Temporally Precise Spiking in the Presence of Synaptic Noise

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Abstract

Spike timing precision and reliability were studied in granule cells of the dentate gyrus using conductance inputs based on natural synaptic properties and injected via dynamic current clamp. Precision and reliability were greater for conductance steps than for current steps, and were greatly enhanced for synaptic conductance waveforms. Precision and reliability were only slightly degraded by realistic trial-to-trial synaptic fluctuations. We therefore examined, in the presence of realistic noise, the effects of 1) varying the ratio of inhibition to excitation, 2) varying the number of inputs and 3) correlated inputs, on both temporal and rate-based features of granule cell coding.

Key words: Dynamic clamp, Inhibition, Spike timing, Natural Statistics, Synapse

1. Introduction

The hippocampal formation has a critical role in spatial and episodic memory processing [1]. Granule cells receive the principal cortical input to the hippocampus and are therefore positioned to have a gating effect on information flow. Hippocampal anatomy and synaptic

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transmission have been extensively studied, however, relating complex behavioral functions to transmission at the cellular level presents a number of difficulties. Inputs to the hippocampus include thousands of synapses from the entorhinal cortex and medial septum [2] and intricate networks of GABAergic interneurons, which provide inhibitory regulation [3]. Such complex circuits cannot be adequately retained in *in vitro* preparations, whereas *in vivo* studies cannot readily address the cellular and biophysical aspects of transmission. Here we have used the dynamic clamp method to inject simulated conductances, with the kinetics and statistical properties of natural synapses, into dentate gyrus granule cells to investigate some of the input/output features of granule cell coding. Dynamic current clamp allows us to manipulate input conductance patterns in order to determine how specific features of the synaptic drive are reflected in granule cell output.

2. Methods

Whole-cell patch clamp recordings were made from granule cells of the dentate gyrus in hippocampal slices prepared from 12-20 day old rats. Slices were maintained, at room temperature, in artificial cerebrospinal fluid containing (in mM): 125 NaCl, 25 $NaHCO_3$,, 2.5 KCl, 1.25 NaH_2PO_4, 2 $CaCl_2$, 1 $MgCl_2$ and 25 D-glucose, bubbled with 95% 0_2 and 5% CO_2. Patch pipettes were filled with intracellular solution containing (in mM): 140 K-gluconate (KCl was used for IPSC recordings), 10 EGTA, 10 HEPES, 20 phosphocreatine, 2 Mg_2ATP, 2 NaGTP (pH 7.3, 310 mOsm). Paired recordings were made from synaptically coupled inhibitory interneurons and dentate gyrus granule cells. The distributions of conductance amplitude, rise time, decay time and latency of postsynaptic currents were compiled to form stimulus libraries, from which our simulated conductances were drawn for use in dynamic

clamp experiments. Data was acquired using an Axopatch 200B amplifier and records were sampled at 10 kHz and filtered at 5 kHz. Analysis was performed using Axograph and Matlab software.

Dynamic current clamp experiments were performed using a homemade analog circuit based on a design by Robinson [4]. The circuit takes a conductance waveform input (G), a user-defined synaptic reversal potential (Erev), and the membrane potential of the neuron (V), and injects the current that would flow through the conductance under these conditions, according to the equation $I = G(V-Erev)$. Synaptic reversal potentials were set to –75 and 0 mV for inhibitory and excitatory conductances, respectively. Multiple hypothetical input neurons were independently assigned either Poisson (mean rate 5 Hz) or rhythmic (10 Hz) inter-spike interval (ISI) distributions. 100 trials of spike trains were randomly generated for each presynaptic neuron. For every spike in every neuron on every trial, a simulated synaptic conductance was created, with properties drawn randomly from experimentally obtained distributions. Excitatory and inhibitory conductance waveforms for each input were summed and injected into the recorded neuron.

3. Results

Injection of square conductance steps or naturalistic synaptic conductance patterns, *via* dynamic clamp, improved spike timing precision in comparison to conventional square current steps (data not shown). Precision was greatest for naturalistic patterns, where spike timing jitter

(defined as the standard deviation of a Gaussian fit to the central peak of the mean crosscorrelogram over all trials) was less than 1 ms. Spike reliability (i.e. spike probability per peak in the peristimulus time histogram; PSTH) was also greatest in response to naturalistic synaptic conductances. These data are consistent with previously published findings using rapidly fluctuating current waveforms [5], and demonstrate that spike responses to repeated trials of a naturalistic stimulus could be precisely and reliably reproduced. However, *in vivo,* synaptic transmission is subject to noise in the form of fluctuations in synaptic amplitude and kinetics. Figure 1A (top row) shows the voltage traces from 100 identical repetitions of a synaptic conductance waveform and (second row) the summed inputs from excitatory (red) and inhibitory (blue) presynaptic neurons. The raster plot (third row) illustrates extremely precise spike timing and almost perfect reliability. The crosscorrelogram (inset) reveals that spike times occurred with a mean jitter of less than 1 ms across all trials. Figure 1B shows traces from the same neuron using fluctuating synaptic stimuli, where the presynaptic spike times were identical to those above, but the amplitudes and kinetics of the synaptic conductances varied randomly from trial to trial, in accord with experimentally observed fluctuations. In the presence of synaptic noise, spike times were less precise and less reliable. Spike timing jitter increased to 2.1 ms, from 0.6 ms in the absence of noise. However, all spike times that occurred reliably in response to non-fluctuating stimuli still occurred reliably in the presence of noise (Figure 1B, lower panel). Thus, synaptic noise did not prevent precise or reliable spiking.

Dentate granule cells receive inputs from excitatory afferents via the perforant path [2] and from multiple classes of inhibitory interneurons [3]. We tested the influence of varying the balance of inhibitory and excitatory inputs, and of varying the total number of inputs. Coding properties were evaluated using the rate-based measures of spike count, count variance, and coefficient of variance (CV), and the time-based measures of jitter and reliability. Increasing the ratio of inhibitory to excitatory inputs reduced granule cell spike count and increased CV but did not change timing or reliability (Figure 2A). Varying the number of presynaptic inputs (at a fixed ratio of 1:4 inhibition to excitation) revealed a maximum in the spike count, which climbed over the range of 10-100 inputs but declined sharply with more than 100 inputs (Figure 2B). Spike count CV and reliability also demonstrated *extrema* at about 100 inputs (Figure 2B), suggesting that there may be an optimal number of inputs for efficient coding whether a rate-based or time-based code is employed.

The hippocampus displays prominent rhythmic activity, including θ (3-14 Hz) and γ oscillations (20-40 Hz), during learning-related behavior such as exploration and REM sleep [6-8]. To test the ability of noisy presynaptic inputs to rhythmically entrain granule cell output, we used waveforms simulating 20 inhibitory and 80 excitatory inputs with varying fractions of rhythmically (10 Hz) firing cells. The remainder of cells fired with Poisson statistics. Figure 3A shows the voltage traces and corresponding raster plots for 100 trials of correlated excitatory (left panel) or inhibitory (right panel) inputs. The rasters reveal entrainment of the postsynaptic response as vertical columns of dots. Rhythmic postsynaptic spiking was apparent with as few

as 4 out of 80 excitatory inputs or 4 out of the 20 inhibitory inputs firing rhythmically. These findings suggest that a small number of correlated inputs, over a larger background of random activity, is sufficient to drive patterned output. The graphs in the Figure 3B show that the rate-based measures of spike count and CV were not much affected by coherent inputs, whereas the time-based measures of jitter and reliability were greatly improved by even modest coherence in either excitatory or inhibitory inputs.

4. Discussion

Our results demonstrate that conductance-based stimuli result in more precise and reliable firing than simple current injection, and that naturalistic stimuli are more reliably and precisely encoded than static stimuli, in agreement with a previous study [5]. Our findings further show that temporal patterns remain reliably encoded, even in the presence of natural synaptic noise. Increasing the ratio of inhibitory to excitatory inputs reduced spike count and increased count variance without altering timing precision or reliability, suggesting that inhibition would tend to reduce the efficiency of rate-based coding, whilst favoring a sparse temporal code. When the total number of inputs was varied, the spike count, count variance and reliability all reached extrema at about 100 inputs, suggesting that there is an optimal number of inputs that 50promotes efficient coding using either a rate or temporal code. Finally, granule cells could be efficiently entrained by a small fraction of coherently firing inputs, on a large background of random inputs. Taken together, our results suggest that these cells can most efficiently participate in a sparse temporal code, driven by a small number of presynaptic

inputs. Under these conditions, granule cell coding remains temporally precise in the presence of synaptic noise.

Acknowledgements

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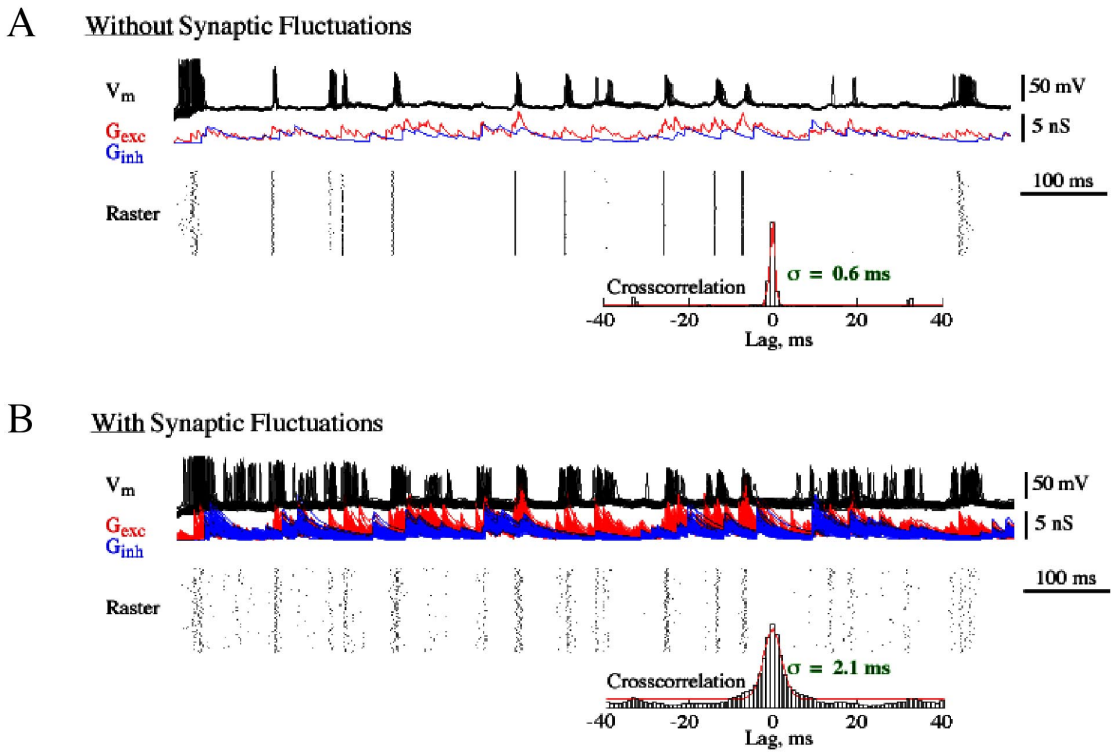

Figure 1. Precise and reliable spiking in the presence of synaptic noise. A) Top (black) traces show the voltage responses of a granule cell to 100 trials of a non-fluctuating synaptic conductance waveform. The summed excitatory (red) and inhibitory (blue) conductances are shown below and each spike in each trial is represented in the raster plot below. Inset shows a Gaussian fit to the peak of the crosscorrelogram, giving a mean spike timing jitter of 0.6 ms. B) Similar data are shown for responses to a fluctuating conductance waveform. The spike times were identical to the pattern used in (A), however, inhibitory and excitatory conductances varied in amplitude and kinetics, according to experimentally obtained distributions. Spike timing jitter was increased to 2.1 ms in the presence of naturalistic noise.

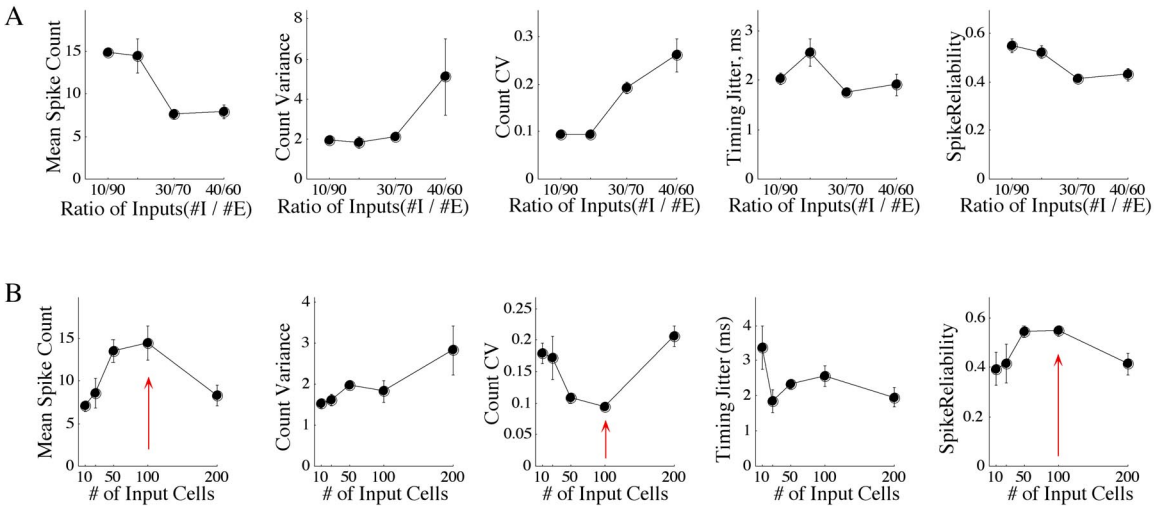

Figure 2. Effects of the ratios of inhibition and excitatory conductances, and of the total number of inputs on spike rate and timing. A) Graphs show the relationship between the ratio of inhibitory to excitatory input conductances on measures of granule cell output: mean spike count, spike count variance, count CV, timing jitter and spike reliability. All experiments used a total of 100 inputs. B) Graphs show data similar to that in (A), for inputs with increasing numbers of hypothetical presynaptic neurons. All experiments used waveforms with a fixed ratio of inhibition to excitation of 1:4. The red arrows indicate the *maxima* for spike count, and reliability and the minimum spike count variance with 100 inputs. All points shown are mean ± SEM for data from 4-5 granule cells.

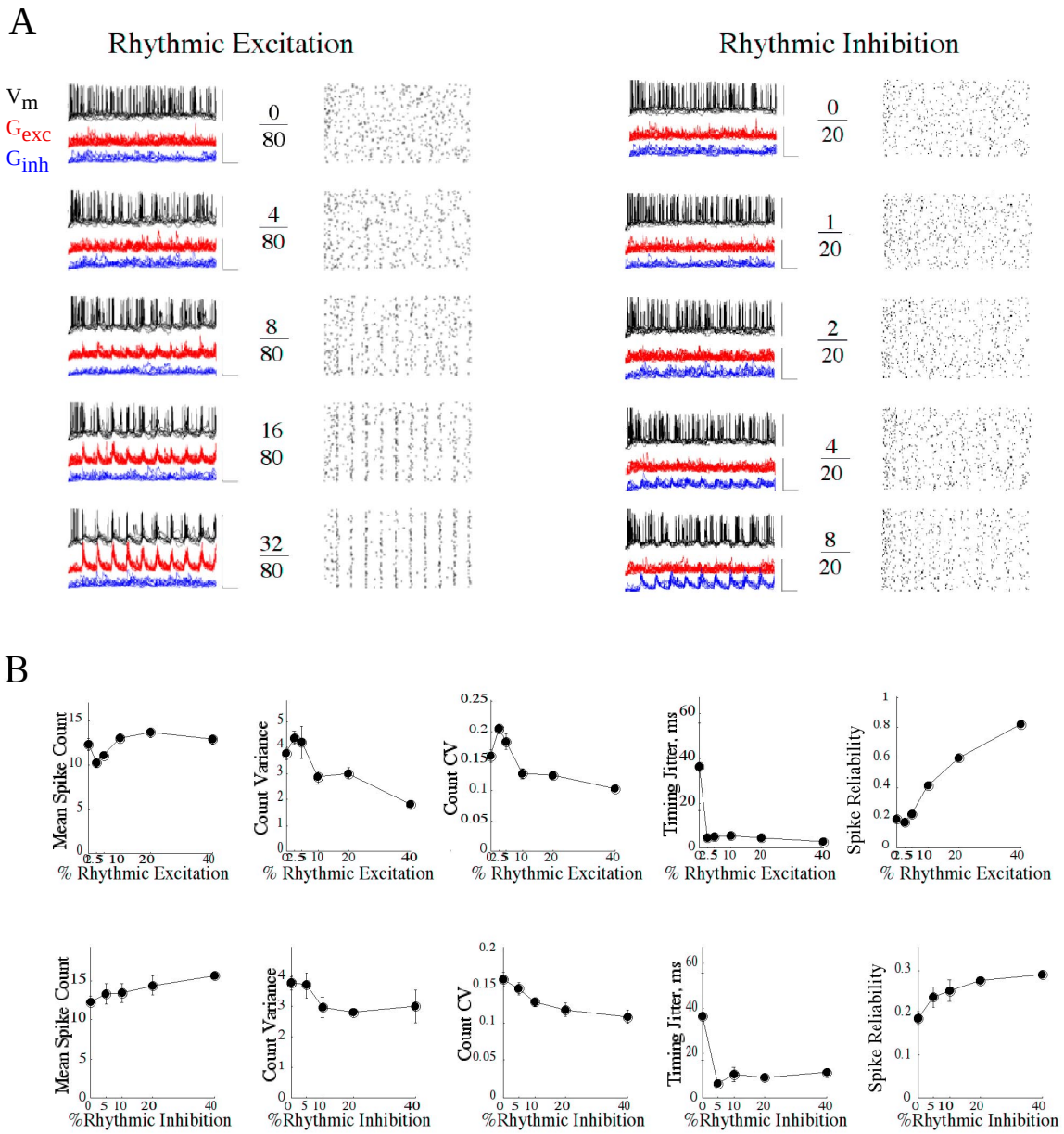

Figure 3. A small number of inputs can entrain granule cell spiking. A) Voltage traces (black) and, below, corresponding excitatory (red) and inhibitory (blue) input conductances are shown for waveforms with increasing fractions of coherent, rhythmic inputs. Scale bars: 100 mV, 20 pS and 100 ms. Vertical columns in the raster plots indicate entrainment with 4 out of 80 excitatory and 4 out of 20 inhibitory inputs firing coherently. B) Data similar to that in Figure 2, showing that entrainment, by either excitatory or inhibitory conductances, resulted in greater precision and reliability, without affecting the rate based measures of spike count and count variance.