Circuit mechanisms revealed by spike-timing correlations in macaque area MT

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Huang X, Lisberger SG. Circuit mechanisms revealed by spike-timing correlations in macaque area MT. J Neurophysiol 109: 851–866, 2013. First published November 14, 2012; doi:10.1152/jn.00775.2012.—We recorded simultaneously from pairs of motion-sensitive neurons in the middle temporal cortex (MT) of macaque monkeys and used cross-correlations in the timing of spikes between neurons to gain insights into cortical circuitry. We characterized the time course and stimulus dependency of the cross-correlogram (CCG) for each pair of neurons and of the auto-correlogram (ACG) of the individual neurons. For some neuron pairs, the CCG showed negative flanks that emerged next to the central peak during stimulus-driven responses. Similar negative flanks appeared in the ACG of many neurons. Negative flanks were most prevalent and deepest when the neurons were driven to high rates by visual stimuli that moved in the neurons’ preferred directions. The temporal development of the negative flanks in the CCG coincided with a parallel, modest reduction of the noise correlation between the spike counts of the neurons. Computational analysis of a model cortical circuit suggested that negative flanks in the CCG arise from the excitation-triggered mutual cross-inhibition between pairs of excitatory neurons. Intracortical recurrent inhibition and afterhyperpolarization caused by intrinsic outward currents, such as the calcium-activated potassium current of small conductance, can both contribute to the negative flanks in the ACG. In the model circuit, stronger intracortical inhibition helped to maintain the temporal precision between the spike trains of pairs of neurons and led to weaker noise correlations. Our results suggest a neural circuit architecture that can leverage activity-dependent intracortical inhibition to adaptively modulate both the synchrony of spike timing and the correlations in response variability.

neuron-neuron correlations; synchrony; neural coding; visual cortex; visual motion processing; response variation; Fano factor; afterhyperpolarization

INTERACTIONS AMONG INTRICATELY connected excitatory and inhibitory neurons shape the activity of neuronal populations and thereby influence the coding of sensory information in the cerebral cortex. How these neural circuits operate is not understood, even though the nature of the sensory code is well known in many areas of the cerebral cortex. Knowledge about how cortical circuits work will further our understanding of how sensory codes are created and transformed as they move through sensory pathways. Our goal in the present paper is to capitalize on analyses of the details of neuronal responses, especially neuron-neuron correlations, to uncover the dynamic interactions between excitatory and inhibitory neurons in the cortex. Our analysis has been performed in the middle temporal (MT) cortex, an extrastriate visual motion area.

Activity between pairs of neurons is often correlated in the interconnected cortical network of the visual cortex (Gawne and Richmond 1993; Toyama et al. 1981b; Ts’o et al. 1986; Zohary et al. 1994). Response correlations can take the form of either covariation of spike counts around the mean responses to repeatedly presented stimuli (referred to as “noise correlations”) or synchrony in spike timing (referred to as “spike-timing correlations”). The likely role of noise correlations in limiting the precision of central estimates of the sensory events has been well documented (Cohen and Maunsell 2009; Huang and Lisberger 2009; Mitchell et al. 2009; Shadlen et al. 1996). In some cases, noise correlations can be beneficial for coding information in neuronal populations (Abbott and Dayan 1999; see review by Averbeck et al. 2006). The role of spike-timing correlations in coding sensory information has been more controversial (Hirabayashi and Miyashita 2005; Kimpo et al. 2003; Palanca and DeAngelis 2005; Shadlen and Newsome 1998; Singer and Gray 1995; Thiele and Stoner 2003). Still, it is widely agreed that information transfer may be facilitated when spikes are synchronized across neurons in a short time window (Bair 1999; Shadlen and Newsome 1994). Furthermore, patterns of spiking and silence across a neural population can be informative (Osborne et al. 2008).

The properties of spike-timing correlations are useful to infer functional connectivity between neurons (Aertsen et al. 1989; Melssen and Epping 1987; Ostojic et al. 2009; Perkel et al. 1967b; Schwarz and Bolz 1991; Toyama et al. 1981a; Ts’o et al. 1986). In the present study, we use spike-timing correlations as a tool to better understand the connectivity within the circuitry of the cerebral cortex. We characterized the shape, time course, and stimulus dependency of the cross-correlations between the spike trains of pairs of neurons in area MT of awake monkeys. Neurons in MT are selectively responsive to moving stimuli and are tuned for the direction and speed of motion. Our analysis is facilitated by the fact that the nature of the neuronal code in area MT is well understood, including the dynamics of the trajectory of instantaneous firing rate (Lisberger and Movshon 1999).

To elucidate the underlying circuit properties, we analyzed in tandem the auto-correlations and cross-correlations of the spike trains of pairs of single neurons. Through simulations of a computational model composed of interconnected integrate-and-fire neurons, we have been able to form a hypothesis about the nature and time course of excitatory and inhibitory interactions within the cortical circuit, to differentiate features of
the correlations that arise from neural circuitry vs. biophysical properties of single neurons, and to show how inhibitory interactions could modulate noise correlations between neurons. Our findings offer a mechanistic explanation of the temporal dynamics of the spike-timing and noise correlations between pairs of neurons and provide insights into how interactions within the cortical network influence sensory coding.

MATERIALS AND METHODS

Two adult male rhesus monkeys were used in the neurophysiological experiments. All animal experiments were performed at University of California, San Francisco (UCSF), using protocols that had been approved in advance by the Institutional Animal Care and Use Committee of UCSF. Procedures were in strict compliance with U.S. Department of Agriculture regulations and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Eye position was monitored using the scleral search coil technique. Surgical methods, electrophysiological recording procedures, and the behavioral paradigms have been described in detail before (Huang and Lisberger 2009). In brief, to record from neurons in cortical area MT, we lowered up to five quartz-shielded tungsten microelectrodes (Thomas Recording, Germany) simultaneously into the posterior bank of the superior temporal sulcus. Electrodes went through guide tubes that were arranged either concentrically or linearly with a center distance of 305 μm between two neighboring guide tubes. Electrical signals were filtered, amplified, and digitized conventionally. Single units were identified with a real-time template-matching system, and the spike waveforms were sorted offline after the experiments (Plexon, Dallas, TX).

Visual stimuli and behavioral paradigm. Visual stimuli were presented on a 20-in. cathode ray tube monitor at a viewing distance of 38 cm, providing a visual field coverage of 56 × 43°. Monitor resolution was 1,280 × 1,024 pixels, and the refresh rate was 85 Hz. All visual stimuli were presented in individual trials while monkeys fixated within a 1.5° × 1.5° window to receive juice rewards. Visual stimuli were patches of random dots. In a typical trial, visual stimuli were illuminated after the animal had fixated for 200 ms. Visual stimuli remained stationary on the display for 250 ms and then moved for 500 ms. Monkeys continued to fixate for another 250 ms after the visual stimuli were turned off. During the motion period, the random dots translated coherently at a specified velocity within a square visual stimuli were turned off. During the motion period, the random-dot pattern was different in each.

RESULTS

We measured the spike train CCG and auto-correlogram (ACG) (Perkel et al. 1967a, a) using a method similar to that used by Bair et al. (2001). We computed

\[ C_g(t) = \frac{1}{M} \sum_{m=1}^{M} \sum_{\tau \in T_1} v_i(t) v_j(t+\tau) \]  

where \( M \) is the total number of stimulus repetitions (trials), \( T_1 \) to \( T_2 \) is the time interval of the spike train under analysis, \( \tau \) varied in 1-ms steps, \( j = k \) for an auto-correlation, and \( j = 1, k = 2 \) for the cross-correlation between neurons \( 1 \) and \( 2 \). To compute the time course of the correlation function, we used an analysis interval of 100 ms (\( T_2 = T_1 + 100 \)) and advanced the interval in 10-ms steps.

We computed the “raw” CCG based on the trial-averaged cross-correlation \( C_{ij} \) between two neurons (Eq. 1), normalized by the geometric mean of the two neurons’ firing rates, corrected for the degree of overlap of the two spike trains at each time lag.

\[ CCG_{raw}(t) = \frac{C_{g}(t)}{C_{jj}^{T1}} \]  

where \( C_{jj}^{T1} \) is the total number of stimulus repetitions (trials), \( T_1 \) to \( T_2 \) is the time interval of the spike train under analysis, \( \tau \) varied in 1-ms steps, \( j = k \) for an auto-correlation, and \( j = 1, k = 2 \) for the cross-correlation between neurons \( 1 \) and \( 2 \). To compute the time course of the correlation function, we used an analysis interval of 100 ms (\( T_2 = T_1 + 100 \)) and advanced the interval in 10-ms steps.

To determine whether the cross-correlation between two neurons was significant, we computed the CCG based on the spike trains in the interval from 0 to 500 ms following the onset of stimulus motion. We smoothed the CCG with a second-order, five-point Savitzky-Golay filter and measured the amplitude of the peak or trough of the CCG within time lags of ±25 ms. We measured the “baseline” of the CCG for time lags from −200 to −50 ms and from 50 to 200 ms relative to zero time lag. We considered the cross-correlation to be significant if the magnitude of the peak of the smoothed CCG exceeded the mean in the baseline intervals by >3 SDs of the 302 values in the baseline intervals. We considered the trough to be significant if it undershot the mean in the baseline intervals by >2.5 SDs.

To objectively classify the CCG based on whether it showed negative troughs next to the central peak, we set several selection criteria and designed an automatic algorithm. We computed the CCG based on the spike trains in the interval from 150 to 450 ms following the onset of stimulus motion. We first determined whether the CCG showed a positive peak within the time lags of ±3 ms, which exceeded the mean in the baseline intervals by >2.5 SDs. For CCGs that met this criterion, we further classified them using the following method. The method searched for a negative trough that undershot from the neighboring 200 values of baseline CCG by >1.7 SDs at either side of the central positive peak. Care was taken so that the search for the “negative trough” was in the neighborhood of the central positive peak but was not trapped in the local minimum. The CCG was considered as group 1 if negative troughs were found at both sides of the central positive peak. If a negative trough was
found only at one side of the central peak, then the CCG was classified as group 2. If the negative trough was found at neither side of the central peak, then the CCG was classified as group 3. The parameters of the algorithm were chosen so that the automated classification matched well with the classification made by visual examination. An ACG was defined to have negative flanks if it had a negative trough within the time lags from 5 ms to 25 ms, which was used to compute the resting membrane potential. The mean in the baseline intervals at lags from 25 ms to 125 ms. We denoted the time lag of the minimum as \( T_{\text{min}} \). We admitted ACG negative flanks only if the value at \( T_{\text{min}} \) was more negative than its two nearest neighbors at the side toward time lag zero so that there was a local maximum between \( T_{\text{min}} \) and zero time lag.

For each pair of neurons, we computed the time course of spike count noise correlation \( r_{\text{sc}} \) within a 100-ms time window sliding at a 10-ms step. Before computing \( r_{\text{sc}} \), we converted the data into \( z \)-scores to normalize spike counts. To avoid some of the possible artifacts of correlation analysis, we removed trials on which the response of either neuron of a pair was \( >5 \sigma \) different from its mean response, and we computed \( r_{\text{sc}} \) only if each neuron of a pair yielded at least 12 distinct values of spike counts.

For each MT neuron, we also computed the time course of the Fano factor in 100-ms intervals as the variance of spike count divided by the mean spike count. For neurons that were tested with random-dot stimuli moving in multiple directions and speeds, the preferred direction (PD) and the PS of the neurons were determined using the same methods as we described previously (Huang and Lisberger 2009). The differences of the PDs and the log ratio of the PSs were used to characterize the separations between two neurons’ stimulus preferences.

Computational model. We constructed a simple neural network model using excitatory and inhibitory integrate-and-fire neurons. In a given experimental trial, the activity of each input neuron was modeled as a spike train whose interspike intervals followed a Poisson distribution with a given mean. The membrane potential \( V_p \) (\( p = 1, 2 \)) of the excitatory model neurons was determined by

\[
\frac{dV_p}{dt} = -\sum_{j=1}^{N_p} G_{\text{ex}}[V_p(t) - E_{\text{ex}}] - \sum_{j=1}^{N_p} G_{\text{in}}[V_p(t) - E_{\text{in}}] - G_{\text{leak}}[V_p(t) - V_{\text{rest}}] - G_{\text{AHP}}[V_p(t) - V_{\text{AHP}}] - G_{\text{adp}}[V_p(t) - E_{\text{adp}}]
\]

where \( G_{\text{ex}} \) is the feedforward (FF) excitatory conductance, \( G_{\text{in}} \) is the FF inhibitory conductance, and \( G_{\text{leak}} \) is the intracortical inhibitory conductance. The membrane potential of the inhibitory model neurons used the same equation without the last term [adaptation (adp) conductance \( G_{\text{adp}} \) and with \( G_{\text{in}} \) replaced by \( G_{\text{r}} \), the intracortical excitatory conductance between the excitatory and inhibitory neurons. We modeled each conductance as

\[
G_{\text{a}} = G_{\text{a, max}} \sum p e^{-\left(\frac{t-t_{\text{sp}}}{\tau}\right)}
\]

where \( t_{\text{sp}} \) is the timing of a spike \( p \) in the presynaptic neuron for each input conductance, in the postsynaptic neuron for \( G_{\text{leak}} \) (leaky conductance), \( G_{\text{AHP}} \) (afterhyperpolarization conductance), and \( G_{\text{adp}} \). Other parameters are: \( t_{\text{sp}} \), a synaptic delay of 2.5 ms for \( G_{\text{ex}}, G_{\text{in}}, G_{\text{r}} \), \( G_{\text{leak}} \), and a time delay of 1 ms for \( G_{\text{adp}}, G_{\text{AHP}}, \) and \( G_{\text{adp}}; G_{\text{a, max}} \) is the maximum conductance. The default values of the model parameters are listed in Table 1 [also see Shadlen and Newsome (1998); Somers et al. (1995, 1998)]. Parameter values that deviated from the default values are mentioned in RESULTS.

Spikes occurred in a model neuron when its membrane potential exceeded its spiking threshold \( V_{\text{thresh}} \). With the caveat that 1) an action potential could not occur within the absolute refractory period, and 2) \( V_{\text{thresh}} \) increased after the absolute refractory period and then decayed exponentially (Eq. 5) to create a relative refractory period [after Somers et al. (1998)]

\[
V_{\text{thresh}}(t) = V_{\text{thresh}}(t_0) + V_{\text{thresh}}(t_0) e^{-\left(\frac{t-t_{\text{sp}}}{\tau_{\text{thresh}}}\right)}
\]

Because fast-spiking neurons show little spike-frequency adaptation (McCormick et al. 1985), we chose not to apply threshold elevation to the inhibitory cortical neurons and relied on an outward AHP current \( (I_{\text{AHP}}) \) to model their modest relative refractory period. In simulations that examined the effects of intrinsic outward currents on spike-timing correlations, we removed connections from the inhibitory to the excitatory model neurons and added a potassium (\( K^+ \)) current

\[
I_{\text{k}} = G_{\text{k}}[V_p(t) - E_{\text{k}}]
\]

where \( G_{\text{k}} \) is determined by Eq. 4 and represents either the calcium (\( Ca^{2+} \))-activated \( K^+ \) current of small (SK) conductance (Stockker 2004) or a hypothetical \( K^+ \) conductance \( G_{\text{h}} \). \( G_{\text{h}} \) has artificially determined magnitude and kinetics that were not constrained by experimental data. The goal of introducing \( G_{\text{h}} \) was to simulate an AHP that mimicked the time course and amplitude of the inhibitory postsynaptic potential (ipsp) generated by intracortical inhibition.

We conducted model simulations using Matlab (MathWorks, Natick, MA). Numerical solutions of the differential equations were obtained using the fourth-order Runge-Kutta method at a time step of 0.001 ms. The spike threshold and the refractory period were chosen to generate an AHP with an amplitude of 10 mV and a decay time constant of 20 ms.

Table 1. Default model parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>E</th>
<th>I</th>
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<tbody>
<tr>
<td>( C_m )</td>
<td>0.33 nF</td>
<td>0.17 nF</td>
</tr>
<tr>
<td>( G_{\text{ex, max}} )</td>
<td>6 nS</td>
<td>6 nS</td>
</tr>
<tr>
<td>( G_{\text{in, max}} )</td>
<td>2 ms</td>
<td>4 ms</td>
</tr>
<tr>
<td>( G_{\text{leak, max}} )</td>
<td>20 nS</td>
<td>20 nS</td>
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<tr>
<td>( G_{\text{AHP, max}} )</td>
<td>20 nS</td>
<td>20 nS</td>
</tr>
<tr>
<td>( G_{\text{adp, max}} )</td>
<td>20 nS</td>
<td>20 nS</td>
</tr>
<tr>
<td>( N_{\text{ff, ex}} )</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>( N_{\text{ff, in}} )</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>( \text{CommonNff, ex} )</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>( \text{CommonNff, in} )</td>
<td>40%</td>
<td>0%</td>
</tr>
</tbody>
</table>

For excitatory neuron (E), inhibitory neuron (I); \( C_m \), membrane capacitance; \( G_{\text{ex, max}} \), maximum conductance, where \( G_{\text{ex}} \) can be \( G_{\text{e}} \), conductance of intracortical excitation [at the synapse from excitatory (e) to inhibitory (i) neuron]; \( G_{\text{in, max}} \), conductance of intracortical inhibition; \( G_{\text{leak}} \), leaky conductance; \( G_{\text{AHP}} \), afterhyperpolarization (AHP) conductance; \( G_{\text{adp}} \), adaptation (adp) conductance. \( N_{\text{ff, ex}} \) and \( N_{\text{ff, in}} \), number of excitatory and inhibitory feedforward (FF) input; \( \text{CommonNff, ex} \) and \( \text{CommonNff, in} \), percentage of excitatory and inhibitory FF input that is shared by two neurons; \( \tau_{\text{sp}} \) and \( \tau_{\text{adp}} \), membrane time constant; \( \tau_{\text{leak}} \), \( \tau_{\text{AHP}} \), and \( \tau_{\text{adp}} \), time constants of adp and AHP conductance; \( \tau_{\text{thresh}} \), spike-timing delay; \( \text{AP}_{\text{max}} \) and \( \text{AP}_{\text{min}} \), amplitude and decaying time constant of action potential; \( \text{Ab}_{\text{ref}} \), absolute refractory period; \( E \), reversal potential of sodium (Na), chloride (Cl), potassium (K), AHP, and adp current; \( V_{\text{thresh}} \), resting membrane potential; \( \text{Vthresh_base} \), membrane potential of baseline spiking threshold; \( \text{Vthresh_elv} \), elevation of spiking threshold; \( \text{Adp} \), absolute refractory period; \( \text{FF input rate} \), firing rates of the input neurons.

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0.25 ms. To simulate the time course of the CCG, we simulated membrane potentials for all four neurons from −150 to 760 ms, relative to the stimulus motion onset. We adjusted the time-varying firing rates of the input neurons to the model excitatory neurons iteratively until the time course of the firing rate of the model excitatory neurons matched the shape of the time course of the averaged geometric mean firing rate of the recorded MT neuron pairs. We then averaged the CCG and ACG across three simulated experiments for each set of model parameters. In the rest of the simulations, we simulated the membrane potentials for all four neurons during a 300-ms interval with a constant firing rate in the input neurons. Each simulated experiment comprised 200 trials; simulation data were analyzed using the methods we had applied to the physiological data.

RESULTS

Our database comprised recordings from 100 neuron pairs in extrastriate area MT. All pairs were recorded simultaneously on separate electrodes so that we could separate the spike waveforms of the two neurons even when they occurred within a short time interval. For each pair, we analyzed the CCG between the spike trains of the two neurons as well as the ACGs of the two individual neurons. We used our data to ask four related questions: 1) How do spike-timing correlations evolve over time during the presentation of visual stimuli? 2) Do spike-timing correlations in area MT depend on visual stimuli? 3) What neural mechanisms could underlie the features of the CCGs and ACGs in our data? 4) What are the implications of these circuit mechanisms for the general issue of coding in neuronal populations?

Time courses of spike-timing cross- and auto-correlations. When we used all of the spikes in the interval from 50 to 450 ms after the onset of motion of a visual stimulus, the CCGs of many MT neuron pairs (53/100) displayed a significant positive peak within ±3 ms of time lag zero (e.g., Fig. 1A); in agreement with previous findings in MT (de Oliveira et al. 1997) and other visual areas (Ts’o et al. 1986). In addition, the CCG of the example neuron pair in Fig. 1A, along with many other pairs, showed negative troughs that flanked the positive central peak and were significantly lower than the baseline level of the CCG. After the negative troughs rebounded at longer time lags, they overshot above zero, showing a hint of damped oscillation (Fig. 1A). Analysis of the time course of the CCG within bin-widths of 100 ms, which moved through the stimulus time in 10-ms steps (Fig. 1D), revealed that the negative flanks evolved over time during presentation of a moving stimulus. Over time, from the bottom to the top of the color image, the negative CCG flanks emerged gradually following the onset of the firing-rate response to the moving stimulus.

The ACGs of the two neurons that contributed to the pair in Fig. 1 also showed significant negative flanks alongside the central ACG peak (Fig. 1, B and C). The flanks of the ACGs comprised a brief, immediate dip at short time lags and a later trough that reached a maximum negative value at a time lag of 6 ms and gradually returned to baseline (Fig. 1B). Analysis of the time course of the ACG in 100-ms windows revealed that the negative flanks in the ACGs of both neurons of the pair in Fig. 1 widened and deepened after the onset of the firing-rate response, shown in Fig. 1, E and F. We think that the negative flanks in the ACG at very short time lags represent the refractory period of the neuron under study. As we move through our presentation, we will provide evidence that the negative flanks of the CCG trough and the delayed negative flanks of the ACG represent a property of the neural circuit.

Across the whole population of 66 neuron pairs in our sample that showed CCGs significantly different from baseline, the averaged CCGs and ACGs both showed the negative flanks that evolved over time. The evolution of the negative flanks in time can be seen both in the full time courses of the correlograms (Fig. 2, A and B) and by comparison of the correlograms calculated using spikes in the two intervals from 50 to 150 ms and from 150 to 450 ms after stimulus onset (Fig. 2, C and D). During the early

![Fig. 1. Spike-timing correlations of an example neuron pair (N1 and N2). The 3 columns show the cross-correlogram (CCG) for the pair and the auto-correlogram (ACG) for the 1st and 2nd neuron in the pair, respectively. A–C: correlation as a function of time lag for all spikes from 50 to 450 ms after the onset of stimulus motion. The orange and black arrowheads in B indicate the immediate dip and the delayed negative flank of the ACG. Red and blue traces show CCG/ACG before and after processing with a Savitzky-Golay (SG) filter, respectively. SG filtering well-preserved the location and shape of the negative flanks in the CCG and ACG but slightly widened the central ACG peak and delayed the immediate dip from ±1 ms to ±2 ms. Coinc/spike, coincidences/spike. D–F: the color of each pixel shows the value of the correlation as a function of the time from the onset of the stimulus motion (y-axis) and the time lag (x-axis). Correlations were computed from the spikes in 100-ms windows centered at the time on the y-axis. The black traces in E and F show the firing rates of the 2 neurons calculated using a bin-width of 10 ms as a function of the time from stimulus onset. Time 0 on the y-axis indicates the stimulus motion onset. The preferred directions (PDs) of the 2 neurons differed by 7°. The preferred speeds (PSs) of the 2 neurons were 24/°s and 26/°s, respectively.](http://jn.physiology.org/doi/abs/10.1152/jn.00775.2012)
response period from 50 to 150 ms after the stimulus motion onset, there were no negative CCG flanks, and the negative ACG flanks were weak. The negative flanks appeared during the later response period from 150 to 450 ms. Another notable feature of the time course of the CCGs and ACGs is that the positive central CCG and ACG peaks narrowed abruptly following the stimulus motion onset (Fig. 2, A and B).

To examine more closely the temporal development of the negative CCG and ACG flanks, we extracted the relationship between correlation and the time from motion onset at time lags of −6 and −25 ms (Fig. 2, A and B). The former time reflects the deepest point in the negative flanks, and the latter time represents the baseline correlation so that their difference, plotted in Fig. 3, indexes the size of the negative flanks (Fig. 3, A and B). The time courses of the CCG and the ACG flanks were very similar. They both decreased in parallel with increases in firing rate (calculated on the same time grid) and reached asymptotes ~150 ms after the onset of stimulus motion. Note that the asymptote levels of the negative CCG and ACG flanks were reached somewhat after the times of the peak firing-rate responses in Fig. 3, A and B, consistent with our suggestion that the negative flanks of the CCG and ACG are caused by the neural circuit rather than by the refractory period of the neurons.

The time courses of the CCG and ACG also tracked well with the time courses of other measures of MT cell responses. For example, the time course of the spike count correlations between the two neurons in a pair (Fig. 3C) agreed well with the time course of the CCG integrated across time lags from −25 to 25 ms (Fig. 3C). We chose to integrate CCG across time lags from −25 to 25 ms, because outside of this range, the majority of CCGs in our data was close to the baseline and had little structure.

Before the stimulus motion onset, the noise correlation and the integrated CCG were relatively high. Soon after the onset of motion, the noise correlation and the integrated CCG decreased quickly. The decline of noise correlations after stimulus onset is consistent with the findings by Churchland et al. (2010)—that the neural variability in the cortical network is reduced after the stimulus onset. In Fig. 3, the time courses of the integrated CCG (Fig. 3C) and the negative CCG flanks (Fig. 3A) were very similar, indicating that the decline in integrated CCG is contributed mainly by the growth of the negative CCG flanks across time. These results are consistent with the finding that the area underneath of the CCG is correlated with the noise correlation (Bair et al. 2001; Brody 1999). We also observed very similar time courses for the integrated ACG and the Fano factor of the individual neurons in our sample (Fig. 3D).

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### Table 1: Coincidence and Firing Rate Correlations

<table>
<thead>
<tr>
<th>Time Lag (ms)</th>
<th>Coincidences/spike (x10^-2)</th>
<th>Firing Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.05</td>
<td>3.0</td>
</tr>
<tr>
<td>25</td>
<td>0.02</td>
<td>3.5</td>
</tr>
<tr>
<td>50</td>
<td>0.01</td>
<td>4.0</td>
</tr>
<tr>
<td>75</td>
<td>0.005</td>
<td>4.5</td>
</tr>
</tbody>
</table>

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![Figure 2: Average spike-timing correlations across 66 neuron pairs. The left and right columns show the CCG and ACG, respectively. A and B: the color of each pixel shows the value of the average correlation as a function of the time from the onset of the stimulus motion (y-axis) and the time lag (x-axis). Correlations were computed from the spikes in 100-ms windows centered at the time on the y-axis. The gray trace in B shows the firing rates of the neurons as a function of the time from stimulus onset calculated using a bin-width of 10 ms. The vertical, dashed lines indicate time lags used to quantify the progression of the negative flanks as a function of time. C and D: average correlation across the sample population. Red and blue traces were computed using spikes that occurred in intervals from 50 to 150 ms or from 150 to 450 ms, respectively, after the onset of stimulus motion.](http://jn.physiology.org/)

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![Figure 3: Comparisons of the time courses of multiple measures of neuronal responses. The left and right columns show the CCG and ACG, respectively. Data are averaged across the neurons in 66 pairs that showed CCGs significantly different from the baseline. In all panels, the dashed, gray curve shows the firing rate calculated using a bin-width of 100 ms, sliding in 10-ms steps, all on the same scale. A and B: the black curves show the size of the negative flank defined as the CCG (A) or ACG (B) at a time lag of ~6 ms minus the baseline CCG at a time lag of ~25 ms. C: the black and gray curves show the CCG integrated across time lags from −25 to 25 ms and the spike-count noise correlation, respectively. Noise correlation was based on the responses from 51 out of the 66 neuron pairs that met the criteria described in MATERIALS AND METHODS. D: the black and gray curves show the integrated ACG and the Fano factor. Shaded ribbons in C and D represent ±1 SE.](http://jn.physiology.org/)
Stimulus dependency of spike-timing correlations. To ask whether spike-timing correlations varied with the strength of a neuron’s responses to the visual stimulus, we computed the CCGs and ACGs for stimuli that moved in different directions relative to the PD of the neurons in the pair under study. We defined the “pair PD” as the motion direction that was closest to optimal for both neurons. When driven by stimuli that moved in the pair-PD, both the CCG and ACG showed negative flanks in the example pair (Fig. 4, A and D). The negative flanks were strong in the population averages for the ACG (Fig. 4E), although less clear in the population averages for the CCG (Fig. 4B).

Next, we rank-ordered the geometric mean of the firing rates for each neuron pair in response to different directions and averaged the CCGs and ACGs for each rank across the neuron pairs. Smaller responses were associated with two changes in the CCG and the ACG. The positive peaks in the correlograms became considerably broader, and the negative flanks decreased in amplitude, and then positive flanks emerged (Fig. 4, A, B, D, and E). As the directions of motion changed from least preferred to PDs, and therefore, the correspondingly evoked firing rates increased, the areas under the CCG and ACG flanks (across time lags from −25 to −5 ms and from 5 to 25 ms) decreased progressively (Fig. 4, C and F). The total area under the CCG integrated across time lags from −25 to 25 ms also decreased as the stimulus directions varied, and the firing rates increased (Fig. 4C). The data in Fig. 4 were obtained from 35 neuron pairs that were recorded simultaneously during tests of direction selectivity (n = 91), showed a peak CCG that was at least three SD above baseline for at least one of the eight tested directions, and had a maximum geometric mean firing rate >25 spikes/s. The analysis window included all spikes during the 500-ms interval of stimulus motion.

Relationship between properties of CCG and ACG in individual neurons. For stimulus motion in the pair-PD, 66 neuron pairs in our data sample showed CCG peaks or troughs that were significantly different from the baseline level, according to criteria outlined in MATERIALS AND METHODS. Of these, 53 had significant positive peaks within ±3 ms of time lag zero. Not all pairs, however, showed clear negative flanks. To capture the basic features of the CCG shapes, we used a quantitative algorithm described in MATERIALS AND METHODS to classify these 66 neuron pairs into three “groups” based on the spike trains in the interval from 150 to 450 ms following the onset of stimulus motion. As illustrated in Fig. 5, A–C, averages of the CCG across group 1 pairs revealed clear, negative CCG flanks, whereas averages across group 2 and 3 pairs showed flanks on one or neither side of the peak. On average, group 1 pairs also showed larger peak values of correlation in the CCG (Fig. 5, A–C and D–F), larger negative flanks in the ACG (Fig. 5, G–I), and larger firing-rate responses to the moving stimulus (Fig. 5, G–I). Figure 5, D and G–I emphasizes again that negative flanks in both the ACG and the CCG emerged only after the onset of the response to stimulus motion. Group 1 pairs contained a large fraction of neurons with negative flanks in the ACG, but not all neurons in group 1 pairs showed negative ACG flanks (Table 2). Finally, note that a small oscillation in the side bands of CCG was seen only in group 1 pairs (Fig. 5A) but not in group 2 and 3 pairs (Fig. 5, B and C), suggesting that the oscillation is linked to the rebound from the negative CCG flanks.

CCG and ACG prior to stimulus motion onset. To separate MT responses to the onset of visual stimuli and the stimulus motion, our visual stimuli were first turned on but remained stationary for 250 ms and then started to move. MT neurons showed a transient response to the onset of stationary stimuli in the interval from 250 to 150 ms before the onset of motion. The transient responses can be seen in Fig. 5, G–I. During this period, CCGs showed a narrow central peak and a broad base (Fig. 6, A–C). ACGs showed a narrow central peak, with small or absent negative flanks (Fig. 6, D–F). MT neurons then showed a period of low firing rates from 120 to 0 ms before the onset of motion. During this period, both CCGs and ACGs showed wide, positive central peaks (Fig. 6). Finally, as before, during the strong responses to stimulus motion, group 1 pairs showed negative flanks in both CCG and ACG (Fig. 6, A and D).

Stimulus preferences and the presence or absence of negative CCG flanks. The similarity or difference of the direction and speed tuning of a pair of neurons was not related strongly to the categorization of their CCG-possessed, negative flanks that fit the definition of group 1, 2, or 3. The distributions of the difference between the PDs and the log ratio of the PSs within a neuron pair are shown in Fig. 7 as both a scatter plot and marginal histograms. Neuron pairs that showed negative CCG

Figure 4. Effect of stimulus direction and firing rate on the shapes of the CCG and ACG. The left and right 2 columns show data for an example pair of neurons and averages across the 35 pairs that provided adequate data, respectively. A, B, D, and E: red curves show data for the “pair PD”, and blue and green curves show data for other, less PDs. The colors are defined according to the geometric mean of the responses of the pair of neurons. A and B: CCGs; D and E: ACGs; C: integrated CCG as a function of the averaged, geometric mean of the firing rates of the neuron pairs. Each symbol shows the response for a single stimulus direction. F: integrated ACG as a function of the mean firing rate of 46 neurons in the 35 neuron pairs. C and F: the blue traces indicate the CCG and ACG integrated across the time lags from −25 to −5 ms and from 5 to 25 ms and then divided by 2. C: the red trace indicates the CCG integrated across time lags from −25 to 25 ms. Error bars represent SEs, spk/sec, spikes/s.
flanks (group 1), such as the example in Fig. 1, tended to have similar preferred directions and speeds (Fig. 7). However, similar preferred stimuli alone were not sufficient to give rise to negative CCG flanks. Neuron pairs that had very similar PDs and PSs were found in all groups. Some pairs had nearly identical PDs and PSs but did not show negative CCG flanks (Fig. 7). The data in Fig. 7 came from 81 pairs for which we obtained both direction and speed-tuning curves.

Effects of spatial patterns. We used two methods to generate the spatial patterns of the random-dot stimuli. Under the fixed-seed condition, the same random-dot pattern was used in each trial. Under the random-seed condition, the random-dot pattern was different in each trial. Stimuli from the fixed- and random-seed conditions were interleaved during the experiment and were pooled in the results presented above. To determine whether spatial patterns of the stimuli influenced our findings, we repeated the analysis of CCG and ACG after separating the trials into groups that used the same vs. different random-dot patterns. Figure 8 shows, for the same example neuron pair presented in Fig. 1, that we found similar negative flanks and time courses of the CCGs and ACGs for the fixed-seed and the random-seed conditions. When averaged across the 66 pairs of neurons in our sample or across the 13 pairs of neurons with group 1 CCGs, the key features of the spike-timing correlations were independent of whether we varied the spatial pattern of the random dots from trial to trial (Fig. 9). The magnitude of the negative flanks in the CCG (Fig. 9, A–D) and the time courses of the ACG across the duration of the moving stimulus (Fig. 9, E and F) were essentially independent of whether the spatial patterns of the stimuli were identical or different across trials.

Neural mechanisms of spike-timing correlations suggested by a computational model. We have found that the spike-timing cross- and auto-correlations undergo temporal changes over the interval of the response to an effective stimulus and that the time courses of the CCG for a pair of neurons and ACG of the individual neurons are strikingly similar. The CCGs of some neuron pairs and the ACGs of many of their constituent neurons developed negative flanks after the onset of the neural response. The negative flanks were not fixed features of the given neuron pairs and appeared to occur when the neuronal responses were strong. One possible explanation of these findings is that the intrinsic properties of the single neurons, such as the refractory period, determine the shapes of their ACGs, and the common features of ACGs are reflected in the CCG of the neuron pairs. Alternatively, the observed features of the CCG and ACG may reflect the dynamic interactions among neurons within a common neuronal circuitry. To understand the mechanisms underlying the time courses of the

![Graph](http://jn.physiology.org/Downloadedfrom/)

**Table 2.** Relationship between pattern of negative flanks on CCGs of neuron pairs and delayed negative flanks on ACGs of individual neurons in the pairs

<table>
<thead>
<tr>
<th>Group based on CCG</th>
<th>Neuron 1</th>
<th>Neuron 2</th>
<th>Neurons 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n=13)</td>
<td>85% (11)</td>
<td>77% (10)</td>
<td>62% (8)</td>
</tr>
<tr>
<td>Group 2 (n=17)</td>
<td>35% (6)</td>
<td>59% (10)</td>
<td>24% (4)</td>
</tr>
<tr>
<td>Group 3 (n=23)</td>
<td>48% (11)</td>
<td>43% (10)</td>
<td>17% (4)</td>
</tr>
<tr>
<td>Unclassified (n=13)</td>
<td>31% (4)</td>
<td>31% (4)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>All pairs (n=66)</td>
<td>48% (32)</td>
<td>52% (34)</td>
<td>24% (16)</td>
</tr>
</tbody>
</table>

CCG, cross-correlogram; ACG, auto-correlogram.
spike-timing correlations, we conducted computational analyses using a simple neural network that is consistent with a canonical circuit of the cerebral cortex (Douglas and Martin 1991, 2004). We aimed to determine the likely causes of the negative flanks of the CCGs and ACGs and to use the details of the CCG and ACG to infer the properties of the dynamic configuration and operation of the cortical circuit.

Figure 10 shows the circuitry of our model. $E_1$ and $E_2$ simulate two excitatory “cortical neurons”, and $I_1$ and $I_2$ simulate two inhibitory neurons. The excitatory and inhibitory neurons are connected in what we will call “intracortical recurrent inhibition”: each model excitatory neuron connects to and receives inhibition back from each model inhibitory neuron. The circuit also creates what we will call “crossed inhibition” in the sense that each model excitatory neuron connects to model inhibitory neurons, which in turn, provide inhibition on the other model excitatory neuron. Of the input neurons for the excitatory model neurons, 40% projected to both $E_1$ and $E_2$ to create “common inputs” that give rise to the positive central peak of the CCG between the spike trains of $E_1$ and $E_2$ (Fig. 10A). The two inhibitory neurons received independent FF inputs that were weak, except in some simulations highlighted later in the paper. Because the inhibitory neurons received inputs from the excitatory neurons whose responses were correlated, the CCG between the spike trains of $I_1$ and $I_2$ also showed a positive central peak (simulation results not shown).

The inputs to the cortical neurons were designed to create stochastic, balanced FF excitation and inhibition, similar to the “high-input regime” suggested by Shadlen and Newsome (1998). As described in MATERIALS AND METHODS, the excitatory neurons had absolute and relative refractory periods, whereas the inhibitory neurons had an absolute refractory period and a modest relative refractory period to model their biological spiking pattern of little spike-frequency adaptation (McCormick et al. 1985). We elicited different levels of responses in the excitatory neurons by varying the firing rate of their input neurons. The spike trains in Fig. 10 show the result from one simulated “trial” using the default model parameters (see MATERIALS AND METHODS).

The model simulations captured the main features of the CCG and ACG observed in our neural data. Figure 10, A and B, shows the excellent agreement of the superimposed CCGs and ACGs of the model simulation results and the example neuron pair that was presented in Fig. 1 under a regime of steady inputs. In these simulations, we varied the maximal conductance of intracortical inhibition ($G_{\text{ie, max}}$) and the strength of the FF input to the excitatory neurons to fit the model to the neural data. The model simulations captured both the negative flanks and the small oscillation at the side-band of CCG in the neural data (Fig. 10A). Next, we set the time-varying firing rate of the input neurons in the model so that the time-varying firing rates of $E_1$ and $E_2$ (Fig. 11B) matched the...
Effects of intracortical inhibition on negative flanks in the CCG and ACG. Intracortical inhibition plays a key role in generating the negative CCG and ACG flanks in our simulations. With the firing rate of the input neurons fixed, we varied the strength of the intracortical inhibition by changing the $G_{\text{ie, max}}$ of the four-model synapses from the inhibitory to the excitatory model neurons (see Eq. 3 in MATERIALS AND METHODS). When there was no intracortical inhibition (i.e., $G_{\text{ie, max}} = 0$), the CCG between $E_1$ and $E_2$ showed only a positive central peak without negative flanks (Fig. 12A). When intracortical inhibition was introduced (i.e., $G_{\text{ie, max}} > 0$), negative flanks emerged in the CCG and deepened as the strength of intracortical inhibition increased (Fig. 12A). The ACGs of excitatory neurons showed parallel effects of inhibition. Without inhibition (Fig. 12D), the excitatory model neurons were essentially isolated from inhibitory neurons, and negative flanks appeared in the ACG only for short values of time lag. As the strength of inputs from the inhibitory neurons increased, delayed negative flanks emerged in the ACG (Fig. 12D). In agreement with our data from MT, the negative CCG flanks and the delayed negative ACG flanks appeared at similar values of time lag (Fig. 12, A and D). With strong intracortical inhibition, both CCG and ACG showed weak oscillation at the gamma-band of 60–80 Hz (Fig. 12, A and D), also in agreement with our data from MT (Fig. 5A).

Variations in the firing rate of the excitatory model neurons, caused by changing the firing rate of the input neurons, had effects on the CCG and ACG, which agreed with the features of our data. When there was no intracortical inhibition, the CCGs between the responses of $E_1$ and $E_2$ showed only positive central peaks without negative flanks, regardless of the firing rates of the neurons (Fig. 12B). At high firing rates, the central CCG peak was slightly narrower (Fig. 12B). Without intracortical inhibition, the size of the immediate negative dips in the ACGs scaled with the firing rate of the excitatory model neurons, but delayed negative ACG flanks never appeared (Fig. 12E). With intracortical inhibition, the negative flanks in the
that a neuron will fire an action potential after it generates a spike.

Mechanisms intrinsic to single neurons, such as Ca$^{2+}$-activated K$^+$ currents, can also give rise to an AHP after a spike (Sah and Davies 2000; Schwindt et al. 1988). In a way that matches intuitively the action of inhibition, an AHP could contribute to negative flanks in the ACG by reducing a neuron’s excitability following a spike. In the simulation results presented so far, the excitatory model neuron had an outward current ($I_{AHP}$) that was modeled after the Ca$^{2+}$ and a depolarization-activated, large-conductance K$^+$ current, $I_{Isk}$ (Sah and Davies 2000). Figure 12, B and E, shows that this $I_{AHP}$ alone does not produce the negative flanks in the CCG and the delayed negative flanks in the ACG, likely due to its rapid activation ($\tau_{AHP} = 1$ ms) and fast decay ($\tau_{AHP} = 1$ ms).

We next ask whether the negative flanks in the CCG and ACG might result from an intrinsic outward AHP current that decays with a longer time constant. We studied models that lacked the intracortical inhibition in the circuitry shown in Fig. 10. We included in the excitatory model neuron a delayed outward K$^+$ current ($I_{Isk}$) to model the Ca$^{2+}$-activated K$^+$ current mediated by the SK channel [see Sah and Davies (2000); Stocker (2004) for review]. In our simulations, $I_{Isk}$ gave rise to a medium-duration AHP (Fig. 13A) and contributed to spike-frequency adaptation (data not shown), as expected for $I_{Isk}$ (Sah and Davies 2000; Schwindt et al. 1988; Stocker 2004). $I_{Isk}$ also gave rise to delayed negative flanks in the ACG (Fig. 13D) comparable with that generated by intracortical inhibition (Fig. 13F). Increases in the maximum conductance of $I_{Isk}$ deepened the delayed negative flanks in the ACG (Fig. 13D) but never yielded negative flanks in the CCG (Fig. 13G).

Fig. 9. Average CCGs for the population of neurons recorded with trials that presented the same vs. different random-dot patterns on different trials. A, C, and E: fixed-seed condition; B, D, and F: random-seed condition. A and B: CCGs were calculated based on spikes in the interval from 150 to 450 ms and averaged across 66 neuron pairs as in Fig. 2C. C–F: CCGs were averaged across 13 neuron pairs in group 1. C and D: CCGs were calculated based on spikes in the interval from 150 to 450 ms; E and F: time courses of CCGs were computed using spikes in 100-ms time windows. The conventions are the same as in Fig. 5, A and D.

CCG and the delayed negative flanks in ACG deepened as the response magnitude increased (Fig. 12, C and F).

Inspection of the model provides an intuition to explain the importance of inhibition for the main effects in the simulated CCGs and ACGs. Increases in firing rate deepen the negative flanks in the CCG and the delayed negative flanks in the ACG, because higher firing rates in $E_1$ and $E_2$ elicit stronger responses in $I_1$ and $I_2$ and create stronger inhibition in $E_1$ and $E_2$ at delays expected for a disynaptic effect and the integration of postsynaptic potentials. Increases in firing rate deepen the immediate ACG dips even in the absence of inhibition because of the refractory period (Fig. 12E). Thus our simulations suggest that the negative CCG flanks and the delayed negative ACG flanks in our data are generated by interactions among neurons in the cortical circuitry rather than by the refractory period of the single neurons.

Effects of intrinsic delayed outward currents on negative flanks in the CCG and ACG. In our model, recurrent inhibition generates an ipsp in an excitatory neuron several milliseconds after the excitatory neuron fires an action potential (Fig. 13C). The delayed, recurrently generated ipsp contributes to the delayed negative flanks in the ACG by reducing the probability...
The model yielded the same results when we replaced \( I_h \) with a hypothetical, intrinsic outward \( K^+ \) current (\( I_o \)), which was contrived to match the membrane potential after a spike (Fig. 13B) to the time delay, amplitude, and time course of the ipsps generated by intracortical inhibition in the model (Fig. 13C). Again, \( I_h \) caused negative flanks in the ACG (Fig. 13E) and only a tiny hint of negative flanks in the CCG (Fig. 13H), much weaker than the negative CCG flanks found when intracortical inhibition was engaged (Fig. 13I). Figure 13 suggests that intrinsic outward currents cannot account for large negative flanks in the CCG, but we cannot rule out the possibility that intrinsic outward currents may contribute to a very small portion of negative CCG flanks. Both intracortical inhibition and delayed outward currents can contribute to the delayed negative flanks in the ACG.

**Structure of neural circuitry and the spike-timing correlations.** In a final step to understand the relationship between the neural circuitry in the cortex and the features of the CCG and ACG, we removed \( I_h \) and \( I_o \) from the model neuron and manipulated the structure of the model circuitry (Fig. 14). The firing rates of \( E_1 \) and \( E_2 \) were kept fixed. In the absence of inhibition, we never saw negative flanks in the CCG or delayed negative flanks in the ACG (Fig. 14). In the presence of inhibition, the presence and structure of the flanks depended on the architecture of the circuit. In the fully connected model circuit with recurrent and cross-inhibition (Fig. 14A), the CCG flanks of the model excitatory neurons resembled those of group 1 pairs and were present on both sides of the positive peak with balanced inhibitory connections. The individual model neurons had delayed negative flanks in the ACG. When the strength of cross-inhibition was asymmetric (Fig. 14B), the CCG flanks of the model neurons resembled those of group 2 pairs and were present only on one side of the positive peak. The ACGs still had delayed negative flanks. This could explain the structure of the group 2 CCGs, but it also is possible that group 2 pairs contained one excitatory neuron and one inhibitory neuron that were recurrently connected, giving rise to asymmetrical, biphasic CCGs. Finally, when inhibition was only present between pairs of excitatory and inhibitory model units, without cross-inhibition between the two excitatory-

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**Fig. 11.** The time courses of simulated CCG and ACG. A and B: the color of each pixel shows the value of the average correlation as a function of the time from the onset of the stimulus motion (y-axis) and the time lag (x-axis). Correlations were computed from the spikes in 100-ms windows centered at the time on the y-axis. The black curve in B shows the firing rate of the model excitatory neurons, calculated using a 10-ms bin. C and D: correlation as a function of time lag for spikes at different times relative to the onset of stimulus motion. The red, green, and blue curves were obtained for spikes in 100-ms intervals centered 50 ms before and 50 or 150 ms after, respectively, the onset of stimulus motion. The orange and black arrowheads in D indicate the immediate dip and the delayed negative flank of the ACG, respectively.

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**Fig. 12.** Effect of changing model parameters on the shape of the simulated CCG and ACG. The top and bottom rows show simulated CCG and ACG, respectively. A and D: blue, black, gray, and red curves show simulations for different strengths of intracortical inhibition. “I strength” indicates the value of \( G_{\text{inh}} \) in the unit of nS. B and E: different colors show simulations for different firing rates in the excitatory model neurons without inhibition. C and F: different colors show simulations for different firing rates in the excitatory model neurons with inhibition (\( G_{\text{exc}} = 20 \) nS). D–F: orange and black arrowheads indicate the immediate dip and the delayed negative flank in the ACG, respectively.
Inhibitory pairs of model neurons (Fig. 14C), the CCG lacked negative flanks, as in the group 3 pairs, but the ACG showed small, delayed negative flanks.

The two remaining alterations of the cortical circuit (Fig. 14, D and E) revealed that the generation of negative CCG and ACG flanks depended importantly on linking intracortical inhibition to the activity of the excitatory model neurons. When I1 and I2 were driven strongly by an independent set of FF inputs but not by E1 and E2 (Fig. 14D), negative flanks were not present on the CCG, and delayed negative flanks did not appear on the ACG, despite the common FF inputs to I1 and I2. In contrast, when the inhibitory cortical neurons received inputs from the same pool of the input neurons that project to the excitatory cortical neurons—linking the activity of the inhibitory neurons to some degree with that of the excitatory neurons (Fig. 14E)—the CCG and ACG showed small, negative flanks.

Intracortical inhibition reduces spike-count noise correlations. In our data, there was a striking matching between the time course of the spike-count noise correlation and those of the negative CCG flanks and the integrated CCG (Fig. 3, A and C). Given that the strength of intracortical inhibition has a large effect on the negative CCG flanks in our computer simulations, we asked whether the strength of inhibition also affected the model’s noise correlations.

The noise correlation changed significantly with the strength of the intracortical inhibition. Figure 15, A and B, shows examples of the larger trial-by-trial correlation in the spike counts of the two neurons in the absence (Fig. 15A) vs. the presence (Fig. 15B) of intracortical inhibition. Averages across 10 simulated experiments at each level of intracortical inhibition revealed a monotonic and statistically significant effect (one-way ANOVA, P < 0.0001), reducing the noise correlation in our simple neural network from 0.35 to 0.2. To control the possible influence of the response magnitude on the noise correlation (de la Rocha et al. 2007), we kept the mean firing rates of E1 and E2 constant at different levels of intracortical inhibition by adjusting the firing rates of the input neurons. These results suggest a causal link from the strength of the excitation-triggered intracortical inhibition to the size of the negative flanks of the CCG, the value of the integrated CCG, and the trial-by-trial noise correlation. Thus our model makes the experimentally testable predictions that the enhancement of intracortical inhibition, time-locked to the spikes of excitatory neurons, should deepen the negative flanks in the CCG and ACG, and reduction of the inhibition should flatten the negative flanks. As a result, the enhancement of (or reduction of) excitation-triggered intracortical inhibition should reduce (or increase) noise correlations between the spike counts of two excitatory neurons.

**DISCUSSION**

Implications for the functional cortical circuitry. Our results emphasize the importance of intracortical connections and suggest functional roles for mutual cross-inhibition and recurrent inhibition. We have shown that these features of the
cortical circuitry have physiological signatures and suggest that they play an important role in regulating the computations performed in the cerebral cortex. Our results suggest that the central peak and negative flanks of the CCG are shaped by common FF inputs and mutual cross-inhibition. Furthermore, recurrent inhibition and intrinsic outward currents appear to contribute to the delayed negative flanks of the ACG.

To infer circuit structure from spike-timing correlations is challenging and the problem is somewhat underconstrained (Brody 1998, 1999; Perkel et al. 1967b). However, the exercise...
is valuable, as it provides useful insight and makes testable predictions to motivate future experimental investigation. In our very simple circuit model, the two inhibitory neurons receive common excitatory inputs, and each inhibits both of the excitatory neurons. Together, these connections give rise to correlated inhibition on the excitatory neurons, which is consistent with the finding of synchrony in the ipsp in simultaneous recordings from nearby pyramidal cells (Hasenstaub et al. 2005). To generate the negative flanks in the CCG and ACG, however, the intracortical inhibition has to be linked to the spiking activity of the excitatory neurons. In our model, direct activation of the inhibitory neurons by the excitatory neurons causes the deepest negative flanks. Shared FF excitation of the excitatory and inhibitory neurons is also effective but produces flanks at a shorter time lag. The relationship between the specific architecture of our model and the features that we see in the CCG and ACG suggests that the features in our model may be relevant in the functioning brain. We suggest that FF inhibition and recurrent intracortical inhibition probably coexist and may work synergistically to generate the negative flanks that we see in the CCG and ACG. We will discuss later how the negative flanks influence the processing of cortical signals.

Our findings, based on spike-timing correlations in awake monkeys, are consistent with in vitro studies of the cortical circuitry in the rodents. The axons of inhibitory interneurons typically arborize locally within a cortical column or laterally across columns (Markram et al. 2004), providing the necessary anatomical basis for recurrent inhibition and cross-inhibition. Direct evidence of recurrent inhibition came from a study by Yoshimura and Callaway (2005), who found that fast-spiking interneurons in layer 2/3 of V1 connect preferentially to neighboring pyramidal cells, which in turn, provide them with recurrent excitation. Furthermore, they found that the recurrently connected inhibitory interneuron and pyramidal cell pairs share common excitatory inputs. To mediate cross-inhibition, inhibitory interneurons may integrate dendritic inputs from a given pyramidal neuron and inhibit a nearby pyramidal neuron via axonal arbors. In addition, Ren and colleagues (2007) found that the activation of a pyramidal neuron may reliably inhibit nearby pyramidal neurons via axo-axonic synapses from an inhibitory interneuron. Inhibitory interneurons are coupled with electrical synapses (Galarreta and Hestrin 1999; Gibson et al. 1999), providing another way to create cross-inhibition.

There may be an interesting relationship among intracortical inhibition, noise correlations, and divisive normalization. Divisive normalization (Heeger 1992) is thought to be important for visual motion processing (Rust et al. 2006; Simoncelli and Heeger 1998) and may occur at multiple stages, including in area MT (Britten and Heuer 1999). In a recent computational study, Tripp (2012) showed that divisive FF normalization (Smith et al. 2006; Tripp 2012) can reduce the noise correlations between the responses of a pair of neurons. The recurrent and cross-inhibition in our model may be involved in feedback normalization. Yet, we do not know how divisive normalization is implemented in the cortical circuitry (Carandini 2004; Kouh and Poggio 2008). Moreover, the role of inhibition in normalization is still controversial (Katzner et al. 2011).

Our model does not have a built-in mechanism to account for the wide CCG and ACG when the firing rate was low, either during the motion period or during the presentation of a stationary stimulus after the initial onset response. The widening of the CCG and ACG under these conditions may be related to recurrent synaptic activity in the network that was not incorporated in our simple model circuit.

Mechanisms that might contribute to negative flanks in the ACG and CCG. We have interpreted the presence of negative flanks in the ACG and CCG as evidence for an important role for intracortical inhibition in normal sensory signaling. The work of others, as well as our own model, has highlighted other possible explanations for the negative flanks in the ACG and CCG. We consider these other explanations here.

First, the intrinsic refractory period is a potential source of the negative flanks in the ACG. The negative ACG flanks imply that the probability for a neuron to generate an action potential is lower than the baseline level for a brief interval following a spike. The intrinsic refractory period is one obvious candidate to create a depression of spiking. We modeled the refractory period after Somers and colleagues (1998) in a way that was designed to capture the events that occur quickly following spike generation, such as sodium-channel inactivation (Aldrich and Stevens 1987) and fast depolarization-activated K currents (Locke and Nernonl 1997). The refractory period created simulated ACGs with very brief negative dips but failed to create either delayed negative flanks in the ACG or negative flanks in the CCG. Second, the currents that cause AHPs should (and in our simulations do) create delayed negative flanks in the ACG. Whether we modeled the AHP currents using I_h, ISK, or a current contrived to cause the same postspike membrane potential as an ipsp, we were not able to simulate significant negative flanks in the CCG. Intracortical inhibition was required in our model to mimic the negative flanks seen in the CCG for pairs of MT neurons, although delayed outward currents may contribute to a very small portion of the negative flanks in the CCG. Third, we think it is unlikely that covariation in response to latency can lead to peaks in the CCGs (Brody 1998, 1999). In characterizing the negative flanks in the CCG (Fig. 5, A–C), we used neuronal responses calculated during the time interval from 150 to 450 ms after the onset of stimulus motion. Because most MT neurons have response latency shorter than 150 ms (Schmolesky et al. 1998), our analysis did not include the initial spikes in the response, and variation in response latency should have had little effect on our results. Fourth, we did not find the side peaks that we would expect to see in the CCGs spanning time lags from –300 to 300 ms if slow covariations in neurons’ excitability played a role in shaping the CCG (Brody 1998).

Finally, the responses of MT neurons in our data were quite irregular, implying that the shape of the CCG cannot be attributed to low background noise and regular interspike intervals (Ostojic et al. 2009). Even though the spiking of MT neurons can follow dynamic visual stimuli quite precisely (Bair and Koch 1996; Buracas et al. 1998), there are indications that they receive stochastic inputs in a high-input regime (Shadlen and Newsome 1998) under the stimulus conditions we used.

Implications for neural coding. The time course and the stimulus dependency of spike-timing correlations both indicate that the response correlation between a given pair of neurons is not fixed but can change dynamically depending on the visual stimuli and the activity level of the underlying network. The spike-timing correlations of a given pair of neurons change with the magnitude of their firing-rate responses. This suggests that intracortical inhibition is engaged when neurons are driven strongly by visual stimuli but is weak when the neural network...
is weakly activated or at baseline. The finding that the magnitude of the negative flanks of the CCG peaked some milliseconds after the peak response magnitude (Fig. 3A) suggests that the recruitment of intracortical inhibition takes time. This delay could include both the synaptic delays and the time required for the interneurons to integrate excitatory inputs.

Our results also suggest two possible functional roles for the inhibition that generates negative flanks in CCGs. First, it may reduce noise correlations in the cortical network. A similar function was suggested by the reduction of response correlations and the desynchronization of network activity by strong visual stimuli [see reviews by Harris and Thiele (2011); Kohn et al. (2009)]. The intrinsic biophysical properties of individual neurons seem to facilitate an increase in noise correlations with response magnitude (de la Rocha et al. 2007). Perhaps activity-dependent intracortical inhibition counterbalances these intrinsic effects and controls (or even suppresses) noise correlations when the cortical network is activated strongly. Our findings are consistent with the idea that balanced excitation and inhibition in recurrent networks can generate negative correlations that cancel the effect of shared input (Renart et al. 2010). Also, FF inhibition could reduce correlated response variability (Middleton et al. 2012).

A second functional role for intracortical inhibition may be to create the negative flanks in the CCG and thereby, to maintain precise synchrony of spike timing as firing rate increases. Inhibition elicited by a strong stimulus drive also contributes to a short integration time window for single neurons (Pouille and Scanziani 2001). Together, these effects could help to improve the efficiency of propagation of synchronized spikes through synapses and may facilitate information transfer in the cortex. Regulation of intracortical inhibition also could adaptively modulate the synchrony of spike timing.

Our results suggest significant time delays between the intracortical inhibition and excitation: the troughs of the CCG negative flanks were reached at time lags of ~6 ms. Thus the inhibition cannot counteract strong, positive correlations at a zero time lag but can limit the temporal spread of the positive correlation. Because of the delay, the area under the CCG curve does not approach zero, suggesting significant noise correlations in the neuron populations even when intracortical inhibition is strong. With the use of a firing-rate model, Bernacchia and Wang (2011) showed that recurrent inhibition that is slower than excitation in a heterogeneous neural network could reduce noise correlations but keep the level of correlations higher than that in the study by Renart et al. (2010).

Our finding of similar time courses for the negative flanks of the CCG, the delayed negative flanks of the ACG, the noise correlation, and the Fano factor of single neurons may reflect a single set of dynamics of the underlying neural network. Activity-dependent inhibition appears to be crucial in shaping the network dynamics and may play a pivotal role in controlling correlated neural activity and the precision of spike synchrony within the cortical network. Because correlations among the responses in neuronal populations have a large impact on coding sensory information (Averbeck et al. 2006), our results indicate that a circuit mechanism involving intracortical inhibition can significantly regulate the representation of sensory information in neuronal populations.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: X.H. and S.G.L. conception and design of research; X.H. performed experiments; X.H. analyzed data; X.H. and S.G.L. interpreted results of experiments; X.H. and S.G.L. prepared figures; X.H. drafted manuscript; S.G.L. and X.H. edited and revised manuscript; X.H. and S.G.L. approved final version of manuscript.

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