Modulation of Firing Rate by Background Synaptic Noise Statistics in Rat Visual Cortical Neurons

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Sceniak MP, Sabo SL. Modulation of firing rate by background synaptic noise statistics in rat visual cortical neurons. J Neurophysiol 104: 2792–2805, 2010. First published August 25, 2010; doi:10.1152/jn.00023.2010. It has been shown previously that background synaptic noise modulates the response gain of neocortical neurons. However, the role of the statistical properties of the noise in modulating firing rate is not known. Here, the dependence of firing rate on the statistical properties of the excitatory to inhibitory balance (EI) in cortical pyramidal neurons was studied. Excitatory glutamatergic and inhibitory GABAergic synaptic conductances were simulated as two stochastic processes and injected into individual neurons in vitro through use of the dynamic-clamp system. Response gain was significantly modulated as a function of the statistical interactions between excitatory and inhibitory synaptic conductances. Firing rates were compared for noisy synaptic conductance steps by varying either the EI correlation or the relative delay between correlated E and I. When inhibitory synaptic conductances exhibited a short temporal delay (5 ms) relative to correlated excitatory synaptic conductances, the response gain was increased compared with noise with no temporal delay but with an equivalent degree of correlation. The dependence of neuronal firing rate on the EI delay of the noisy background synaptic conductance suggests that individual excitatory pyramidal neurons are sensitive to the EI balance of the synaptic conductance. Therefore the statistical EI interactions encoded within the synaptic subthreshold membrane fluctuations are able to modulate neuronal firing properties.

INTRODUCTION

Interactions of excitatory and inhibitory (EI) synaptic inputs are crucial for cortical circuit function. EI interactions have been shown to play a crucial role in regulating and establishing cortical receptive field properties (Borg-Graham et al. 1998; Connors et al. 1988; Douglas and Martin 2004; Douglas et al. 1991; Ferster and Jagadeesh 1992; Hirsch and Martinez 2006; Ozeki et al. 2009). Recent studies have suggested that EI balance, or the ratio of excitatory to inhibitory synaptic inputs, is one form of EI interaction that helps establish the intrinsic excitability of the cortex (Leger et al. 2005; Maffei et al. 2004; Trevelyan and Watkinson 2005; Xing and Gerstein 1996). It has been shown that correlated activity within the cortical network critically influences the response of individual neurons within the network (de la Rocha et al. 2007; Destexhe et al. 2001; Fellous et al. 2003; Nirenberg and Latham 2003; Pillow et al. 2008; Rauch et al. 2003). Besides the EI balance, other possible EI interactions exist within the cortical network that might regulate neuronal information processing such as the correlated firing and relative timing of excitation and inhibition. Such interactions have implications for neuronal process-

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ing where global network activity seems to modulate receptive field properties of individual neurons (Sceniak et al. 1999; Series et al. 2003).

Recent studies have shown that noisy background synaptic activity modulates the responsiveness of cortical neurons relative to a quiescent state (Chance et al. 2002; Fellous et al. 2003; Higgs et al. 2006; Mitchell and Silver 2003; Prescott and De Koninck 2003). Noisy background synaptic activity composed of excitatory and inhibitory synaptic conductances, simulated using the dynamic-clamp technique, have been shown to modulate response firing rate gain. Whether individual neurons are capable of detecting particular EI statistical interactions embedded within the noisy background signals has not been addressed previously.

A given excitatory pyramidal cortical neuron receives thousands of synaptic inputs from many neurons within the circuit (Douglas and Martin 1991, 2004; Thomson et al. 2002b). The pattern of activity converging on a given pyramidal neuron contains the sum of these synaptic inputs. Background synaptic activity can originate from either feed-forward or recurrent feedback drive from either excitatory or inhibitory neurons or a combination of these sources (Douglas and Martin 2004; Stepanyants et al. 2009). By simulating the pattern of activity converging on a given neuron, the interactions and statistics of excitatory and inhibitory synaptic conductance inputs can be controlled to determine their effects on firing rate. Such patterns of activity represent the relative correlation and synchrony of excitation and inhibition.

This study addresses to what extent the firing rate encoding of individual neurons is modulated by the EI interactions that define the background synaptic noise conductance. The EI interactions tested include the degree of correlation between excitation and inhibition and the relative temporal delay or phase between correlated excitation and inhibition. Using the dynamic-clamp system and a stochastic model to simulate in vivo-like synaptic conductances (Destexhe et al. 2001, 2003; Fellous et al. 2003), we were able to design particular synaptic conductance stimuli that isolated the effects of these particular EI interactions. Synaptic noise signals with identical mean, SD, and EI correlation were generated that differed in whether there was a relative delay between excitation and inhibition.

Understanding the effects of global network activity on the information processing of individual neurons is a necessary component to determining how network states contribute to perception and sensation (Fregnac 2003; de la Rocha et al. 2007; El Boustani et al. 2009). Classifying the population of synaptic inputs from the cortical network according to the statistical interactions between the excitatory and inhibitory synaptic inputs that make up the network allows us to deter-
mine the response modulation from network activity in a reduced model system. Given the complexity of cortical networks, this allows one to reduce the problem to manageable comparisons and more straightforward interpretations. Our results indicate that neurons are sensitive to these subtle statistical interactions between excitation and inhibition and need to be considered in models of cortical function.

**Methods**

All procedures and protocols used in this study adhere to published guidelines of the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee at Case Western Reserve University. Rat brain slices were cut from dissected visual cortex of young adult (28–32 days postnatal) Long-Evans rats (Charles River Laboratories, Wilmington, MA). Animals used for the data in Figs. 6 and 7 were 14–21 days old. Initially, rats were anesthetized with isoflurane (4%). The brain was dissected and temporarily (<30 s) placed in ice-cold (1–4°C) oxygenated (95% O2, 5% CO2) artificial cerebral spinal fluid (ACSF), composed of the following (in mM): 126 NaCl, 1 NaH2PO4, 25 NaHCO3, 25 dextrose, 3 KC1, 2 MgSO4, and 2 CaCl2. Brain slices were cut in ice-cold oxygenated ACSF into 350-µm slices and placed in a holding chamber with 30–35°C ACSF that gradually (<30 min) equilibrated to room temperature (25°C).

Brain slices were transferred from the holding chamber after 1–2 h and placed in a submersion-recording chamber with a heated water jacket (Warner Instruments, Hamden, CT). Slices were perfused with oxygenated 30–35°C gravity-fed ACSF (2–4 ml/min). ACSF temperature was maintained with a ThermoClamp-1 (Automate Scientific, CA) equipped with a water immersion objective (20X, with 2X after magnification) with near-infrared wavelength illumination, differential interference contrast optics (DIC), and a CCD camera (OLY-150, Olympus America) with contrast enhancement.

**Electrophysiology**

Membrane potentials and currents were collected using a Multi-clamp 700B patch clamp amplifier (Axon Instruments, Foster City, CA) and digitized with a Digidata 1440A analog to digital converter that was controlled by the pClamp 10.2 software package (Axon Instruments). Recording electrodes were filled with a K-glucurate–based internal solution composed of the following (in mM): 100 K-gluconate, 20 KCl, 10 HEPES, 4 Na-ATP, and 0.3 Na-GTP (pH 7.3 and 290–300 mOsm). Some experiments (Figs. 6 and 7) were performed with the following internal solution (in mM): 100 K-glucurate, 20 KC1, 10 phosphocreatine, 5 MgCl2, 10 HEPES, 4 Na-ATP, and 0.3 Na-GTP (pH 7.3 and 290–300 mOsm). Some experiments (Figs. 6 and 7) were performed with the following internal solution (in mM): 100 K-glucurate, 20 KC1, 10 phosphocreatine, 5 MgCl2, 10 HEPES, 4 Na-ATP, and 0.3 Na-GTP (pH 7.3 and 290–300 mOsm). Electrode resistance ranged from 4 to 8 MΩ, and whole cell patch recordings were made with seal resistances of 1–3 GΩ. Successful whole cell recordings had resting membrane potentials of ~57 mV or more negative. Average electrode series resistance ranged from 10 to 30 MΩ after whole cell patching. Recordings with seals <1 GΩ or resting potentials greater than ~57 mV were not included in the analysis.

Excitatory pyramidal neurons were selected from within rat primary visual cortical layer 5. Pyramidal neurons were selected to establish the most homogeneous population possible. Pyramidal neurons were selected initially based on spiking and intrinsic electrical membrane properties and confirmed through histological reconstructions using biocytin fills (Sceniak and Maciver 2006, 2008).

**Dynamic clamp**

Conduction injection was accomplished through use of a computer-based dynamic-clamp system. The computer contained an Intel-based motherboard running the real-time Linux operating system (RTAI, www.rtai.org), with an open source data acquisition hardware driver (COMEDI, www.comedi.org) and open source dynamic-clamp software (RTXI; Dorval et al. 2001). Data acquisition and control was accomplished through a National Instruments data acquisition board (PCI-6251, Austin, TX) and interface breakout box (BNC-2090, National Instruments). The dynamic-clamp system sampled voltage measurements at 15 kHz. The computer used for the dynamic-clamp system contained a dual microprocessor-based motherboard (Intel, Core 2 Duo, Santa Clara, CA) running at 2.53 GHz. Stimuli were constructed and delivered via custom written RTXI modules according to the equations described below.

**Point conductance model**

The synaptic conductance injected into the soma of each cell was generated from the point conductance model to simulate noisy background synaptic activity (Destexhe et al. 2001, 2003; Fellous et al. 2003). Excitatory and inhibitory synaptic conductances were combined by Ohm’s law and Kirchhoff’s current law to produce a total synaptic current to drive individual neurons to produce action potentials (Fig. 1). The total synaptic current, I_syn, was calculated in real time from the instantaneous membrane potential measure, V_m, and the time dependent excitatory, g_e(t), and inhibitory, g_i(t) synaptic conductances

\[
I_{\text{syn}} = g_e(t)(V_m - E_e) + g_i(t)(V_m - E_i)
\]

The reversal potential for glutamatergic excitation and GABAergic inhibition were \(E_e = 0 \text{ mV}\) and \(E_i = -75 \text{ mV}\), respectively (Fig. 1), consistent with previous reports (Chance et al. 2002; Fellous et al. 2003).

The excitatory and inhibitory conductances used to simulate noisy background synaptic activity were defined by two stochastic processes based on the Ornstein-Uhlenbeck process originally introduced to describe Brownian motion (Destexhe et al. 2001). The time-dependent equations for these two processes for excitation, \(g_e(t)\), and inhibition, \(g_i(t)\), were as follows

\[
\frac{dg_e(t)}{dt} = \frac{1}{\tau_e}[g_e(t) - g_{e0}] + \sqrt{D_e} \xi_e(t)
\]

\[
\frac{dg_i(t)}{dt} = \frac{1}{\tau_i}[g_i(t) - g_{i0}] + \sqrt{D_i} \xi_i(t)
\]

The stochastic processes for excitation and inhibition were defined by the mean conductances, \(g_{e0}\) and \(g_{i0}\), the time constants, \(\tau_e\) and \(\tau_i\), and the noise diffusion coefficients, \(D_e\) and \(D_i\). The stochastic process for excitation and inhibition also contained a Gaussian white noise random variable, \(\xi_e(t)\) and \(\xi_i(t)\), respectively, each with zero mean and unit SD. The SD of these stochastic processes is known analytically (Destexhe et al. 2001; Gillespie 1996)

\[
\sigma^2 = \frac{D\tau}{2}
\]

Throughout all experiments, the SD of excitation, \(\sigma_e\), and inhibition, \(\sigma_i\), were matched (\(\sigma_e = \sigma_i\)). The inhibitory mean, \(\mu_i\), was greater than \(\mu_e\). The time constants for excitation, \(\tau_e\), and inhibition, \(\tau_i\), were 2.7 and 10.5 ms, respectively. The mean excitatory conductance, \(\mu_e\), and the excitatory diffusion coefficient, \(D_e\), were varied during the experiments to elicit action potential discharge (Fig. 1). These parameters (\(\mu_e\), \(\sigma_e\), and \(\sigma_i\)) were optimized for each cell to achieve a range of firing rates.

The degree of correlation between the stochastic processes for excitation and inhibition was defined by taking the matrix product of a Gaussian random number, \(\chi_e(t)\) and the Cholesky factorization (C = LL^T) of the correlation matrix, X. The correlation matrix for generating two noise signals with a correlation of 0.5 is given by
Therefore a new random variable, \( \chi(t) \), was generated with a defined degree of correlation between excitation and inhibition

\[
X = \begin{bmatrix} 1 & 0.5 \\ 0.5 & 1 \end{bmatrix}
\]

(4)

Therefore a new random variable, \( \chi(t) \), was generated with a defined degree of correlation between excitation and inhibition.
predictor correlation (pdc) is the degree of correlation before a time shift. The time shift decreases the correlation (at time = 0) in a manner that depends on Δτ; larger delays decrease the correlation more than smaller delays. Therefore the new EI correlation was calculated for excitatory and inhibitory conductances, g_x(t) and g_i(t), after the imposed time shift. This calculation yields the correlation with an EI delay (see RESULTS and Fig. 1) and permits comparison to unshifted input conductances (i.e., EI synaptic conductances with no delay).

Data analysis

All data analyses were performed using custom-written functions in Matlab R2009a (The Mathworks, Natick, MA) and functions written in C++ under Linux. All statistics are expressed as the median unless otherwise stated. Statistical significance was determined using the Wilcoxon signed rank sum test and analysis of covariance (ANCOVA) where appropriate. Time-locked voltage responses were analyzed to determine spike rates correlated to their corresponding conductance injections. Spikes were analyzed off-line by determining voltage deflections above a threshold (>-10 mV). The correlation, cross-correlation, autocorrelation, and power spectra were calculated using Matlab functions.

Sigmoid, Michaelis-Menten, functions were fitted to the firing rate responses, using nonlinear constrained optimization (fmincon, Matlab function). For response functions where there was a response decrease with an increase in the sampled parameter, x (normalized correlation), or an increase in the sampled parameter, y (conductance), the following sigmoid functions were used

\[ R(x) = R_{\text{max}} - R_{\text{max}} \frac{x^n}{(x^n + c_{50}^n)} + b \]

and

\[ R(y) = R_{\text{max}} \frac{y^n}{(y^n + c_{50}^n)} + b \]

respectively. The parameters \( R_{\text{max}}, n, b, \) and \( c_{50} \) represent the maximal firing rate, acceleration rate exponent, response offset rate, and the value of \( x \) or \( y \) that produces one half the maximal response, respectively. The offset, \( b \), was set to the spontaneous firing rate (0 in all cases). The maximal response, \( R_{\text{max}} \), was constrained to within ±50% of the empirical maximum response. The half-saturation value, \( c_{50} \), was constrained to the maximum of the sampled parameters, \( x \). The acceleration exponent, \( n \), was constrained to be between 0.1 and 10. The slope of the sigmoid function was calculated as the first derivative of the sigmoid function evaluated at the half-maximal value, \( c_{50} \), or

\[ \text{slope} = \frac{R_n}{4c_{50}} \]

Conductance-based model neuron

Neuron model simulations were performed using the Matlab software package (Mathworks, Natick, MA). Differential equations for the Hodgkin-Huxley–like model were solved numerically using fourth-order Runge-Kutta. The differential equations were solved for each time step (0.01 ms, 100 kHz) for 2 s of total time. The differential equation used to describe the neuron total current was as follows

\[ C_m \frac{dV_m}{dt} = I_{\text{syn}} - g_{\text{leak}}(V_m - E_{\text{leak}}) - I_{Na} - I_K - I_M - I_A - I_L - I_{NaP} \]

where the membrane capacitance, \( C_m \), the leak conductance, \( g_{\text{leak}} \), the leak reversal potential, \( E_{\text{leak}} \), the synaptic current \( I_{\text{syn}} \), was defined by

\[ I_{\text{syn}} = -g_{\text{syn}}(V_m - E_{\text{e}}) - g_{\text{syn}}(V_m - E_{i}) \]

where the excitatory, \( g_{\text{e}} \), and inhibitory, \( g_{\text{i}} \), conductances were defined by the point conductance model described above with excitatory synaptic reversal potential, \( E_{\text{e}} = 0 \) mV and inhibitory synaptic equilibrium potential, \( E_{\text{i}} = -80 \) mV. The \( Na^+ \) and \( K^+ \) reversal potentials were calculated through the Nernst equation, where the internal and external concentrations for \( Na^+ \) and \( K^+ \) were (in mM) 20, 150, 100, and 6, respectively, and the temperature was equal to 30°C.

Action potentials

The spike \( Na^+ \) and \( K^+ \) currents were defined as

\[ I_{Na} = \overline{g}_{Na}(V_m - E_{Na}) \cdot m^3 \cdot h_{Na} \]

\[ I_{K} = \overline{g}_{K}(V_m - E_{K}) \cdot m^4 \]

where the maximal conductance \( \overline{g}_{Na} = 50 \mu S \), sodium reversal \( E_{Na} = 50 \) mV, \( \overline{g}_{K} = 5 \mu S \), and \( E_{K} = -72 \) mV. The activation and inactivation dynamics were modeled as first order processes, where

\[ \tau_m(V_m) \frac{dm}{dt} = m_{\text{a}}(V_m) - m \]

and

\[ \tau_h(V_m) \frac{dh}{dt} = h_{\text{a}}(V_m) - h \]

The steady-state activation (\( m_a \)) and inactivation (\( h_a \)) equations and the time constants, \( \tau_m \) and \( \tau_h \), were defined by Winograd et al. (2008).

Spike-frequency adaptation

The spike-frequency adaptation current \( I_{M} \) was defined as

\[ I_{M} = \overline{g}_{M} \cdot p \cdot (V_m - E_{K}) \]

where

\[ \frac{dp}{dt} = (p_{m} - p) / \tau_p(V_m) \]

with \( \overline{g}_{M} = 0.13 \mu S \). The steady-state activation (\( p_{m} \)) equation for the \( I_{M} \) current and the time constant, \( \tau_p(\tau_{p,m} = 1.1 \) s), were defined by Winograd et al. (2008).

The Connors-Stevens current \( I_A \) was defined as follows

\[ I_A = \overline{g}_{A} \cdot m^3 \cdot h \cdot (V_m - E_A) \]

where \( \overline{g}_{A} = 0.5 \mu S \), and the activation and inactivation dynamics were modeled as first-order processes as described above (Eqs. 13 and 14), using the steady-state activation (\( m_a \)) and inactivation (\( h_a \)) equations defined by Dayan and Abbott (2005).

Hyperpolarization-activated current

The hyperpolarization-activated cationic current \( I_{H} \) was defined as follows

\[ I_{H} = \overline{g}_{H} \cdot m \cdot (V_m - E_{H}) \]

where \( \overline{g}_{H} = 0.03 \mu S \) and \( E_{H} = -43 \) mV. The activation dynamics were modeled as first-order processes as above (Eq. 13) using the steady-state (\( m_a \)) equation defined by Huguenard and McCormick (1992). Persistent sodium conductance

\[ I_{NaP} = \overline{g}_{NaP} \cdot m \cdot h \cdot (V_m - E_{Na}) \]

where \( \overline{g}_{NaP} = 1.1 \mu S \) and \( E_{Na} \) was defined as above. The activation dynamics were modeled as above (Eq. 13) and the steady-state (\( m_a \) and \( h_a \)) equations were as defined by Wu et al. (2005).
RESULTS

Construction of in vivo–like synaptic noise barrages with defined statistical properties

To determine the extent to which EI synaptic interactions modulate neuronal response output, we studied neuronal firing rate output in excitatory cortical pyramidal neurons as a function of the statistical interaction between excitatory and inhibitory synaptic inputs, using a dynamic-clamp system (Fig. 1). Noisy synaptic conductances for excitation and inhibition were generated based on the Ornstein-Uhlenbeck (O-U) stochastic point conductance model (see METHODS).

In vivo, neurons receive a variety of inputs from both excitatory and inhibitory neurons, and the correlation between these inputs depends on the circuitry. Correlations are sensitive to both the synchrony and the timing of the inputs. Therefore, we examined how neurons respond to correlations between excitatory and inhibitory synaptic conductances using two approaches to vary correlation between E and I. Correlations caused by synchrony of E and I can be simulated using Cholesky factorization to empirically define the degree of correlation (see METHODS). Using this approach, synaptic noise signals were generated that ranged from conditions where excitatory and inhibitory synaptic conductances were completely uncorrelated (corr = 0.0, data not shown) to conditions where excitation and inhibition were completely correlated (corr = 1.0; Fig. 1A). Figure 1B shows an intermediate level of correlation between excitation and inhibition (corr = 0.5).

To simulate correlations between excitation and inhibition that depend on the relative timing of E and I, correlated excitatory and inhibitory conductance arrays were time shifted relative to each other to produce a given temporal delay (EI delay; Fig. 1C). In all cases, excitatory and inhibitory noise used to produce synaptic noise with an EI delay were initially generated with a correlation of 1.0 before time shifting the inhibitory noise array to produce the EI delay. We refer to this initial correlation as the predelay correlation (pdc = 1.0). The delay causes the correlation between E and I to be reduced (Fig. 1C). EI delays ranged from 0 to 200 ms. With the exception of Fig. 1, D and E, inhibition always followed excitation. For conditions where excitation and inhibition were correlated (Fig. 1B) or correlated with an EI delay (Fig. 1C), the means and SD of the synaptic conductances were held constant across conditions. This allowed us to isolate the effects of correlation and temporal-delay on firing rate responsiveness independent of EI input statistics.

To directly compare firing rate responses for noise that is systematically varied in EI correlation with no EI delay (e.g., as in Fig. 1, A and B) to noise with a fixed correlation but with a varying EI delay (e.g., as in Fig. 1C), it is necessary to match the responses for actual correlation. For a given temporal delay between excitatory and inhibitory synaptic conductances, there is a corresponding correlation measure that depends on the magnitude of the delay (Fig. 1D): increasing the EI delay decreases the degree of correlation. To determine the degree of EI correlation in the presence of the EI delay, the cross-correlation of the noise conductances (20 kHz, 2 s; pdc = 1.0) was calculated at a range of EI delays. These EI delays appear as a horizontal shift in the cross-correlation peak (Fig. 1C, bottom). The correlation for each EI delay corresponds to the cross-correlation of the two time-shifted signals at time = 0 (Fig. 1, A–C).

To create a transformation from EI delay to correlation, correlation was plotted as a function of EI delay (gray curve, Fig. 1D). The average delay versus correlation function was estimated as the mean correlation for 20 repeats (black curve, Fig. 1D). Fitting separate exponential functions (dashed curve, Fig. 1E and F) to the average correlation values (solid black curve, Fig. 1D) as a function of negative EI delays (inhibition before excitation, Fig. 1E) and positive EI delays (inhibition after excitation, Fig. 1F) provided a complete description of the transformation from EI delay to correlation. This transformation could be used to determine the correlation of any two noise signals (pdc = 1.0) that contained an EI delay. For example, a 5-ms EI delay between excitatory and inhibitory noise signals yields a correlation of 0.5 (with inhibition following excitation). The values obtained from this transformation then allowed direct comparison of neuronal spike rate responses for two different noise signals with equivalent correlations defined by either 1) EI delay or 2) Cholesky factorization without an EI delay.

Effects of EI correlation and timing on neuronal firing rates

To determine whether neurons can detect the EI noise balance statistics between the stimuli constructed as described above, synaptic noise signals were generated and introduced into pyramidal neurons in layer 5 of visual cortical slices using the dynamic-clamp technique, and the resulting neuronal spiking responses were recorded. For a given noise conductance step composed of a combination of excitation and inhibition, conditions where excitation and inhibition were correlated by varying degrees (corr = 0–1) were compared with conditions where excitation and inhibition were completely correlated (pdc = 1.0) but were offset by an EI delay (delay = 0–50 ms) such that inhibition lagged excitation (Fig. 2). The mean and SD of excitation and inhibition were optimized for each recorded neuron to produce a moderate firing rate (7–30 Hz) when excitation and inhibition were uncorrelated with no time delay (corr = 0.0). Each conductance step (2 s, 15-kHz sample rate) was repeated two times, and the firing rates were averaged. Representative mean firing rate responses are shown for three neurons (Fig. 2). Firing rate responses showed a clear dependence on both EI correlation (Fig. 2, A1–A3) and EI temporal delay (Fig. 2, B1–B3). Response rates were consistently reduced when E and I noise conductances were correlated and contained little temporal delay. Similar dependence on EI correlation and response enhancement for noise containing an EI delay were observed when intracellular calcium was buffered with EGTA in the patch pipette (Supplementary Fig. S1).

To directly compare firing rates for noise steps with and without EI delays, the degree of EI correlation was estimated for EI noise with a temporal delay using the exponential fits of correlation shown in Fig. 1F. Neuronal mean firing rate responses for noise with correlations defined by EI delay were plotted as a function of correlation (Fig. 2, C1–C3, black). For comparison, spiking responses for noise with equivalent EI correlations but no delay (gray) were overlaid on the delay

1 The online version of this article contains supplemental data.
plots (Fig. 2, C1–C3, gray). The change in mean firing rate response as a function of correlation was steeper for noise containing an EI delay and elevated for small EI temporal delay values (<10 ms; Fig. 2, C1–C3). Thus in the presence of an EI delay, the response gain was increased at high EI correlations, and responses saturated and stabilized at a high firing rate over a wide range of low EI correlations. In contrast, in the absence of EI delay, responses appeared more linear over the entire range of EI correlations.

Firing rate response curves were fitted with empirical functions. Fits for the same three neurons as shown in Fig. 2 are shown in Fig. 3, A1–A3. For EI noise with a temporal delay, firing rate responses as a function of EI correlation were sigmoid shaped and fitted with a sigmoidal, Michaelis-Menten equation (black curves, Fig. 3, A1–A3). However, firing rate responses as a function of EI correlation without an EI temporal delay were well fit by a linear regression (gray curves, Fig. 3, A1–A3). To make statistical comparisons across the population, parameters were extracted from the fits. For delay data, the maximum response, linear region ($c_{50}$), and slope of the response function in the linear region were estimated from the sigmoidal fits (see Methods). For EI noise responses without a temporal delay, comparable measures were extracted from the linear fits.

Across the population of recorded neurons ($n = 29$), the parameters of the sigmoid fits to the response versus EI delay noise steps were compared with the linear fits of the response versus no EI delay steps (Fig. 4). Although the no delay EI steps produced responses that were linear over the range of EI correlations tested, the EI delay responses displayed responses that were linear only near the higher EI correlation values (median $c_{50} = 0.79$; Fig. 4A). For very low correlation EI noise (corr = 0.1), the firing rate responses to EI noise with a temporal delay and without an EI delay (Fig. 4, B and C) were not significantly different ($r^2 = 0.97$, median response % difference (delay – no delay) = 2.9, $P > 0.05$, Wilcoxon rank sum test). For EI noise steps with moderately correlated EI noise (corr = 0.75; Fig. 4, D and E), firing rate responses were significantly greater ($r^2 = 0.97$, median response % difference (delay – no delay) = 17.5, $P = 2.8 \times 10^{-6}$, Wilcoxon rank sum test), across the population, for EI noise steps with a temporal delay than with no delay. Therefore on average, response enhancement resulting from EI temporal delay tends to occur from correlated noise (corr = 0.75) rather than essentially uncorrelated noise (corr = 0.1), and the responses are not significantly different for very low correlation EI noise.

The slope of the response versus correlation tuning curves was compared for EI noise with an EI temporal delay (estimated at the $c_{50}$ value, or linear region, for sigmoid fits, see Methods) to EI noise steps with no delay (linear fits; Fig. 4, F and G). On average, the slopes were uncorrelated ($r^2 = 0.53$) and significantly greater for EI noise steps with a temporal delay [median slope % difference (delay – no delay) = −61.6, $P = 38 \times 10^{-6}$, Wilcoxon rank sum test]. Overall, there is much greater sensitivity (spike rate per corr, slope) to change in EI delay than with no delay. Therefore on average, the slopes were uncorrelated ($r^2 = 0.53$) and significantly greater for EI noise steps with a temporal delay [median slope % difference (delay – no delay) = −61.6, $P = 38 \times 10^{-6}$, Wilcoxon rank sum test]. Overall, there is much greater sensitivity (spike rate per corr, slope) to change in EI delay than with no delay.
in firing rate as a function of EI correlation when an EI temporal delay is present.

The extent to which the SD of the dynamic clamp command current, $I_{\text{syn}}$, might be responsible for differences in the firing rate observed with and without an EI temporal delay was also examined (Figs. 3, B1–B3, and 5). To test this, firing rate responses for stimuli with and without an EI temporal delay were plotted versus the SD of the current injected into each neuron from the combined E and I conductances ($I_{\text{syn}}$, see METHODS; Fig. 3, B1–B3). Responses for representative neurons are shown next to their corresponding firing rate versus correlation curves (Fig. 3, right and left columns, respectively). The mean firing rates for EI noise with a delay (black, Fig. 3, B1–B3) were consistently greater compared with responses for stimuli with no EI delay (gray, Fig. 3, B1–B3), even for matched $I_{\text{syn}}$ SD. To make statistical comparisons across the population of neurons, firing rates as a function of the SD of $I_{\text{syn}}$ were fitted with sigmoidal functions (Fig. 3, B1-B3). Responses resulting from conductance steps with no EI temporal delay (gray curve) were well fit with a linear regression. EI delay noise steps were fitted with sigmoidal functions (black curve). B1–B3: firing rate responses are shown as a function of the SD of the dynamic clamp command current, $I_{\text{syn}}$, for noise steps with a temporal delay (black) and without an EI temporal delay (gray) next to the corresponding response vs. correlation plots. Gray line is the linear regression of the response vs. $I_{\text{syn}}$ SD for the no EI delay condition.

**Effects of EI balance on neuronal firing rates**

To determine the effects of synaptic EI noise statistics across a range of EI balances (defined as the ratio of mean excitation to inhibition, $\mu_e/\mu_i$), we sampled a range of excitatory mean conductances, $\mu_e$, for a given excitatory SD, $\sigma_e$, and a fixed level of mean inhibition, $\mu_i$, with SD, $\sigma_i$ (3 repeats of each excitatory mean conductance amplitude; 1-s step at 15 kHz). The response gain function (spike rate vs. mean excitatory conductance) was estimated for conductance steps with no noise ($\sigma_e = 0$ nS, $\mu_e = 15$ nS, $\mu_i = 0$ nS), noise with a defined correlation between excitation and inhibition (corr = 0.5, delay = 0 ms; $\sigma_e = 15$ nS, $\mu_e = 15$ nS, $\sigma_i = 15$ nS) and noise ($\sigma_e = 15$ nS, $\mu_e = 15$ nS, $\sigma_i = 15$ nS) with an EI delay (delay = 5 ms, corr = 0.5; Fig. 6, A and B). The correlations of the two random processes were identical (corr = 0.5; see Fig. 1D).

Conductance steps with noise that contained an EI delay (○) and with no EI delay (●) were compared with conductance steps (with the same mean conductance) with no noise (Fig. 6, C–F). Response functions resulting from conductance steps...
with EI noise regardless of the presence of an EI delay (dashed and gray, Fig. 6, A and B) were shifted to the left and yielded higher firing rates for the same mean conductance compared with conductance steps with no noise (black curve, Fig. 6, A and B). Across the population (n = 11; Fig. 5C), there was a significant increase in responsiveness for noise steps both with no EI delay and with an EI delay [median $R_{\text{max}}$ % change (noise – no noise) = 7 and 14%; $P = 0.005$ and $P = 0.005$, Wilcoxon signed rank sum test, respectively]. For noise conductance steps with an EI delay, there was a significant leftward shift of the response versus conductance function [median $c_{50}$ % change (noise – no noise) = −10%; $P = 0.04$, Wilcoxon signed rank sum test] and an increase in the slope [median slope % change (noise – no noise) = 8%; $P = 0.01$, Wilcoxon signed rank sum test] compared with noiseless conductance steps (Fig. 6, D and F).

Synaptic noise composed of correlated excitation and inhibition with an EI delay (delay = 5 ms, corr = 0.5) was compared with correlated noise with no EI delay (corr = 0.5, delay = 0 ms; Figs. 6, A and B). Across the population ($n = 29$), there was a significant leftward shift of the response vs. EI correlation slopes (Fig. 6, B and C) compared with noiseless correlation (median slope % difference (delay – no delay) = 2.9). Vertical arrow indicates the median in B, D, and E. Fitted response estimates are shown for high EI correlation (corr = 0.75). The mean firing rates with and without delay are correlated ($r^2 = 0.97$), and responses are significantly greater ($P = 2.8 \times 10^{-6}$, Wilcoxon rank sum test) for noise steps with an EI temporal delay [median response % difference (delay – no delay) = 17.5]. For scatter plots in B, D, and E: the mean firing rate responses are shown as spikes/s. F and G: the response vs. EI noise correlation slopes are shown for noise input with an EI temporal delay vs. no EI delay. The response slopes were estimated from the sigmoid fits and linear regressions, respectively. On average, the response vs. EI correlation slopes were significantly less ($P = 3 \times 10^{-6}$; Wilcoxon rank sum test) for noise steps lacking an EI delay [median slope % difference (delay – no delay) = −61.6] and were not significantly correlated ($r^2 = 0.53$).
Synaptic noise in a Hodgkin-Huxley–like model neuron

To study whether the effects of EI interactions described above can be accounted for by spike currents and/or slow spike-frequency adaptation currents, the responses to background synaptic noise were examined using a conductance-based, Hodgkin-Huxley–like model neuron (see Methods and Fig. 8). As with the dynamic-clamp recordings, the noisy synaptic conductances for excitation and inhibition were generated using the stochastic O-U model (see Methods). The model neuron contained Na\(^{+}\) and K\(^{+}\) action potential conductances, a leak conductance, spike frequency adaptation conductances (\(I_{M}\) and \(I_{A}\)), the hyperpolarization-activated conductance (\(I_{P}\)), and a persistent sodium conductance (\(I_{NAP}\)), with conductance values chosen from estimates of cortical pyramidal neurons in the literature (see Methods).

Analogous to the patch-clamp experiments, the firing rate of the conductance-based model neuron was quantified for conductance steps where excitatory and inhibitory synaptic conductances were correlated by varying degrees (corr = 0.0–1.0; Fig. 8A) to conductance steps where excitatory and inhibitory synaptic conductances were correlated (pdc = 1.0) but contained varying degrees of EI delay (0–200 ms, inhibition follows excitation; Fig. 8B). The correlation of EI noise steps containing an EI delay was estimated as described above in Fig. 1, D and F, and mean firing rates were plotted as a function of correlation. Firing rate responses resulting from stimulation with noise steps with an EI temporal delay were enhanced (black points, Fig. 8C) for moderately correlated noise (corr = 0.4–0.6) compared with noise with no EI delay (gray points, Fig. 8C).

Next, the data were fitted as described above for neuronal recordings. The response as a function of correlation was linear for noise with no EI delay (gray curve, Fig. 8C) and saturating for noise with an EI delay (black curve, Fig. 8C), similar to that observed from neuronal recordings. However, when the firing rate was plotted as a function of command current, \(I_{syn}\) SD, the response enhancement was no longer observed (Fig. 8D). The linear regression fits of firing rate versus the SD of \(I_{syn}\) were statistically identical (\(P \approx 0.05\), ANCOVA). Therefore unlike the neuronal recordings, the difference in response between noise steps with an EI delay and with no delay can be accounted for by differences in the SD of the synaptic current that result from the summed EI conductances. These modeled conductances are therefore insufficient to account for the observed firing rate properties in the presence of delayed inhibition. These results suggest that there are at least two mechanisms that contribute to neuronal responses to correlated E-I noise with a delay: one mechanism that is sensitive to the SD of the synaptic currents and
can be generated by activation of conductances present in the model and a second mechanism that depends on additional channels or properties.

**DISCUSSION**

Previous studies have shown that barrages of synaptic activity shape the time constants and integrative properties of neocortical neurons (Borg-Graham et al. 1998; Destexhe et al. 2003; Leger et al. 2005; Shu et al. 2003; Wehr and Zador 2003; Zsiros and Hestrin 2005). The effects of barrages of synaptic conductances have been observed both in vitro and in response to visual stimulation in vivo (Destexhe et al. 2003; Douglas and Martin 2004; Leger et al. 2005; Shu et al. 2003). Therefore subthreshold synaptic conductances play a crucial nonlinear role in synaptic integration and in shaping network behavior by affecting response properties of individual neurons.

Diverse effects have been reported for the modulation of firing rate from the combination of DC steps and noisy background synaptic input conductances delivered through the dynamic-clamp system. Some have reported a divisive effect from background synaptic noise (Chance et al. 2002; Mitchell and Silver 2003; Prescott and De Koninck 2003), whereas others have shown either a multiplicative effect or a mixture of effects across cell types (Higgs et al. 2006; Murphy and Miller 2003). Barrages of synaptic activity as seen in vivo would induce conductance changes without additional DC current steps (Graham and Schramm 2009). Therefore we measured the response gain resulting from noisy conductance steps without an additional DC step to simulate biologically realistic synaptic stimulation. We found that noise has a multiplicative rather than divisive effect on response gain, consistent with observations by Higgs et al. (2006) from neocortical pyramidal cells in vitro, as well as model results (Murphy and Miller 2003).

**FIG. 6.** Noise modulates the response gain as a function of the statistical balance between excitation and inhibition. A and B: the firing rate (Hz) response as a function of injected conductance mean is shown for 2 representative neurons. Black curves indicate conductance steps with no noise. Gray curves indicate conductance steps with the same mean conductance as the corresponding black curve with the addition of a synaptic noise ($\sigma_e = 15$ nS, $\sigma_i = 15$ nS, $\mu_e = 15$ nS, $\mu_i =$ conductance step) composed of excitatory and inhibitory conductances with correlation of 0.5 and no EI delay. Dashed curves indicate response functions with mean conductance equal to the corresponding black curve with the addition of a synaptic noise ($\sigma_e = 15$ nS, $\sigma_i = 15$ nS, $\mu_e = 15$ nS, and $\mu_i =$ conductance step) composed of excitatory and inhibitory synaptic conductances with a correlation of 0.5 (pdc = 1.0, delay = 5 ms; Fig. 1). C–F: across the population ($n = 11$), synaptic noise increased the firing rate responsiveness. Individual function fitted parameters (see METHODS), $R_{\text{max}}$, $n$, and $c_{50}$, and the calculated slope were compared for conductance injection steps with noise vs. no noise. Open circles represent parameter estimates from response curves with no noise compared with conductance steps with synaptic noise composed of EI conductances with an EI delay (5 ms) and a correlation of 0.5. Solid points represent estimates from response curves with no noise compared with conductance steps with synaptic noise composed of EI conductances with no EI delay and a correlation of 0.5.
The results presented here showed that the firing rates of individual excitatory pyramidal cortical neurons are modulated by the statistical properties of the synaptic noise conductance that they receive. Specifically, individual neurons showed response gain enhancement for synaptic noise conductance steps where inhibition was delayed relative to excitation for correlated O-U processes compared with noisy conductance steps where excitation and inhibition have a comparable degree of correlation but lacked an EI delay. Comparing firing rate as a function of EI delay indicated that such responsiveness enhancement occurs when correlated (\(\text{corr} = 0.5\)) inhibition follows excitation within the range of 1–10 ms. These temporal delays are consistent with EI temporal interactions as short as a single monosynaptic delay. Such delays might result from either feed-forward inhibition or recurrent lateral interactions and have been observed during spontaneous activity (Douglas and Martin 2004; Okun and Lampl 2008; Thomson et al. 2002a).

Firing rate responses to noise steps with an EI delay showed enhanced firing rates relative to no EI delay even when plotted as a function of the SD of the dynamic clamp command, \(I_{\text{syn}}\). Firing rate as a function of \(I_{\text{syn}}\) SD was linear over the range of

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**FIG. 7.** Population analysis of modulation of response gain by EI balance noise statistics. Correlated excitation and inhibition that contained a temporal delay (inhibition lagging excitation) had a greater effect of increasing response gain than noise with an equivalent correlation (\(\text{corr} = 0.5\)), which lacked a temporal delay. Individual sigmoid function fitted parameters (see METHODS), \(R_{\text{max}}, n,\) and \(c_{50}\) and the calculated slope were compared. Parameters for response rate vs. injected mean conductance curves for cases where the injected conductance contained synaptic noise defined by correlated excitatory and inhibitory synaptic conductances with a temporal delay (delay = 5 ms, \(\text{corr} = 0.5\)) to those with an equivalent correlation (\(\text{corr} = 0.5\)) and no temporal delay. Vertical arrow indicates parameter median. Response slope and maximal response, \(R_{\text{max}},\) showed significantly greater values for conditions where there is a temporal delay compared with no delay (\(P = 0.02\) and 0.014, respectively, Wilcoxon signed rank sum test).
FIG. 8. Effects of synaptic noise in a conductance-based model simulation. A–C: firing rate responses are shown as a function of the EI correlation for noise conductance steps. Responses were averaged over 10 repeats. Firing rate is shown as a function of the EI correlation (A) and as a function of EI temporal delay (B). C: the firing rate responses for EI noise with a temporal delay (black points) are elevated relative to responses with no EI temporal delay (gray points). The solid black and gray curves represent sigmoid and linear fits to the data, respectively. D: the firing rate response from C is shown plotted as a function of the SD of the model current drive, Isyn. Unlike the neuron recordings, both the responses from the noise steps with a temporal delay (black points) and with no delay (gray points) are well fit by the same linear regression (ANCOVA).

EI correlations (0–1), whereas the same relation was not well fit by a linear regression when an EI temporal delay was present. The slope of the linear regression for the response versus Isyn SD was also not correlated between the delay and no delay step responses. Therefore the firing rate response enhancement resulting from the presence of an EI temporal delay was not explained by the command current, Isyn SD.

Near spike threshold for these neurons (approximately −40 mV), the combined EI synaptic noise current \( I_{syn} = g_e(V_m - E_e) - g_i(V_m - E_i) \) used in our study shows distinct properties of the autocorrelation function (Supplementary Fig. S2A) and power spectrum (Supplementary Fig. S2B) for noise with an EI delay (5 ms, black traces) compared with no EI delay (gray traces). The power spectrum of the combined EI noise indicated that high-frequency oscillations were present when an EI delay was present (Supplementary Fig. S2B). Previous reports have shown that neurons are able to track transients \( \lesssim 200 \) Hz with no attenuation, well above that predicted from the cut-off from passive membrane properties (Kondgen et al. 2008). Therefore it is possible that such oscillations were responsible for the response gain enhancement observed with noise containing an EI delay. The oscillation frequencies were within the range of cortical oscillations induced by cortical network activity observed in vivo (Fries et al. 2007).

The statistical interactions between excitation and inhibition used to define the fluctuating synaptic conductances in our study correspond to biologically realistic circuitry. We used the O-U model to simulate the summed activity of a barrage of either glutamatergic or GABAergic synaptic inputs. The correlation between the excitatory and inhibitory inputs simulated the circuitry behind the converging synaptic inputs of a given recorded neuron. Uncorrelated EI synaptic noise would correspond to independent excitation and inhibition, whereas correlated EI noise would correspond to circuitry with a common input for excitation and inhibition (Fig. 9). EI noise with delayed inhibition could result from disynaptic (or polysynaptic) inhibition from a common input source. Such canonical circuits have been described for neocortical pyramidal neurons and therefore reflect realistic and plausible synaptic drive (Douglas and Martin 2004; Ferster and Miller 2000; Wehr and Zador 2003).

Cortical responses in vivo are driven by dynamic changes in the balance of excitation to inhibition. In vivo whole cell recordings of visually evoked activity have shown that the ratio of excitation to inhibition depends on the visual stimulus and the level of network activity (Azouz and Gray 2008; Monier et al. 2008). Stimulus selective spiking arises through changes in the EI balance, relative timing, and degree of synchrony for optimal and nonoptimal stimuli (Anderson et al. 2001; Azouz and Gray 2008; Borg-Graham et al. 1998; Monier et al. 2008). Although it is well established that the relative strength and timing of E and I vary during visual stimulation, it is not clear how EI timing and synchrony control the firing rates. Spatially extended visual stimuli induce a reduction in spike rates.
through surround suppression (Anderson et al. 2001; Sceniak et al. 1999). This spike rate reduction results from a concomitant increase in synaptically driven inhibition and decrease in excitation (Anderson et al. 2001). During spontaneous high-conductance UP-states in vivo, it has also been shown that the balance of excitation to inhibition varies throughout the UP state (Haider et al. 2006; Rudolph et al. 2007).

Not only is the excitatory to inhibitory balance dynamically modulated by stimulus drive, the history of this activity alters the circuit through plasticity. For example, the balance between excitation and inhibition is dynamically shifted by differential sensitivity of excitation and inhibition to synaptic depression, adaptation, and homeostatic plasticity (Heiss et al. 2008; Maffei et al. 2006; Varela et al. 1999). In addition, plasticity could alter the relative EI timing and correlation through activity-dependent changes in local circuitry. In somatosensory cortex, trains of stimuli induce adaption of feedforward connections from the thalamus but do not alter intracortical synaptic responses (Chung et al. 2002). In other experiments, it has been shown that, although depression of EPSCs in feedforward and feedback pathways within the cortex exhibit similar dependencies on the frequency of stimulation, inhibitory synapses from feedback pathways are more depressed than those from feedforward pathways when stimulated at high frequencies (Dong et al. 2004).

Our results indicate that an EI noise temporal delay modulates response gain for a single excitatory pyramidal neuron. More complex models will need to be tested that take into account the spatial arrangement of synaptic inputs as well as synaptic plasticity (Azouz 2005). It will be important to examine whether the effects observed here are present in other types of cortical neurons, such as various classes of inhibitory neurons, because different cell types likely have unique statistical patterns of synaptic input for excitation and inhibition. In addition, a recent study showed that subthreshold membrane potential fluctuations from synaptic inputs reflect the sensory drive and degree of network correlation (El Boustani et al. 2009). Further studies will be needed to measure the full range of synaptic input statistics present in vivo. In particular, determining the impact of synaptic patterns that arise from specific visual stimuli will be important for characterizing the relevance of neuronal sensitivity to EI temporal interactions to visual processing.

Understanding the modulatory effects of synaptic background noise on response properties of neocortical neurons is a necessary component to decoding cortical processing. It will be essential to consider these effects to form accurate models of cortical function. Not only is our understanding of the effects of EI interactions on cortical responses important for the understanding of normal cortical function, it is also expected to provide insight into the mechanisms of diseases linked to cortical dysfunction (Uhlhaas and Singer 2006).

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