The role of background synaptic noise in striatal fast spiking interneurons

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Abstract

Striatal fast spiking (FS) interneurons provide inhibition to each other as well as to medium spiny projection (SP) neurons. They exhibit Up-states synchronously with SP neurons, and receive GABAergic and AMPA synaptic input during both Up- and Down-states. The synaptic input during Down-states can be considered as noise and might affect signal detection. We investigate what role this background noise might play for Up-state firing in FS neurons. We investigate this in a 127 compartments FS model neuron, with Na, KDr and KA conductances, and activated through AMPA and GABA synapses. The model neuron is well constrained by experimental data.

Key words: Striatum, Fast Spiking Interneurons, Stochastic Resonance, Transient A current, Up states

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1 Introduction

The basal ganglia are important for the executive functions of the forebrain. Disturbances within the basal ganglia produce motor and neurophychiatric disorders [10]. Medium spiny projection (SP) neurons, the predominant cell type in the striatum, are the first stage in cortex-basal ganglia processing and in turn control the output from the basal ganglia. SP neuron membrane potential fluctuates between a "down-state" potential of -80 to -90 mV, and an "up-state" potential near -55 mV [11; 12; 9; 7], during which action potentials are generated [11; 12]. Fast spiking (FS) interneurons, a major source of GABAergic input to SP neurons [4], represent another important striatal cell type. Both neuronal types receive glutamatergic inputs from the same set of cortico-striatal projection neurons. The functional role of FS interneurons, which might be to suppress SP neuron firing during up-states [5], depends on signal processing characteristics of these neurons.

SP neurons and FS interneurons receive synaptic inputs during both up-states and down-states [1]. Down-state synaptic activity can be considered "noise", in that firing during the down-state would obscure the distinct pattern of up-state firing, which can be considered the "signal" to be transmitted. Though SP neurons have hyperpolarized down-states that prevent firing, FS interneurons have down-state potentials closer to firing threshold. Thus, a compelling question is whether down-state activity has an adverse effect on the ability of FS interneurons to reliably signal up-states. An intriguing alternative is that down-state activity may improve signal detection in FS interneurons. The enhancement of sub-threshold periodic signals produced by low levels of noise is known as stochastic resonance (SR).

In the present study, we use a computer model of an FS interneuron to investigate the effect of down-state activity on signal detection.

2 Methods

A 127 compartments model of a fast spiking (FS) interneuron was created using the GENESIS simulation software [2]. The morphology consisted of a soma and three primary dendrites, each with two branching points [6]. Action potentials were generated by the fast Na and delayed rectifier (KDr) currents in the soma. A transient K current (KA) in the soma and primary dendrites was adjusted to produce the experimentally observed spike latency in each dendritic compartment [1]. Maximal conductances of these three voltage dependent channels were optimized using simulated annealing that comes with the GENESIS package. The spike latency, spike threshold, and frequency-

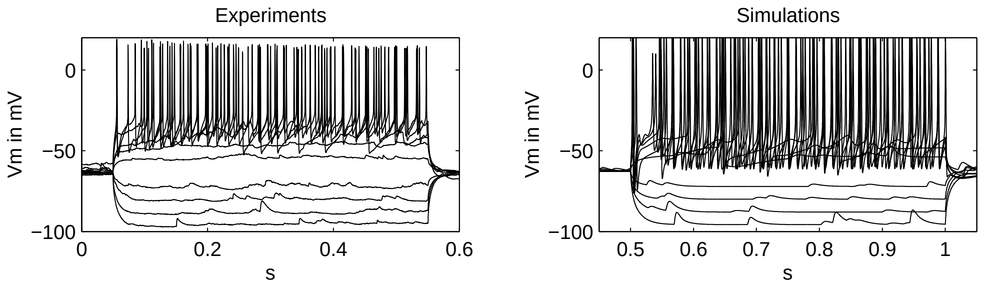

Fig. 1. Response of cultured neuron (left), and model neuron (right), to current steps increasing 0.02nA between -0.08 and +0.12 nA.

current relationship similar to that measured in FS interneurons *in vitro* was reproduced, see also Fig. 1 [1].

Corticostriatal input to the FS model neuron was represented by AMPA synaptic conductances placed in each dendritic compartment. Fast GABAergic synapses representing local striatal inputs were placed in the soma and proximal part of the dendritic tree. These locations, and also the amplitude and density of the AMPA and GABA synaptic channels, were adjusted to match amplitude distribution and population reversal potential measured in triple co-cultures [1] (full manuscript in preparation). Each synapse was activated by a Poisson distributed input train with frequency 0.11 Hz to reproduce the experimentally observed down-state inter-event interval distribution. To evaluate the effect of down-state activity, additional simulations used input frequencies between 0.01 and 1 Hz per Poisson train, which encompassed the range of down-state input frequencies measured experimentally [1].

Up-states were generated by adding a Poisson input train, with periodically varying input frequency, to both AMPA and GABA synapses. The output signal to noise ratio (SNR) was measured as the number of interspike intervals corresponding to the input period divided by the number of all other interspike intervals (SNRisi). Because striatal up-states are not strictly periodic, an alternative measure of SNR was calculated as the ratio of up-state spikes to total spikes (SNRphase).

3 Results and discussion

Figure 2 illustrates two different shapes of up-state input signals that were used in the present study. The frequency of each of the input Poisson trains was either changed continuously in a sinusoidal manner (sinusoidal input) or abruptly increased solely during the simulated up-states (rectangular input). Maximal frequency during up-states was similar in both cases and set to 800 Hz, the experimentally observed value [1]. For sinusoidal modulation, the up-

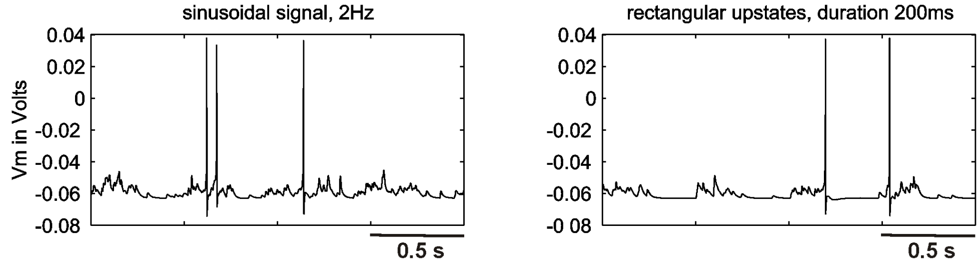

Fig. 2. Membrane potential of a model FS interneuron in response to sinusoidal (left), and rectangular up-state signals (right) in addition to the background noise signal.

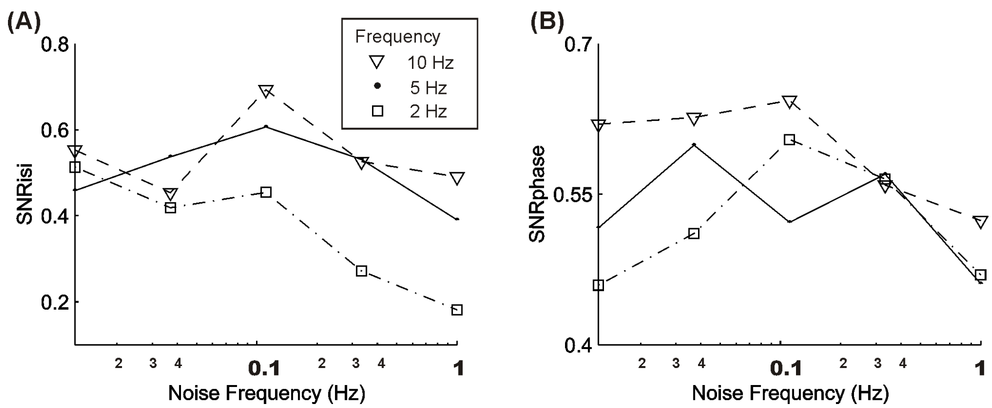

Fig. 3. SNR for sinusoidal up-states: (A) SNRisi; (B) SNRphase. SNRisi peaks at intermediate noise values for 5 and 10 Hz sinusoidal inputs; SNRphase peaks at intermediate noise values for 2 and 5 Hz sinusoidal inputs.

state is considered the highest frequency part of the up-state input signal, with duration 1/4 the sinusoid period.

The results show that the effect of down-state noise depends on the up-state shape as well as the measure of SNR. An increase in noise predominantly produces a decrease in SNR, but SR is sometimes observed. When sinusoidal up-states are used (Fig 3) and a periodic analysis of SNR is employed, the higher frequency (shorter duration) up-states exhibit SR: the maximum SNRisi is observed for background noise=0.11 hz for 5 Hz and 10 Hz signals (Fig 3A). However, when an aperiodic analysis is applied, SR is exhibited for the lower frequency (longer duration) up-states: maximum SNRphase is observed for background noise = 0.11 or 0.03 Hz for 2 Hz and 5 Hz signals (Fig 3B).

High frequency sinusoids necessarily have short duration up-states; thus with the input frequencies used in this study, at most one spike is generated per up-state, and most up-states have no spikes. Consequently, intermediate values of down-state noise increases the number of up-states with spikes, which increases SNRisi. With lower frequency sinusoids, the longer duration up-states can support multiple spikes per up-state in response to intermediate noise values.

This situation increases the SNRphase, but decreases SNRisi due to increases in interspike intervals other than the period duration when multiple spikes occur during a single up-state.

SR also is seen with rectangular up-states when SNRisi is the measure of SNR (Fig 4A). SNRisi is not independent of duration as seen with sinusoidal inputs, but decreases with longer up-states due to the appearance of several spikes per up-state which increase the number of interspike intervals that are smaller than the signal period. In contrast, SR is not seen using SNRphase as the measure for any up-state duration. Because the frequency of down-state spikes is so low, SNRphase is close to one for all duration up-states even for intermediate noise levels. For higher down-state noise, the percentage increase in noise spikes is greater than that of signal spikes; thus SNR phase decreases.

Though stochastic resonance in the peripheral nervous system is well documented [3], stochastic resonance in central neurons is rare. Rudolph and Destexhe [8] demonstrated SR in a model neocortical neuron. They found that an increase in strength of the background noise, but also an increase in correlation of the input, will affect the responsiveness of the system. Unlike that result, the SR in this research is less robust, probably due to two major differences. The first difference is cell type: neocortical pyramidal neuron vs striatal fast spiking interneuron. The second difference, which we believe to be more significant, is the form of the input signal. Rudolph and Destexhe used synchronous inputs on a randomly chosen, yet time-invarying set of synaptic inputs, whereas the synaptic inputs in our study were asynchronous, and changed from trial to trial. This variation in up-states is observed experimentally, but hinders the ability of noise to boost spike production only during up-states. Our hypothesis is supported by the observation that SR was most distinct for SNRisi applied to high frequency sinusoids, which decreases the asynchronous nature of the synaptic inputs. Because striatal up-states are not strictly periodic, SNRphase is the appropriate measure of SNR, and thus it is unlikely that down-state noise facilitates up-state spike generation in FS interneurons.

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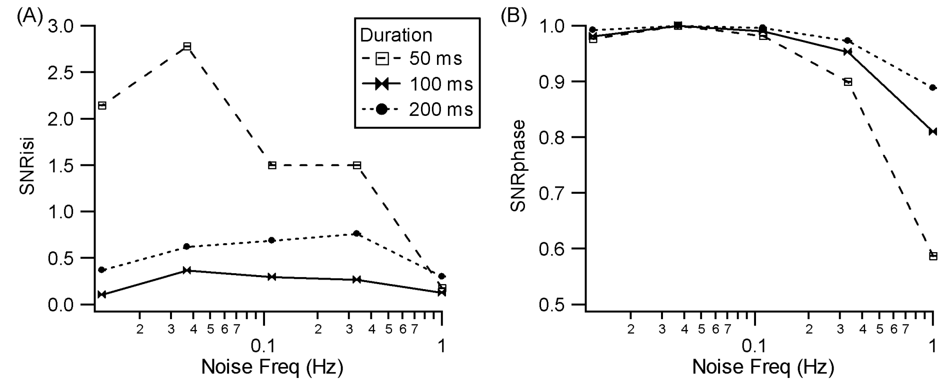

Fig. 4. SNR for rectanglular upstates of durations between 50 and 200 ms, (A) SNRisi; (B) SNRphase. SR is seen only with SNRisi.

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