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A SPONTANEOUS STATE OF WEAKLY CORRELATED SYNAPTIC EXCITATION AND INHIBITION IN VISUAL CORTEX

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Abstract

Cortical spontaneous activity reflects an animal's behavioral state and affects neural responses to sensory stimuli. The correlation between excitatory and inhibitory synaptic input to single neurons is a key parameter in models of cortical circuitry. Recent measurements demonstrated highly correlated synaptic excitation and inhibition during spontaneous "up-and-down" states, during which excitation accounted for approximately 80% of inhibitory variance (Shu et al., 2003; Haider et al., 2006). Here we report *in vivo* whole-cell estimates of the correlation between excitation and inhibition in the rat visual cortex under pentobarbital anesthesia, during which up-and-down states are absent. Excitation and inhibition are weakly correlated, relative to the up-and-down state: excitation accounts for less than 40% of inhibitory variance. Although these correlations are lower than when the circuit cycles between up-and-down states, both behaviors may arise from the same circuitry. Our observations provide evidence that different correlational patterns of excitation and inhibition underlie different cortical states.

Keywords

primary visual cortex; spontaneous activity; excitation; inhibition; correlation; *in vivo*

INTRODUCTION

Cortical spontaneous activity may be a signature of neural circuitry (Tsodyks and Sejnowski, 1995; van Vreeswijk and Sompolinsky, 1996; Brunel, 2000), is modulated by attentional state (Steriade et al., 2001; Rudolph et al., 2005; Poulet and Petersen, 2008; Goard and Dan, 2009; Constantinople and Bruno, 2011; Nichols et al., 2011), and influences stimulus encoding (Kisley and Gerstein, 1999; Anderson et al., 2000; Petersen et al., 2003; Sachdev et al., 2004; Hasenstaub et al., 2007; Ringach, 2009; Destexhe, 2011; Mulders and Robertson, 2011) and synaptic plasticity (Mazzoni et al., 1991; Rokni et al., 2007; Legenstein et al., 2010; Humble et al., 2011; Hinton et al., 2012). A key parameter in models of cortical circuitry underlying such activity is the balance of synaptic excitation and inhibition (Kumar et al., 2008; Murphy and Miller, 2009; Sanchez-Vives et al., 2010; Vogels et al., 2011). The time averages of excitation and inhibition appear approximately equal (Destexhe et al., 2001). Because neural activity is stochastic, it is important to also characterize correlations in the deviations of excitation and inhibition from their time-averaged values (Salinas and Sejnowski, 2000; Hertz, 2010; Renart et al., 2010). Notably, predictions for these correlations were recently derived as tests of models of cortical circuitry (Hertz, 2010; Renart et al., 2010).

There are few experimental estimates of the excitatory–inhibitory correlation in single neurons, because it seems to require clamping a neuron almost simultaneously at excitatory and inhibitory reversal potentials, which has been achieved only recently in retinal flat mount (Cafaro and Rieke, 2010). Prior to this, the correlation could be determined only for “up-and-down” cortical states in which the local field potential is highly correlated with the activity of single neurons. The use of the local field potential as an external cue revealed highly correlated excitation and inhibition, with excitation accounting for approximately four-fifths of inhibitory variance (Shu et al., 2003; Haider et al., 2006). However, the correlation between excitation and inhibition in pairs of nearby neurons under anesthetic conditions in which up-and-down states are absent was lower (Okun and Lampl, 2008), thus raising but leaving open the question: what is the correlation between excitatory and inhibitory inputs onto a single neuron?

Since the local field potential is typically insufficiently correlated with the activity of single neurons to be used as an external cue, we developed methods to estimate the excitatory–inhibitory correlation of single neurons without an external cue. We demonstrate these methods in pentobarbital-anesthetized rats in which up-and-down states are absent (Pare et al., 1998; Doi et al., 2007). The state of the cortex under pentobarbital anesthesia is physiologically interesting because pentobarbital-induced coma is clinically relevant (Claassen et al., 2002; Brown et al., 2010). Pentobarbital anesthesia has furthermore provided a backdrop, not only for the detection of plasticity (Morishita et al., 2010; Engineer et al., 2011), but also its induction on short time scales (Meliza and Dan, 2006; Froemke et al., 2007). Remarkably, plasticity induced under pentobarbital anesthesia appears to have behavioral consequences (Froemke et al., 2013).

We show that pentobarbital induces a cortical state in which excitation and inhibition are weakly correlated, relative to the up-and-down state: excitation accounts for less than 40% of inhibitory variance. Although the correlations we observed are lower than when the circuit cycles between up-and-down states (Shu et al., 2003; Haider et al., 2006), both behaviors may arise from the same circuitry, indicating that different correlational patterns of excitation and inhibition underlie different cortical states.

EXPERIMENTAL PROCEDURES

Physiology

We used post-critical period female Long-Evans rats of age 6–12 weeks. Each rat was anesthetized by intraperitoneal injection of sodium pentobarbital (80 mg/kg). Animals were maintained in an areflexic state for the rest of the experiment by further intraperitoneal injections of sodium pentobarbital when necessary. Animals were warmed with a thermostatically controlled heat lamp to maintain the body temperature at 37 °C. Lidocaine was topically applied at all points at which incisions were made. A tracheotomy was performed to secure the airway. Animals were not artificially respired. The animal was placed in a custom-made stereotaxic apparatus. A cisternal drain was performed. Soft tissue over the skull was retracted. A craniotomy and durotomy were performed to expose the visual cortex. The cortical surface was kept moist with normal saline or 4% agarose in normal saline. After the visual cortex was located by multiunit extracellular recording with a parylene-coated tungsten electrode (MicroProbes for Life Sciences, Gaithersburg, MD, USA), the eyes were covered to prevent visual stimulation. All procedures were approved by the University of Texas at Austin Institutional Animal Care and Use Committee.

Whole-cell recordings

Blind whole-cell recordings *in vivo* were obtained (Pei et al., 1991; Ferster and Jagadeesh, 1992; Margrie et al., 2002). As a reference electrode, a silver–silver chloride wire was inserted into muscle near the base of the skull, and covered with 4% agarose in normal saline to reduce changes in the surrounding fluid and concomitant changes in associated junction potentials. The potential of the CSF was assumed to be uniform and equal to that of the reference electrode. Pipettes (3–6 M Ω) were pulled from 1.5 mm outer diameter, 1 mm inner diameter KG-33 borosilicate glass capillaries (King Precision Glass, Claremont, CA, USA) on a P-2000 micropipette puller (Sutter Instruments, Novato, CA, USA) to record from neurons 250 to 850 μ m below the cortical surface. Pipettes were filled with (in mM) 140 Cs-methanesulfonate, 10 phosphocreatine disodium, 5 TEA-Cl, 5 QX-314, 0.5 MK-801, 4 BAPTA, and 10 HEPES, pH 7.3 with CsOH (Sigma–Aldrich, St. Louis, MO, USA). We held each neuron near 0 mV for 3–5 min before acquiring data to facilitate the use-dependent block of *N*-methyl-D-aspartate (NMDA) channels by MK-801 (Corlew et al., 2007; Madara and Levine, 2008; Liu et al., 2010). Voltage clamping was performed with a MultiClamp 700B patch-clamp amplifier (Molecular Devices, Sunnyvale, CA, USA). Series resistances ranged from 50 to 80 M Ω for voltage-clamp recording. Series resistances were measured every 6 min, and holding potentials in each 6-min block were corrected by the mean of the series resistances at the start and end of the block, multiplied by the time-averaged current during the block. A junction potential of 10 mV was subtracted from all holding potentials. Traces were digitized at 15 kHz, and low-pass filtered at 300 Hz before analysis.

Data analysis

The quadratic fits in Figs. 2 and 3 were performed using the MATLAB function `lsqcurvefit` which employs the trust-region-reflective algorithm; confidence intervals for the correlation coefficients were estimated using the MATLAB function `nlparci` which is based on asymptotic normality (Mathworks, Natick, MA). Some of the error bars for the correlation coefficients in Fig. 3B extend above unity and thus include mathematically disallowed values of r_{EI} . These values were estimated from the quadratic equation (Eq. (2)) without enforcing the constraint that correlation values must lie between -1 and 1 . The error estimates are probably overly conservative since we may obtain error estimates that lie completely within the mathematically allowed range by more refined frequentist or Bayesian error estimation procedures that enforce the constraint (Feldman and Cousins, 1998; Riess et al., 1998; Perlmutter et al., 1999).

The peaks in Figs. 4 and 5 were detected on traces which were further smoothed to avoid spurious peaks due to high-frequency noise and voltage-clamp errors; we used the MATLAB function `smooth` with a 30-ms span and local regression using weighted linear least squares and a first degree polynomial model. We only accepted peaks with amplitudes greater than three standard deviations of the power above 300 Hz in our raw traces; and with amplitudes above a threshold of 0.01 times the largest peak amplitude; the conclusions that we draw are not affected if the threshold is raised to 0.10 times the largest peak amplitude.

Data on which the two-tailed paired *t*-test was used were consistent with a Gaussian distribution (Lilliefors test, $p > 0.05$).

Computational model

The model was implemented using Brian (Goodman and Brette, 2008, 2009). The model consists of integrate-and-fire neurons with membrane time constant of 20 ms, resting potential of -70 mV, spike threshold of -50 mV, reset potential of -90 mV, and absolute refractory period of 3 ms. There are 100 excitatory neurons and 25 inhibitory neurons.

Spikes from excitatory neurons trigger exponentially decaying (post)synaptic conductances with a time constant of 5 ms, and reversal potential of 0 mV. Spikes from inhibitory neurons trigger exponentially decaying (post)synaptic conductances with a time constant of 10 ms, and reversal potential of -70 mV. Synaptic conductances are specified as fractions of the leak conductance. The amplitudes of the exponentials are called synaptic weights.

Synaptic weights are drawn randomly at the start of each simulation, and thereafter remain constant in time. Each excitatory neuron connects to all 125 neurons; the synaptic weight for each connection is independently drawn from $W_E \cdot \mathcal{N}_L(0, 1)$, where $W_E=0.02$, and $\mathcal{N}_L(0, 1)$ is a lognormal distribution with location parameter 0 and shape parameter 1 (Song et al., 2005; Curto et al., 2009). Inhibitory neurons connect to all 125 neurons; the synaptic weight for each connection is independently drawn from $X \cdot W_E \cdot \mathcal{N}_L(0, 1)$, where X is a parameter to be specified later that differs between unimodal and bimodal states.

Feedforward excitatory input to the 125 recurrently connected neurons is provided by nine groups of 10 neurons per group, with each neuron spiking with an independent Poisson rate of 1 Hz. Let N index neuron groups one through nine. Each neuron in group N connects to all 100 excitatory neurons with synaptic weight independently drawn from $T_N \cdot W_0 \cdot \mathcal{N}_L(0, 1)$; and connects to all 25 inhibitory neurons with synaptic weight independently drawn from $T_N \cdot Y \cdot W_0 \cdot \mathcal{N}_L(0, 1)$; where the respective T_N for group N was $[1/1000, 1/800, 1/400, 1/200, 1/100, 1/200, 1/400, 1/800, 1/1000]$, $Y=2$, and W_0 is a parameter to be specified later that differs between unimodal and bimodal states.

For the unimodal state in Fig. 4A, $X=3.5$, $W_0=25$. For the bimodal state in Fig. 4B, $X=1$, $W_0=75$.

This integrate-and-fire network model is in the spirit of models with reduced numbers of variables that capture aspects of models with many more variables having more direct biophysical interpretations (Parga and Abbott, 2007). The negative reset in this model heuristically implements, without increasing the number of variables, the suggestion from biophysically more complete models that several types of potassium channels are required for up-and-down states (Bazhenov et al., 2002; Compte et al., 2003; Kang et al., 2004; Hill and TONI, 2005; Parga and Abbott, 2007; Sanchez-Vives et al., 2010). This reduced variable model is meant to capture only some crucial aspects of the biophysically more complete models, in particular, the ability to transition between a network in an asynchronous state and a network displaying up-and-down states.

RESULTS

We developed a method to estimate the excitatory–inhibitory correlation of single neurons without an external cue, as the local field potential is generally insufficiently correlated with the activity of single neurons to be used as such a cue. If excitation (blue) and inhibition (red) of equal variance are perfectly correlated, when summed (black) they cancel perfectly to produce zero variance (Fig. 1A). In contrast, if excitation and inhibition are uncorrelated, their sum will have non-zero variance (Fig. 1B). This suggests that the correlation between excitation and inhibition can be inferred from their sum.

The idea can be formalized by writing the synaptic current I_V when the neuron is clamped at membrane potential V as the weighted sum of the excitatory and inhibitory synaptic conductances:

$$I_V = G_E(V - V_E) + G_I(V - V_I) + G_L(V - V_L), \quad (1)$$

where G_E , G_I and G_L are the excitatory, inhibitory, and leak conductances; V_E , V_I and V_L are their respective reversal potentials. We assume that fluctuations of the current are due to fluctuations in excitation and inhibition. After mean subtraction, squaring, and time averaging, we obtain the variance of the current $\langle \Delta I_v^2 \rangle$ as a quadratic function of the membrane potential (Salinas and Sejnowski, 2000):

$$\langle \Delta I_v^2 \rangle = \langle \Delta G_E^2 \rangle (V - V_E)^2 + \langle \Delta G_I^2 \rangle (V - V_I)^2 + 2 \langle \Delta G_E \Delta G_I \rangle \times (V - V_E)(V - V_I), \quad (2)$$

whose coefficients contain the excitatory variance $\langle \Delta G_E^2 \rangle$, inhibitory variance $\langle \Delta G_I^2 \rangle$, and excitatory–inhibitory covariance $\langle \Delta G_E \Delta G_I \rangle$. Importantly, these yield the single neuron excitatory–inhibitory correlation coefficient r_{EI} that we seek:

$$r_{EI} = \frac{\langle \Delta G_E \Delta G_I \rangle}{\sqrt{\langle \Delta G_E^2 \rangle} \sqrt{\langle \Delta G_I^2 \rangle}}. \quad (3)$$

Accordingly, we can obtain the desired estimate by measuring the variance of the synaptic current at different membrane potentials and fitting a quadratic function to the data. The covariance $\langle \Delta G_E \Delta G_I \rangle$ depends on units, but r_{EI} has the form of Pearson's correlation coefficient and contains a normalization that makes it insensitive to different units being used for the excitatory and inhibitory conductances; Eqs. (1) and (2) assume the same units are used for all conductances.

We measured the correlation of excitatory and inhibitory synaptic inputs with whole-cell voltage-clamp recordings of spontaneous synaptic currents in visual cortex neurons of pentobarbital-anesthetized rats. We used a cesium-based intracellular solution containing pharmacological blockers of voltage-dependent channels to satisfy as closely as possible the assumption of a linear membrane. We detrended the data, and checked that it was consistent with the assumption of ergodicity by testing for covariance stationarity (augmented Dickey–Fuller test, $p < 0.01$; Kwiatkowski–Phillips–Schmidt–Shin test, $p > 0.10$; Seth, 2010).

The basic experimental protocol was to clamp each neuron at three different membrane potentials for 2 min. The protocol was repeated as many times as possible, and analyses always used the same number of repetitions at each membrane potential. Fig. 2A shows synaptic currents from an example neuron. Hyperpolarization (−81 mV) to near the inhibitory reversal potential revealed inward, excitatory currents. Depolarization (−11 mV) to near the excitatory reversal potential revealed outward, inhibitory currents. At an intermediate potential (−45 mV) a mix of inward and outward currents was observed. Traces were sampled at 10-ms intervals to form distributions of current amplitudes (Fig. 2B), from which current variances at each membrane potential were estimated (Fig. 2C). Eqs. (2) and (3) can be applied to the skewed distributions we observed, because they were derived without assuming Gaussianity. Using Eqs. (2) and (3), with respective excitatory and inhibitory reversal potentials of −10 and −85 mV, we estimated this neuron's excitatory–inhibitory correlation coefficient $r_{EI} = 0.42 \pm 0.19$ (90% confidence interval (CI)). Across neurons for which the experimental protocol was completed (Fig. 2D), mean $r_{EI} = 0.38 \pm 0.22$ (90% CI).

The above confidence intervals do not include uncertainties due to systematic errors, whose impact we now estimate. A potential source of systematic error is membrane nonlinearity, because a linear relation between membrane current and membrane potential (Eq. (1)) was a crucial assumption that led to the quadratic relation between current variance and membrane potential (Eq. (2)). We checked the assumption of membrane linearity by examining time-

averaged membrane currents at different membrane potentials. These were well described by a linear relationship in each neuron ($r^2 > 0.97$; Fig. 3A), consistent with membrane nonlinearity being a relatively small source of systematic error. Systematic errors also arise from uncertainties in the excitatory, inhibitory, and junction potentials, which depend on the composition and pH of the extracellular solution, factors that are variable across animals. The ranges of plausible values for the excitatory reversal (V_E), inhibitory reversal (V_I) and junction potentials (V_J) are $-10 \text{ mV} > V_E > 10 \text{ mV}$ (Collingridge et al., 1988; Hestrin et al., 1990; Colquhoun et al., 1992; Spruston et al., 1995; Otmakhova et al., 2002); $-95 \text{ mV} > V_I > -75 \text{ mV}$ (Bormann et al., 1987; Johnston and Wu, 1995; Davson and Segal, 1996); and $0 > V_J > 15 \text{ mV}$ (Barry and Lynch, 1991; Bieda and Copenhagen, 2000; Wehr and Zador, 2003). We found that, except for the excitatory reversal potential, varying each across its range of uncertainty with the others fixed did not significantly affect r_{EI} estimates, indicating that uncertainties in r_{EI} due to uncertainties in inhibitory reversal and junction potentials are negligible compared to those due to uncertainties in the excitatory reversal potential (Fig. 3B). The correlation coefficients in Fig. 2D were obtained with inhibitory reversal and junction potentials fixed near their respective midpoints ($V_I = -85 \text{ mV}$, $V_J = 10 \text{ mV}$), and with the excitatory reversal potential ($V_E = -10 \text{ mV}$) chosen to minimize the non-systematic uncertainty (Fig. 3B). However, other plausible excitatory reversal potentials led to higher r_{EI} estimates (Fig. 3B, red and blue diamonds). These considerations suggest that the estimates of Fig. 2D provide a reasonable lower bound, but only a weak upper bound on r_{EI} .

To place a stronger upper bound on r_{EI} , we consider a description of the excitatory and inhibitory currents as filtered Poisson processes, as the currents appear to consist of distinct events (Fig. 2A). We smoothed the excitatory and inhibitory currents to identify events by peaks in the traces (Fig. 4A, C). The excitatory interevent interval distribution was approximately linear on a logarithmic scale (Fig. 4B; population mean $r = 0.94$, std 0.04, $n = 9$ neurons), as was the inhibitory interevent interval distribution (Fig. 4D; population mean $r = 0.91$, std 0.08, $n = 12$ neurons). This is consistent with the exponential inter-event distributions expected for Poisson processes. Although deviations from exponential behavior are present, we believe they are small enough for the purpose of estimating an upper bound. Across neurons for which excitatory and inhibitory currents were recorded, the mean excitatory event rate was 2.7 times greater than the mean inhibitory event rate (Fig. 4E). (Because of the lower rate of inhibitory events, a longer time is required to accumulate events contributing to the tail of the amplitude histogram of the inhibitory current (Fig. 2B); the lower rate of inhibitory events may accordingly contribute to the greater scatter of estimates, from segments of a particular duration, of the inhibitory current variance (Fig. 2C).) We assume that the maximum possible correlation between two Poisson processes with different rates occurs when they share maximum common input, i.e. the high rate process is the sum of the low rate process and an independent Poisson process. Because we wish to estimate the maximum possible correlation, we impose identical filter time courses for these processes, as filter time courses that differ between the processes lead to lower correlations; for example, two filtered Poisson processes driven by a single Poisson process will have unity correlation coefficient if they have identical filter time courses, but a correlation coefficient less than unity if they have different filter time courses. In this family of scenarios, the maximum correlation coefficient is inversely proportional to the square root of the ratio of the high rate to the low rate (Fig. 4F, solid line) (Papoulis and Pillai, 2002). Simulations indicate that this also holds for filtered Poisson processes (Fig. 4F, triangles) (Grigoriu, 1995; Field, 2008). The plot shows the expected unity maximum correlation coefficient for unity rate ratio. The observed excitatory–inhibitory rate ratio of 2.7 corresponds to maximum $r_{EI} = 0.61$. As maximum $r_{EI}^2 = 0.37$, we conclude that excitation accounts for less than four-tenths of inhibitory variance, which is considerably less than the approximately four-fifths in up-and-down states (Shu et al., 2003; Haider et al., 2006), but

consistent with that suggested for other cortical states (Okun and Lampl, 2008). The maximum $r_{EI} = 0.61$ is consistent with the upper bound of our first estimate $r_{EI} = 0.38 \pm 0.22$ (90% CI). Table 1 shows r_{EI} estimates, upper and lower bounds for each neuron.

The preceding are our main results, but we also noticed an interesting interaction between the amplitude and timing of inward and outward events from our measurements at intermediate holding potentials. Outward net inhibitory currents were often preceded by inward net excitatory currents (Figs. 2A and 5A). We quantified this observation by splitting the current into upper “inhibitory” and lower “excitatory” traces, and extracting the intervals between each peak in the inhibitory trace and the nearest preceding peak in the excitatory trace (Fig. 5A, connected bold and faint red circles). We did the same for traces whose inhibitory peaks were randomized. For the example neuron in Fig. 5A, small intervals in excitatory–inhibitory peak pairs occurred more frequently in the data than if inhibitory peaks had occurred randomly with respect to excitatory peaks (Fig. 5B, Wilcoxon rank sum test, $p < 0.05$); across neurons, the median interval was smaller for data peak pairs than for randomized peak pairs (Fig. 5C; two-tailed paired t -test, $p < 0.05$). The smaller than expected intervals are consistent with positive excitatory–inhibitory correlations (Figs. 2D and 3B). We detected in one neuron a modest correlation between excitatory and inhibitory peak amplitudes in peak pairs with interval less than 50 ms (Fig. 5D), and a weak correlation in only two other neurons, consistent with excitatory–inhibitory correlations being less than the maximum allowed by their different rates (Figs. 2D, 3B, and 4F). The smaller than expected intervals in peak pairs (Fig. 5C) held for pairs whose excitation lay in the largest quartile of excitatory peak amplitudes (Fig. 5E, red upright triangles; two-tailed paired t -test, $p < 0.05$), but not for pairs whose excitation lay in the smallest quartile of excitatory peak amplitudes (Fig. 5E, blue-inverted triangles; two-tailed paired t -test, $p > 0.80$), suggesting that strong excitation was closely followed by inhibition, but that weak excitation occurred randomly with respect to inhibition.

DISCUSSION

We have presented the first measurements that do not require the use of an external cue, of the excitatory–inhibitory correlation in single cortical neurons. We used two novel complementary methods which assumed that neurons are well described by a single compartment model, and that spontaneous activity is ergodic. The first method based on a quadratic fit further assumed a linear membrane; while the second method based on rate differences between excitation and inhibition further assumed that each is a filtered Poisson process. We used a single compartment model so that our conclusions can be compared with other experimental estimates and with theoretical predictions of the excitatory–inhibitory correlation (Shu et al., 2003; Haider et al., 2006; Okun and Lampl, 2008; Cafaro and Rieke, 2010; Hertz, 2010; Renart et al., 2010). We checked and showed that the remaining assumptions were plausible, and considered the effect of systematic uncertainties. We found that the degree of correlation between excitatory and inhibitory inputs is weaker than in up-and-down states (Shu et al., 2003; Haider et al., 2006). The difference between highly correlated excitation and inhibition in up-and-down states and our results is not a discrepancy. Rather, distinct correlational patterns of excitation and inhibition may contribute to the characteristic cortical states associated with changes in behavioral mode.

Intuition suggests that if the main source of excitation to each cortical neuron is weak thalamic input that only occasionally elicits spikes, then a cortical neuron will receive thalamic excitation accompanied by inhibition only rarely, when the thalamic excitatory input causes an inhibitory cortical neuron to spike. In this regime the excitatory input rate is high since it reflects primarily subcortical synaptic inputs, while the inhibitory input rate, which is derived solely from cortical synaptic inputs, is low. The resulting excitatory–

inhibitory correlation is low because the subcortical inputs are the dominant source of synaptic activity. However, if the thalamic input were strong enough to excite many cortical neurons almost simultaneously, the mutual excitation of cortical neurons via intracortical connectivity would create a regime in which cortical inputs, instead of subcortical inputs, are the dominant source of synaptic activity. In this regime, a cortical neuron will receive strongly correlated excitation and inhibition.

We use a simple model to show that different correlations can indeed arise in different states of the same circuitry. Models with different spontaneous states have been constructed (Brunel, 2000; Parga and Abbott, 2007), but the single neuron excitatory–inhibitory correlation for the different states has not been reported. We therefore checked this in a model in which recurrently connected excitatory and inhibitory integrate-and-fire neurons receive feedforward thalamocortical excitation from Poisson-spiking neuron groups (Fig. 6A) (Goodman and Brette, 2008). With strong recurrent inhibitory and weak feedforward excitatory synapses, the relationship between excitatory and inhibitory input to model neurons (Fig. 6B) was similar to what we observed (Fig. 2A); but weak inhibitory and strong feedforward synapses resulted in up-and-down transitions (Fig. 6C). The absence or presence of up-and-down states was confirmed by respective unimodal (Fig. 6D) and bimodal (Fig. 6E) current amplitude distributions (Metherate and Ashe, 1993; Steriade et al., 1993; Cowan and Wilson, 1994; Pare et al., 1998). In the unimodal state, model neurons had $r_{EI}=0.34\pm0.07$ (std); but in the up-and-down state $r_{EI}=0.86\pm0.05$ (std). This difference is similar to that between the previously reported high correlations (Shu et al., 2003; Haider et al., 2006) and the lower correlations we have measured, and supports the hypothesis that we studied different states of the same circuitry.

We propose a test of our simple model. The analysis of currents at the intermediate potential indicating that excitation is followed by inhibition more closely than expected (Fig. 5A–C) is not applicable to up-and-down states, which do not have well-isolated peaks, so we instead consider the cross-correlation of the upper “inhibitory” and (sign-inverted) lower “excitatory” traces (Fig. 5A). Across neurons, the cross-correlation exhibited a positive peak at negative lag, consistent with excitatory synaptic inputs preceding inhibitory inputs (Fig. 6F). Our simple network model showed similar behavior in the unimodal state (Fig. 6G), but predicts qualitatively different behavior for the bimodal state (Fig. 6H). This measurement has not yet been performed for up-and-down states, and is hence a prediction of the model.

The correlation coefficient we have measured is the zero-lag value of the second-order correlation function, and thus contains only partial information about the excitatory–inhibitory correlation. It is insufficient for inferring the peak correlation, which may occur at non-zero lags, and gives no information about higher order cumulants, which are present in non-Gaussian processes. The peak- and zero-lag correlations are virtually indistinguishable in some cortical models (Hertz, 2010; Renart et al., 2010). Non-zero lag correlations can be measured in voltage-clamp experiments that employ quick changes of membrane potential (Cafaro and Rieke, 2010). The zero-lag correlation coefficient we have measured is nonetheless valuable for comparing experiment and theory (Hertz, 2010; Renart et al., 2010). The degree of excitatory–inhibitory correlation we observed is similar to that in an asynchronous cortical network model, but the mean excitatory and inhibitory input we observed is much less than in the model (Renart et al., 2010). It would therefore be interesting to apply the methods we have developed to the activated state under urethane anesthesia, which may be a better realization of the asynchronous cortical network model (Clement et al., 2008; Renart et al., 2010). We did not determine whether the neurons we recorded are excitatory or inhibitory. It would therefore also be interesting to determine whether the excitatory–inhibitory correlation is different between excitatory and inhibitory neurons, which may distinguish between cortical models in which excitatory and inhibitory

neurons receive similar (Tsodyks and Sejnowski, 1995; van Vreeswijk and Sompolinsky, 1996; Brunel, 2000; Kumar et al., 2008; Hertz, 2010; Renart et al., 2010) or dissimilar (Lundqvist et al., 2010; Hill et al., 2012) synaptic inputs. It would also be interesting to determine if neurons in different cortical layers have different excitatory–inhibitory correlations (Sanchez-Vives and McCormick, 2000; Sakata and Harris, 2009; Atencio and Schreiner, 2010; Zhou et al., 2010).

Finally, we note that the variability of membrane potential, synaptic excitation and inhibition also depends on sensory stimulus and cortical area (Heil, 1997; Stiebler et al., 1997; DeWeese et al., 2003; Monier et al., 2003; Tan et al., 2004, 2007; Finn et al., 2007; Gutnisky and Dragoi, 2008; Herikstad et al., 2011; Hansen et al., 2012; White et al., 2012). The covariability of excitation and inhibition should therefore also be measured for different sensory stimuli in different cortical areas. Determining the excitatory–inhibitory correlation via a quadratic fit may be extended to sensory stimulus-evoked responses, with the time average replaced by the trial average.

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Abbreviations

CI	confidence interval
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid

References

- Anderson J, Lampl I, Reichova I, Carandini M, Ferster D. Stimulus dependence of two-state fluctuations of membrane potential in cat visual cortex. *Nat Neurosci.* 2000; 3:617–621. [PubMed: 10816319]
- Atencio CA, Schreiner CE. Columnar connectivity and laminar processing in cat primary auditory cortex. *PLoS One.* 2010; 5:e9521. [PubMed: 20209092]
- Barry PH, Lynch JW. Liquid junction potentials and small cell effects in patch-clamp analysis. *J Membr Biol.* 1991; 121:101–117. [PubMed: 1715403]
- Bazhenov M, Timofeev I, Steriade M, Sejnowski TJ. Model of thalamocortical slow-wave sleep oscillations and transitions to activated States. *J Neurosci.* 2002; 22:8691–8704. [PubMed: 12351744]
- Bieda MC, Copenhagen DR. Inhibition is not required for the production of transient spiking responses from retinal ganglion cells. *Vis Neurosci.* 2000; 17:243–254. [PubMed: 10824678]
- Bormann J, Hamill OP, Sakmann B. Mechanism of anion permeation through channels gated by glycine and gamma-aminobutyric acid in mouse cultured spinal neurones. *J Physiol.* 1987; 385:243–286. [PubMed: 2443667]
- Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. *N Engl J Med.* 2010; 363:2638–2650. [PubMed: 21190458]
- Brunel N. Dynamics of sparsely connected networks of excitatory and inhibitory spiking neurons. *J Comput Neurosci.* 2000; 8:183–208. [PubMed: 10809012]
- Cafaro J, Rieke F. Noise correlations improve response fidelity and stimulus encoding. *Nature.* 2010; 468:964–967. [PubMed: 21131948]
- Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia.* 2002; 43:146–153. [PubMed: 11903460]

- Clement EA, Richard A, Thwaites M, Ailon J, Peters S, Dickson CT. Cyclic and sleep-like spontaneous alternations of brain state under urethane anaesthesia. *PLoS One*. 2008; 3:e2004. [PubMed: 18414674]
- Collingridge GL, Herron CE, Lester RA. Synaptic activation of *N*-methyl-D-aspartate receptors in the Schaffer collateral-commissural pathway of rat hippocampus. *J Physiol*. 1988; 399:283–300. [PubMed: 2900332]
- Colquhoun D, Jonas P, Sakmann B. Action of brief pulses of glutamate on AMPA/kainate receptors in patches from different neurones of rat hippocampal slices. *J Physiol*. 1992; 458:261–287. [PubMed: 1338788]
- Compte A, Sanchez-Vives MV, McCormick DA, Wang XJ. Cellular and network mechanisms of slow oscillatory activity (<1 Hz) and wave propagations in a cortical network model. *J Neurophysiol*. 2003; 89:2707–2725. [PubMed: 12612051]
- Constantinople CM, Bruno RM. Effects and mechanisms of wakefulness on local cortical networks. *Neuron*. 2011; 69:1061–1068. [PubMed: 21435553]
- Corlew R, Wang Y, Ghermazien H, Erisir A, Philpot BD. Developmental switch in the contribution of presynaptic and postsynaptic NMDA receptors to long-term depression. *J Neurosci*. 2007; 27:9835–9845. [PubMed: 17855598]
- Cowan RL, Wilson CJ. Spontaneous firing patterns and axonal projections of single corticostriatal neurons in the rat medial agranular cortex. *J Neurophysiol*. 1994; 71:17–32. [PubMed: 8158226]
- Curto C, Sakata S, Marguet S, Itskov V, Harris KD. A simple model of cortical dynamics explains variability and state dependence of sensory responses in urethane-anesthetized auditory cortex. *J Neurosci*. 2009; 29:10600–10612. [PubMed: 19710313]
- Davson, H.; Segal, MB. *Physiology of the CSF and blood–brain barriers*. Boca Raton: CRC Press; 1996.
- Destexhe A. Intracellular and computational evidence for a dominant role of internal network activity in cortical computations. *Curr Opin Neurobiol*. 2011; 21:717–725. [PubMed: 21715156]
- Destexhe A, Rudolph M, Fellous JM, Sejnowski TJ. Fluctuating synaptic conductances recreate in vivo-like activity in neocortical neurons. *Neuroscience*. 2001; 107:13–24. [PubMed: 11744242]
- DeWeese MR, Wehr M, Zador AM. Binary spiking in auditory cortex. *J Neurosci*. 2003; 23:7940–7949. [PubMed: 12944525]
- Doi A, Mizuno M, Katafuchi T, Furue H, Koga K, Yoshimura M. Slow oscillation of membrane currents mediated by glutamatergic inputs of rat somatosensory cortical neurons: in vivo patch-clamp analysis. *Eur J Neurosci*. 2007; 26:2565–2575. [PubMed: 17949423]
- Engineer ND, Riley JR, Seale JD, Vrana WA, Shetake JA, Sudanagunta SP, Borland MS, Kilgard MP. Reversing pathological neural activity using targeted plasticity. *Nature*. 2011; 470:101–104. [PubMed: 21228773]
- Feldman GJ, Cousins RD. Unified approach to the classical statistical analysis of small signals. *Phys Rev D*. 1998; 57:3873–3889.
- Ferster D, Jagadeesh B. EPSP–IPSP interactions in cat visual cortex studied with in vivo whole-cell patch recording. *J Neurosci*. 1992; 12:1262–1274. [PubMed: 1556595]
- Field, RV. Sandia. 2008. Stochastic models: theory and simulation. Report SAND2008-1365
- Finn IM, Priebe NJ, Ferster D. The emergence of contrast-invariant orientation tuning in simple cells of cat visual cortex. *Neuron*. 2007; 54:137–152. [PubMed: 17408583]
- Froemke RC, Merzenich MM, Schreiner CE. A synaptic memory trace for cortical receptive field plasticity. *Nature*. 2007; 450:425–429. [PubMed: 18004384]
- Froemke RC, Carcea I, Barker AJ, Yuan K, Seybold BA, Martins AR, Zaika N, Bernstein H, Wachs M, Levis PA, Polley DB, Merzenich MM, Schreiner CE. Long-term modification of cortical synapses improves sensory perception. *Nat Neurosci*. 2013; 16:79–88. [PubMed: 23178974]
- Goad M, Dan Y. Basal forebrain activation enhances cortical coding of natural scenes. *Nat Neurosci*. 2009; 12:1444–1449. [PubMed: 19801988]
- Goodman D, Brette R. Brian: a simulator for spiking neural networks in python. *Front Neuroinform*. 2008; 2:5. [PubMed: 19115011]
- Goodman DF, Brette R. The Brian simulator. *Front Neurosci*. 2009; 3:192–197. [PubMed: 20011141]

- Grigoriu, M. Applied non-Gaussian processes: examples, theory, simulation, linear random vibration, and MATLAB solutions. Englewood Cliffs, NJ: PTR Prentice Hall; 1995.
- Gutnisky DA, Dragoi V. Adaptive coding of visual information in neural populations. *Nature*. 2008; 452:220–224. [PubMed: 18337822]
- Haider B, Duque A, Hasenstaub AR, McCormick DA. Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. *J Neurosci*. 2006; 26:4535–4545. [PubMed: 16641233]
- Hansen BJ, Chelaru MI, Dragoi V. Correlated variability in laminar cortical circuits. *Neuron*. 2012; 76:590–602. [PubMed: 23141070]
- Hasenstaub A, Sachdev RN, McCormick DA. State changes rapidly modulate cortical neuronal responsiveness. *J Neurosci*. 2007; 27:9607–9622. [PubMed: 17804621]
- Heil P. Auditory cortical onset responses revisited. I. First-spike timing. *J Neurophysiol*. 1997; 77:2616–2641. [PubMed: 9163380]
- Herikstad R, Baker J, Lachaux JP, Gray CM, Yen SC. Natural movies evoke spike trains with low spike time variability in cat primary visual cortex. *J Neurosci*. 2011; 31:15844–15860. [PubMed: 22049428]
- Hertz J. Cross-correlations in high-conductance states of a model cortical network. *Neural Comput*. 2010; 22:427–447. [PubMed: 19842988]
- Hestrin S, Nicoll RA, Perkel DJ, Sah P. Analysis of excitatory synaptic action in pyramidal cells using whole-cell recording from rat hippocampal slices. *J Physiol*. 1990; 422:203–225. [PubMed: 1972190]
- Hill S, Tononi G. Modeling sleep and wakefulness in the thalamocortical system. *J Neurophysiol*. 2005; 93:1671–1698. [PubMed: 15537811]
- Hill SL, Wang Y, Riachi I, Schurmann F, Markram H. Statistical connectivity provides a sufficient foundation for specific functional connectivity in neocortical neural microcircuits. *Proc Natl Acad Sci U S A*. 2012; 109:E2885–E2894. [PubMed: 22991468]
- Hinton, GE.; Srivastava, N.; Krizhevsky, A.; Sutskever, I.; Salakhutdinov, RR. Improving neural networks by preventing co-adaptation of feature detectors. 2012. arXiv:12070580
- Humble J, Furber S, Denham SL, Wennekers T. STDP pattern onset learning depends on background activity. *Adv Exp Med Biol*. 2011; 718:19–31. [PubMed: 21744207]
- Johnston, D.; Wu, SM-S. Foundations of cellular neurophysiology. Cambridge, Mass: MIT Press; 1995.
- Kang S, Kitano K, Fukai T. Self-organized two-state membrane potential transitions in a network of realistically modeled cortical neurons. *Neural Netw*. 2004; 17:307–312. [PubMed: 15037349]
- Kisley MA, Gerstein GL. Trial-to-trial variability and state-dependent modulation of auditory-evoked responses in cortex. *J Neurosci*. 1999; 19:10451–10460. [PubMed: 10575042]
- Kumar A, Schrader S, Aertsen A, Rotter S. The high-conductance state of cortical networks. *Neural Comput*. 2008; 20:1–43. [PubMed: 18044999]
- Legenstein R, Chase SM, Schwartz AB, Maass W. A reward-modulated hebbian learning rule can explain experimentally observed network reorganization in a brain control task. *J Neurosci*. 2010; 30:8400–8410. [PubMed: 20573887]
- Liu BH, Li P, Sun YJ, Li YT, Zhang LI, Tao HW. Intervening inhibition underlies simple-cell receptive field structure in visual cortex. *Nat Neurosci*. 2010; 13:89–96. [PubMed: 19946318]
- Lundqvist M, Compte A, Lansner A. Bistable, irregular firing and population oscillations in a modular attractor memory network. *PLoS Comput Biol*. 2010; 6:e1000803. [PubMed: 20532199]
- Madara JC, Levine ES. Presynaptic and postsynaptic NMDA receptors mediate distinct effects of brain-derived neurotrophic factor on synaptic transmission. *J Neurophysiol*. 2008; 100:3175–3184. [PubMed: 18922945]
- Margrie TW, Brecht M, Sakmann B. In vivo, low-resistance, whole-cell recordings from neurons in the anaesthetized and awake mammalian brain. *Pflugers Arch*. 2002; 444:491–498. [PubMed: 12136268]
- Mazzoni P, Andersen RA, Jordan MI. A more biologically plausible learning rule for neural networks. *Proc Natl Acad Sci U S A*. 1991; 88:4433–4437. [PubMed: 1903542]

- Meliza CD, Dan Y. Receptive-field modification in rat visual cortex induced by paired visual stimulation and single-cell spiking. *Neuron*. 2006; 49:183–189. [PubMed: 16423693]
- Metherate R, Ashe JH. Ionic flux contributions to neocortical slow waves and nucleus basalis-mediated activation: whole-cell recordings in vivo. *J Neurosci*. 1993; 13:5312–5323. [PubMed: 8254377]
- Monier C, Chavane F, Baudot P, Graham LJ, Fregnac Y. Orientation and direction selectivity of synaptic inputs in visual cortical neurons: a diversity of combinations produces spike tuning. *Neuron*. 2003; 37:663–680. [PubMed: 12597863]
- Morishita H, Miwa JM, Heintz N, Hensch TK. Lynx1, a cholinergic brake, limits plasticity in adult visual cortex. *Science*. 2010; 330:1238–1240. [PubMed: 21071629]
- Mulders WH, Robertson D. Progressive centralization of midbrain hyperactivity after acoustic trauma. *Neuroscience*. 2011; 192:753–760. [PubMed: 21723924]
- Murphy BK, Miller KD. Balanced amplification: a new mechanism of selective amplification of neural activity patterns. *Neuron*. 2009; 61:635–648. [PubMed: 19249282]
- Nichols JA, Nichols AR, Smirnakis SM, Engineer ND, Kilgard MP, Atzori M. Vagus nerve stimulation modulates cortical synchrony and excitability through the activation of muscarinic receptors. *Neuroscience*. 2011; 189:207–214. [PubMed: 21627982]
- Okun M, Lampl I. Instantaneous correlation of excitation and inhibition during ongoing and sensory-evoked activities. *Nat Neurosci*. 2008; 11:535–537. [PubMed: 18376400]
- Otmakhova NA, Otmakhov N, Lisman JE. Pathway-specific properties of AMPA and NMDA-mediated transmission in CA1 hippocampal pyramidal cells. *J Neurosci*. 2002; 22:1199–1207. [PubMed: 11850447]
- Papoulis, A.; Pillai, SU. Probability, random variables, and stochastic processes. Boston: McGraw-Hill; 2002.
- Pare D, Shink E, Gaudreau H, Destexhe A, Lang EJ. Impact of spontaneous synaptic activity on the resting properties of cat neocortical pyramidal neurons in vivo. *J Neurophysiol*. 1998; 79:1450–1460. [PubMed: 9497424]
- Parga N, Abbott LF. Network model of spontaneous activity exhibiting synchronous transitions between up and down States. *Front Neurosci*. 2007; 1:57–66. [PubMed: 18982119]
- Pei X, Volgushev M, Vidyasagar TR, Creutzfeldt OD. Whole cell recording and conductance measurements in cat visual cortex in-vivo. *Neuroreport*. 1991; 2:485–488. [PubMed: 1912484]
- Perlmutter S, Aldering G, Goldhaber G, Knop RA, Nugent P, Castro PG, Deustua S, Fabbro S, Goobar A, Groom DE, Hook IM, Kim AG, Kim MY, Lee JC, Nunes NJ, Pain R, Pennypacker CR, Quimby R, Lidman C, Ellis RS, Irwin M, McMahon RG, Ruiz-Lapuente P, Walton N, Schaefer B, Boyle BJ, Filippenko AV, Matheson T, Fruchter AS, Panagia N, Newberg HJM, Couch WJ. Measurements of Omega and Lambda from 42 highredshift supernovae. *Astrophys J*. 1999; 517:565–586.
- Petersen CC, Hahn TT, Mehta M, Grinvald A, Sakmann B. Interaction of sensory responses with spontaneous depolarization in layer 2/3 barrel cortex. *Proc Natl Acad Sci U S A*. 2003; 100:13638–13643. [PubMed: 14595013]
- Poulet JF, Petersen CC. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. *Nature*. 2008; 454:881–885. [PubMed: 18633351]
- Renart A, de la Rocha J, Bartho P, Hollender L, Parga N, Reyes A, Harris KD. The asynchronous state in cortical circuits. *Science*. 2010; 327:587–590. [PubMed: 20110507]
- Riess AG, Filippenko AV, Challis P, Clocchiatti A, Diercks A, Garnavich PM, Gilliland RL, Hogan CJ, Jha S, Kirshner RP, Leibundgut B, Phillips MM, Reiss D, Schmidt BP, Schommer RA, Smith RC, Spyromilio J, Stubbs C, Suntzeff NB, Tonry J. Observational evidence from supernovae for an accelerating universe and a cosmological constant. *Astron J*. 1998; 116:1009–1038.
- Ringach DL. Spontaneous and driven cortical activity: implications for computation. *Curr Opin Neurobiol*. 2009; 19:439–444. [PubMed: 19647992]
- Rokni U, Richardson AG, Bizzi E, Seung HS. Motor learning with unstable neural representations. *Neuron*. 2007; 54:653–666. [PubMed: 17521576]

- Rudolph M, Pelletier JG, Pare D, Destexhe A. Characterization of synaptic conductances and integrative properties during electrically induced EEG-activated states in neocortical neurons in vivo. *J Neurophysiol.* 2005; 94:2805–2821. [PubMed: 16014785]
- Sachdev RN, Ebner FF, Wilson CJ. Effect of subthreshold up and down states on the whisker-evoked response in somatosensory cortex. *J Neurophysiol.* 2004; 92:3511–3521. [PubMed: 15254074]
- Sakata S, Harris KD. Laminar structure of spontaneous and sensory-evoked population activity in auditory cortex. *Neuron.* 2009; 64:404–418. [PubMed: 19914188]
- Salinas E, Sejnowski TJ. Impact of correlated synaptic input on output firing rate and variability in simple neuronal models. *J Neurosci.* 2000; 20:6193–6209. [PubMed: 10934269]
- Sanchez-Vives MV, McCormick DA. Cellular and network mechanisms of rhythmic recurrent activity in neocortex. *Nat Neurosci.* 2000; 3:1027–1034. [PubMed: 11017176]
- Sanchez-Vives MV, Mattia M, Compte A, Perez-Zabalza M, Winograd M, Descalzo VF, Reig R. Inhibitory modulation of cortical up states. *J Neurophysiol.* 2010; 104:1314–1324. [PubMed: 20554835]
- Seth AK. A MATLAB toolbox for Granger causal connectivity analysis. *J Neurosci Methods.* 2010; 186:262–273. [PubMed: 19961876]
- Shu Y, Hasenstaub A, McCormick DA. Turning on and off recurrent balanced cortical activity. *Nature.* 2003; 423:288–293. [PubMed: 12748642]
- Song S, Sjostrom PJ, Reigl M, Nelson S, Chklovskii DB. Highly nonrandom features of synaptic connectivity in local cortical circuits. *PLoS Biol.* 2005; 3:e68. [PubMed: 15737062]
- Spruston N, Jonas P, Sakmann B. Dendritic glutamate receptor channels in rat hippocampal CA3 and CA1 pyramidal neurons. *J Physiol.* 1995; 482(Pt 2):325–352. [PubMed: 7536248]
- Steriade M, Nunez A, Amzica F. A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J Neurosci.* 1993; 13:3252–3265. [PubMed: 8340806]
- Steriade M, Timofeev I, Grenier F. Natural waking and sleep states: a view from inside neocortical neurons. *J Neurophysiol.* 2001; 85:1969–1985. [PubMed: 11353014]
- Stiebler I, Neulist R, Fichtel I, Ehret G. The auditory cortex of the house mouse: left-right differences, tonotopic organization and quantitative analysis of frequency representation. *J Comp Physiol A.* 1997; 181:559–571. [PubMed: 9449817]
- Tan AY, Zhang LI, Merzenich MM, Schreiner CE. Tone-evoked excitatory and inhibitory synaptic conductances of primary auditory cortex neurons. *J Neurophysiol.* 2004; 92:630–643. [PubMed: 14999047]
- Tan AY, Atencio CA, Polley DB, Merzenich MM, Schreiner CE. Unbalanced synaptic inhibition can create intensity-tuned auditory cortex neurons. *Neuroscience.* 2007; 146:449–462. [PubMed: 17320296]
- Tsodyks MV, Sejnowski T. Rapid state switching in balanced cortical network models. *Network.* 1995; 6:111–124.
- van Vreeswijk C, Sompolinsky H. Chaos in neuronal networks with balanced excitatory and inhibitory activity. *Science.* 1996; 274:1724–1726. [PubMed: 8939866]
- Vogels TP, Sprekeler H, Zenke F, Clopath C, Gerstner W. Inhibitory plasticity balances excitation and inhibition in sensory pathways and memory networks. *Science.* 2011; 334:1569–1573. [PubMed: 22075724]
- Wehr M, Zador AM. Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. *Nature.* 2003; 426:442–446. [PubMed: 14647382]
- White B, Abbott LF, Fiser J. Suppression of cortical neural variability is stimulus- and state-dependent. *J Neurophysiol.* 2012; 108:2383–2392. [PubMed: 22896720]
- Zhou Y, Liu BH, Wu GK, Kim YJ, Xiao Z, Tao HW, Zhang LI. Preceding inhibition silences layer 6 neurons in auditory cortex. *Neuron.* 2010; 65:706–717. [PubMed: 20223205]

Fig. 1.

Correlated and uncorrelated excitation and inhibition can be distinguished by their sum. (A) Perfectly correlated excitation (blue) and inhibition (red) cancel perfectly in their sum (black). In the corresponding histograms on the right, the variances of excitation and inhibition are non-zero, but the variance of their sum is zero. (B) Uncorrelated excitation and inhibition do not cancel when summed. The variances of excitation, inhibition and their sum are non-zero.

Fig. 2.

Single neuron excitatory–inhibitory correlation coefficients. (A) Synaptic currents at each of 3 membrane potentials; 30-s segments (left); 500 ms close-up from one repetition (right). (B) Histograms of current amplitudes. All horizontal axes represent the same relative range of currents. To conveniently display a highly skewed distribution, the -11 mV histogram represents currents greater than 250 pA by a single bar. (C) Plot of current variances versus membrane potential, and best fit quadratic. (D) Estimated single neuron excitatory–inhibitory correlation coefficients r_{EI} (error bars are 90% CI) for 7 neurons. The neuron in (A–C) is the 5th.

Fig. 3.

Systematic uncertainties: membrane nonlinearity, reversal and junction potentials. (A) Time-averaged membrane current versus membrane potential for each of the seven neurons in Fig. 2D; current versus membrane potential data are well fit by a linear model in all seven neurons ($r^2>0.97$). (B) Correlation coefficients r_{EI} for each of the seven neurons in Fig. 2D calculated with different assumed reversal and junction potentials within the experimentally plausible range: r_{EI} depended mainly on the excitatory reversal potential ($V_E=-10$ mV: black; $V_E=0$ mV: blue; $V_E=+5$ mV: red). For any given V_E , changing the inhibitory reversal potential (V_I) or the junction potential (V_J) did not significantly affect r_{EI} estimates, indicating that uncertainties in r_{EI} due to uncertainties in V_I and V_J are negligible compared to those due to uncertainties in V_E . Correlation coefficients in Fig. 2D were obtained with V_I and V_J fixed near their respective midpoints ($V_I=-85$ mV, $V_J=10$ mV), and with $V_E=-10$ mV chosen to minimize the non-systematic uncertainty indicated by the error bars (90% CI). Higher r_{EI} estimates are obtained with $V_E=0$ mV and $V_E=+5$ mV, suggesting that the estimates in Fig. 2D provide a reasonable lower bound, but only a weak upper bound on r_{EI} .

(For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 4.

Using the ratio of excitatory to inhibitory rates to estimate an upper bound for the single neuron excitatory–inhibitory correlation. (A) Detected peaks (blue asterisks) in smoothed (sign-inverted) excitatory currents from one neuron (B) Logarithmically-scaled histogram of inter-event intervals for the neuron in (A). (C) Detected peaks (blue asterisks) in smoothed inhibitory currents from another neuron. (D) Logarithmically-scaled histogram of inter-event intervals for the neuron in (C). (E) Mean excitatory rate versus mean inhibitory rate across neurons. (F) Maximum cross-correlation versus ratio of the high rate to the low rate. Solid line is the analytic solution ($y = x^{-1/2}$) for Poisson processes; triangles are simulation results for filtered Poisson processes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 5.

Excitatory and inhibitory peaks at the intermediate membrane potential. (A) Mean-subtracted current at the intermediate membrane potential from an example neuron showing detected positive excitatory and negative inhibitory peaks (blue asterisks), and the pairing (red lines) of each inhibitory peak (bold red circles) with the nearest preceding excitatory peak (faint red circles). (B) Histograms of intervals between data inhibitory peaks and nearest preceding excitatory peaks (black squares); and randomized inhibitory peaks and nearest preceding excitatory peaks (gray circles) for the neuron in (A). (C) Median interval between randomized inhibitory peaks and nearest preceding excitatory peaks versus median interval between data inhibitory peaks and nearest preceding excitatory peaks (seven neurons). (D) Excitatory versus inhibitory peak amplitudes in excitatory–inhibitory peak pairs with interval less than 50 ms, from a different neuron than in (A). (E) Median interval for randomized peak pairs versus data peak pairs as in (C), but conditioned on pairs whose excitation lay in the largest (red upright triangles) or smallest (blue-inverted triangles) quartiles of excitatory peak amplitude (seven neurons).

Fig. 6.

Single neuron excitatory-inhibitory correlations in different model network states. Note A–E, G, and H refer to the model, but (F) shows data. (A) The model consists of recurrently connected excitatory and inhibitory integrate-and-fire neurons which receive feedforward excitation from Poisson-spiking neuron groups. (B) Excitatory (blue) and inhibitory (red) conductances in a model parameter regime without up-and-down states. Conductances are normalized by the leak conductance. (C) Excitatory and inhibitory conductances in a model parameter regime with up-and-down states. (D) Unimodal current amplitude distributions for the model neuron in (B). All horizontal axes represent the same relative range of currents. To conveniently display a highly skewed distribution, the 0 mV histogram represents currents greater than 1.1 units by a single bar. (E) Bimodal current amplitude distributions for the model neuron in (C). All horizontal axes represent the same relative range of currents. (F) Cross-correlations between upper and (sign-inverted) lower halves of currents at the intermediate potential, for single neurons (gray), and mean across neurons (black). (G, H) Cross-correlations between upper and (sign-inverted) lower halves of currents at the intermediate potential for the respective model parameter regimes in (B, C), for randomly selected single model neurons (gray), and mean across neurons (black).

Table 1

Excitatory–inhibitory correlation coefficient estimates, lower and upper bounds. The mean of the upper bounds from the rate differences (0.63) is different from the upper bound from the mean rate difference mentioned in the text (0.61); the conclusions that we draw are not affected by this slight difference

Neuron	Correlation coefficient r_{EI} (from Fig. 2D)	r_{EI} lower bound (from Fig. 2D)	r_{EI} upper bound (from Fig. 2D)	r_{EI} upper bound (from Fig. 4E, F)
1	0.41	0.30	0.51	0.74
2	0.41	0.10	0.71	0.60
3	0.35	0.27	0.42	0.59
4	0.36	0.00	0.72	0.68
5	0.42	0.21	0.62	0.63
6	0.40	0.18	0.61	0.72
7	0.35	0.07	0.62	0.44
Mean	0.38	0.16	0.60	0.63