*Up states of converging corticostriatal neurons must be nearly synchronous*

Because each striatal projection neuron receives excitatory synaptic input from a large number of corticostriatal neurons, there was no a priori reason to expect that corticostriatal neuron membrane potential fluctuations or firing patterns would resemble those of the striatal cells. If corticostriatal neurons have episodic periods of depolarization (and firing) that are responsible for those of striatal neurons, then the time course of fluctuations of the striatal cell membrane potential will reflect both the duration of the cortical episode and the shape of the cross-correlation among cortical neurons. If cortical neurons fired in very short episodes compared with striatal neurons, then the striatal neuron’s up state would primarily reflect the time course of correlation among inputs rather than the firing pattern of each corticostriatal cell. If the duration of the cortical firing episodes were comparable with the up state of striatal neurons, the striatal neuron’s up state should still be longer, and the difference would reflect the degree of desynchrony among the converging cortical cells. These relationships are represented schematically in Fig. 10. The up states (and envelope of firing) of cortical neurons are represented as square pulses, and their width and degree of correlation (among up state onsets) are shown in three extreme cases. In the first (Fig. 10, left), cortical cells all have up states of the same duration and are very precisely timed. The input to the striatal neuron mimics the up state of any one of the cells. In Fig. 10, middle, the cortical cells have less synchronized up states, leading to a longer episode of depolarization in the striatal neuron than that of any cortical cell. In Fig. 10, right, the cortical up states are much shorter in duration, and much less synchronized, leading to a broad and poorly defined input to the striatal neurons receiving convergent cortical input. The present finding is that membrane potential changes and firing patterns in corticostriatal cells are quantitatively similar to, and specifically no shorter than, those of striatal neurons. This indicates a relatively high degree of synchrony of up and down state transitions among cortical neurons converging onto any one striatal spiny neuron. Broad peaks in cross-correlations of cortical neuronal activity consistent with this type of synchrony among cortical neurons have been observed in visual cortex (Kruger and Aiple 1988; Ts’o and Gilbert 1988; Nelson et al. 1992) and frontal cortex (Vaadia et al. 1995). Our results are also consistent with the finding of Steriade et al. (1993) that at the low frequencies associated with the up and down state transitions there can be synchrony in cortical field potentials. It might be argued that the nonlinear properties of striatal neurons would on average shorten the durations of up states of striatal neurons, interfering with the interpretation given above. In a recent study of striatal spiny neurons, the up state dwell times were shown to be dependent to some degree on their membrane potential (Wilson and Kawaguchi 1996). In that study, depolarization of striatal neurons by subthreshold constant current injection could increase the durations of the up states by ∼20%. When the nonlinear properties of the striatal neurons were almost
completely abolished with the use of a combination of ion channel blockers, the durations of up states were increased but only by about the same amount. The nonlinearities of the striatal neuron membrane reduce the durations of up states by imposing a threshold level of synaptic barrage required to achieve an up state transition and to maintain a cell in the up state. Both the inward and outwardly rectifying potassium currents, being hyperpolarizing, oppose the up state. If the durations of cortical excitation were shorter and the correlation among them were broader, the voltage dependence of the striatal cell membrane might be much more important for determining striatal up state durations, as in Fig. 10, right. This mechanism may be much more important in unanesthetized animals, in which up state durations are longer and more variable (Wilson 1993), but the durations of striatal neuron up states in anesthetized rats in the present experiments are likely to underestimate the total duration of the episode of converging cortical excitation by only a few percent. Thus the degree of synchrony in the cortical input may be somewhat less perfect than that implied by the equality of average up state dwell times in this study, and may resemble most the situation indicated in Fig. 10, middle.

The subthreshold membrane potential shifts in these experiments are not simply an artifact of anesthesia. Very similar membrane potential shifts have been reported in experiments on awake animals (Hull et al. 1970; Wilson and Groves 1981). However, the temporal pattern of membrane potential shifts in awake animals is, if anything, less periodic than that reported here for urethane- and ketamine/xylazine-anesthetized rats (Wilson 1993).

Aperiodicity of up states is not noise

The periodicity in the up and down state transitions in both cortical and striatal neurons is evident by inspection of the recordings, by the peak at 1 Hz in the magnitude spec-
Fig. 10. Up states of converging corticostriatal neurons must be nearly synchronous. Three extreme models for synchronicity of converging up states are shown in schematic form. Left: corticostriatal cells have up states of the same duration and are very synchronized, and the input to the striatal neuron mimics the up state of any of the corticostriatal neurons. Voltage-dependent shaping of the response of the striatal cell is minimal. Middle: corticostriatal neurons have less synchronized up states, leading to longer episodes of depolarization in the striatal neuron than in any of the individual corticostriatal inputs. A moderate amount of voltage-dependent shaping of the striatal response is possible. Right: corticostriatal inputs are much less synchronized and shorter in duration, leading to a long and poorly defined input to the striatal neurons, and a maximal degree of up state duration changes by voltage-dependent properties of the striatal cell.
constant of the postsynaptic neuron is long compared with the time between synaptic events. Thus much of the fine temporal structure of the input is, in this idealized model of a neuron, blurred by the poor high-frequency response of the postsynaptic membrane (Gerstein and Mandelbrot 1964; Segundo 1968; Stevens 1964). Because most cortical (and striatal) neurons have time constants of tens of milliseconds, high-frequency components in the input spike train (> 10 or 20 Hz) are expected to be lost during processing by the postsynaptic neuron. This low-pass characteristic of many neurons is expected to be made worse by the dendritic location of much of the synaptic input. On the other hand, if the effective membrane time constant were shorter than expected because of the action of voltage-sensitive conductances embedded in the cell membrane, high-frequency responsiveness of the neurons might be increased at certain voltages, and some very fast components of the synaptic input pattern might be preserved or even amplified (Softky 1994; Wilson 1992).

An approximation to the response of a passive neuron to a random barrage of synaptic input can be obtained by assuming that the duration of the conductance change of each synapse is short enough to be treated as a delta function and small enough to produce a voltage-independent current. In that case the synaptic barrage is reduced to a distributed white noise current, and the response of a neuron subjected to the barrage is predictable from the transfer impedances from the synaptic to the recording locations (Tuckwell 1988). For an isopotential cell, the magnitude spectrum obtained is the same as that of an RC circuit, which is linearly decreasing with a slope of 1/Hz at frequencies greater than the cutoff frequency for the RC circuit \( 1/(2\pi CR) \) and constant at frequencies below the cutoff. Placing the white noise input on a distal dendrite will not affect the cutoff frequency (which is determined by the membrane time constant), but will reduce the response at higher frequencies, making the rolloff of log magnitude no longer linear with the frequency. This result is easily obtained from inspection of the transfer impedance of a linear cable in the frequency domain. Intuitively, it follows from the relationship between the rolloff and the membrane time constant, with the shorter time constants associated with charge redistribution making additional small increases in slope in the above-cutoff frequency range. The simulation shown in Fig. 5 confirms that general result for the more realistic, but similar case of synaptic conductance changes with finite rise and fall times, and with voltage-dependent potassium conductances known to be acting in the subthreshold range of membrane potentials. The spectra obtained for corticostriatal and striatal neurons were clearly not those expected if the arrival of synaptic inputs were Poisson. Although the linear decrease in log magnitude as a function of log frequency observed in both cell types is consistent with a Poisson process seen through by a relatively simple low-pass filter, the cutoff frequency of the filter is not consistent with the properties of either neuron type. To obtain the observed spectrum, the postsynaptic neurons would be required to have a membrane time constant of \( \approx 150 \) ms. None of the neurons in the sample had time constants approaching this. Thus, despite its appearance as a relatively constant depolarization, the up state is not due simply to an increase in the strength of an otherwise unpatterned synaptic input. The spectra in the individual states were not only unlike that predicted for a Poisson process, but were identical to that of the state transitions themselves. This suggests that the state transitions and the more rapid fluctuations in synaptic activity are reflections of a single pattern of input with a spectrum like that shown in Fig. 6.

High-frequency oscillations in corticostriatal cells are not transmitted to striatal spiny neurons

A large proportion of corticostriatal neurons exhibited periodic 40-Hz subthreshold membrane potential oscillations, exclusively in the up state. We have previously shown that these oscillations are due to periodic inhibition (Cowan and Wilson 1994). Their ability to impose a pattern on the firing of corticostriatal cells as demonstrated here indicates that there is a strong 40-Hz component in the pattern of synaptic input to striatal neurons. However, no striatal neuron in the present sample showed any sign of this component in the spectrum of their membrane fluctuations. Either this component is not coherent among converging corticostriatal neurons, or it is removed by the postsynaptic properties of the striatal neurons.

High variance of interspike intervals is partially due to slow subthreshold membrane potential fluctuations

Recent studies of cortical neurons have focused on the high variability of their interspike intervals. Models of cortical neurons employed in these studies (which are equally applicable to both corticostriatal and striatal neurons) have shown that such high variability cannot arise from a simple integrate-and-fire mechanism subjected to Poisson synaptic input (Powers and Binder 1995; Shadlen and Newsome 1994; Softky 1994; Softky and Koch 1993; Usher et al. 1994). These authors point out that, as also described by Segundo et al. (1968), a passive neuron subjected to a large number of irregular and independent synaptic conductances will tend to integrate their synaptic input into an overall DC membrane potential shift. If the synapses are many and each is weak, the fluctuations will be small compared with the constant membrane potential shift, and if it is depolarized to firing threshold by this input the cell will fire as if it were depolarized with constant current. For striatal and for many cortical neurons, this means the cell will fire rhythmically at a rate determined by the overall level of depolarization and the duration of spike afterpotentials. In vivo, for example in the recordings described here, such regular firing is almost never observed. A large portion of the high variability of the interspike intervals observed in vivo is due to the presence of the subthreshold membrane potential fluctuations, which add a separate source of variance to the interspike interval distribution. However, when the spike intervals containing down states are removed from the interspike interval distribution, the variability is decreased by \( \approx 42\% \), leaving average CVs of 0.84 and 0.79 for corticostriatal and striatal neurons, respectively. The remaining variability is still too high to arise from the Poisson synaptic input to an integrate-and-fire mechanism (Holt et al. 1996). Another possible reason for the irregularity of interspike intervals has also been attributed.
to the presence of inhibition (Shadlen and Newsome 1994; Tuckwell 1988), but Poisson inhibition superimposed on equally unpatterned excitation does not produce this effect in a robust fashion (Softky 1994; Wilbur and Rinzel 1983), thus bringing into question the two initial assumptions of the model, which are the integrate-and-fire representation of the neuron, and the unpatterned nature of the synaptic input.

The effectiveness of inhibition in models achieving irregular firing rates relies on its ability to balance the excitation, maintaining the membrane potential near, but on the average below, threshold. If the average membrane potential crosses threshold, regular firing will result. If inhibition can maintain the membrane potential just below threshold, fluctuations in the membrane potential will occasionally cause it to cross threshold, and irregular firing will result. Inhibition is not a robust mechanism for maintaining this delicate balance, because to make it so it must be very precisely adjusted to match the level of excitation. Although we cannot rule out this type of mechanism for balancing excitation, the subthreshold potassium currents present in striatal and cortical pyramidal cells (Foehring and Surmeier 1993; Nisenbaum and Wilson 1995) are an ideal mechanism for balancing excitation because of their voltage dependence and their presence at the site of the excitatory synaptic input (Wilson 1995). In striatal neurons potassium currents have been shown to perform exactly as required by the models, to maintain the average membrane potential just below threshold in the presence of powerful episodic excitation (Wilson and Kawaguchi 1996). This allows the cells to maintain an irregular firing rate due to fast membrane potential fluctuations occurring during the episodes. Although this mechanism could not be appreciated from the analysis of extracellularly recorded spike trains, it is readily apparent in intracellular recordings. However, this mechanism alone cannot account for all of the irregularity observed in the spike trains of striatal and corticostriatal neurons. At its best it would produce an effectively random firing pattern (i.e., a CV of 1.0). The firing of both neuron classes studied here was more irregular than that, because of episodic firing. The analysis of these episodes of firing, and of the membrane potential fluctuations within them, has shown that the effective pattern of synaptic input to the neurons varies substantially from the random synaptic barrage used in computer models. It is unlikely that this pattern results from the cellular properties of either corticostriatal or striatal neurons, because neither of these neurons show any signs of resonance at the low frequencies that dominate the spectrum of membrane potential fluctuations. The most likely explanation is that the frequency composition of synaptic membrane potential fluctuations represents the presence of a nonperiodic but far from random pattern of input to the cells.

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REFERENCES


TS’O, D. Y. AND GILBERT, C. D. The organization of chromatic and spatial


