Behavioral/Systems/Cognitive

$GABA_A$ Inhibition Controls Response Gain in Visual Cortex

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$GABA_A$ inhibition is thought to play multiple roles in sensory cortex, such as controlling responsiveness and sensitivity, sharpening selectivity, and mediating competitive interactions. To test these proposals, we recorded in cat primary visual cortex (V1) after local iontophoresis of gabazine, the selective $GABA_A$ antagonist. Gabazine increased responsiveness by as much as 300%. It slightly decreased selectivity for stimulus orientation and direction, often by raising responses to all orientations. Strikingly, gabazine affected neither contrast sensitivity nor cross-orientation suppression, the competition seen when stimuli of different orientation are superimposed. These results were captured by a simple model in which $GABA_A$ inhibition has the same selectivity as excitation and keeps responses to unwanted stimuli below threshold. We conclude that $GABA_A$ inhibition in V1 helps enhance stimulus selectivity but is not responsible for competition among superimposed stimuli. It controls the sensitivity of V1 neurons by adjusting their response gain, without affecting their input gain.

Introduction

Information processing in sensory cortex relies on interactions between excitatory and inhibitory circuits, mediated by a diversity of GABAergic interneurons (Markram et al., 2004; Ascoli et al., 2008). As the specific functions of these interneurons are investigated, however, a broader question remains unanswered: in what way does GABA inhibition shape the output of excitatory neurons?

In primary visual cortex (V1), GABA inhibition has been proposed to play a fundamental role in establishing selectivity for stimulus orientation and direction of motion (Rose and Blakemore, 1974; Sillito, 1979; Tsumoto et al., 1979). According to this view, the sharpness of the orientation tuning curve of a neuron would depend critically on inhibition suppressing responses at the flanks of the curve (Vidyasagar et al., 1996; Sompolinsky and Shapley, 1997; Ferster and Miller, 2000).

Inhibition in V1 has also been proposed to control sensitivity and to mediate competition between stimuli. The responsiveness of V1 neurons decreases when the contrast of an optimal stimulus increases (contrast saturation) or when an orthogonal stimulus is superimposed (cross-orientation suppression). These phenomena are collectively known as contrast gain control, or normalization (Heeger, 1992; Busse et al., 2009). They have been ascribed to GABA inhibition from other cortical neurons (Morrone et al., 1982; Bonds, 1989; Carandini and Heeger, 1994; Carandini et al., 1997; Somers et al., 1998).

These proposals were initially supported by experiments that sought to block $GABA_A$ inhibition with bicuculline. Bicuculline was seen to reduce selectivity for orientation and direction, abolishing selectivity entirely in some cells (Pettigrew and Daniels, 1973; Rose and Blakemore, 1974; Sillito, 1975, 1979; Tsumoto et al., 1979; Sillito et al., 1980). Moreover, bicuculline was reported to abolish cross-orientation suppression (Morrone et al., 1987).

The intervening years, however, brought results that question the interpretation of these phenomena. Intracellular measurements indicate that inhibitory currents are as tuned for orientation as excitatory currents (Anderson et al., 2000; Monier et al., 2003; Mariño et al., 2005), putting in doubt their involvement in establishing selectivity for orientation (Ferster and Miller, 2000). Indeed, orientation selectivity appears to be immune to intracellular blockade of inhibitory currents (Nelson et al., 1994). Moreover, recent studies that used bicuculline have generally found much smaller effects than the earlier studies (Sato et al., 1996; Ozeki et al., 2004; Li et al., 2008). Finally, numerous properties of cross-orientation suppression make it unlikely to arise from intracortical inhibition (Freeman et al., 2002; Li et al., 2006; Priebe and Ferster, 2006).

Possible reasons for the disagreement across studies are that bicuculline has substantial side effects and that its impact on a network may depend critically on what portion of the cells it affects. Bicuculline has unwanted effects on calcium-dependent potassium channels (Kurt et al., 2006), so its use "should be discontinued in the study of inhibition" (Debarbieux et al., 1998).

A much more selective antagonist of $GABA_A$ receptors is SR95531, or gabazine (Kurt et al., 2006). Using local iontophoretic administration of gabazine, we examined the role of $GABA_A$ inhibition in determining neuronal responsiveness and selectivity in V1.

Materials and Methods

Experiments were performed at the Smith-Kettlewell Eye Research Institute. All procedures were approved by the Institutional Animal Care and Use Committee.

Surgical protocol. Eight adult female cats were initially anesthetized with ketamine (22 mg/kg) and xylazine (1.1 mg/kg). After venous can-

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nulation and tracheotomy, anesthesia was maintained for the subsequent 60–85 h with fentanyl (typically 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$), supplemented by inhalation of N_2O mixed with O_2 (typically in a ratio of 70:30) and, as needed, with sodium pentothal (up to 2 $mg \cdot kg^{-1} \cdot h^{-1}$). A craniotomy was performed over area V1. The pupils were dilated with atropine. Nictitating membranes were retracted with phenylephrine, and the eyes were protected with gas-permeable contact lenses. Muscle relaxation was induced with pancuronium bromide (0.15 $mg \cdot kg^{-1} \cdot h^{-1}$). The animals were artificially respirated and received an antibiotic (cephazolin, 20 mg/kg, twice a day), an anti-cholinergic agent (atropine sulfate, 0.05 mg/kg, daily), and an anti-inflammatory steroid (Dexamethasone, 0.4 mg/kg, daily). Fluid balance was maintained by intravenous infusion. Body temperature was maintained near 37°C with a heating pad. Depth of anesthesia was assessed from the EEG, the heart rate, and the level of expired CO_2 concentration.

Recordings and microiontophoresis. Microiontophoresis was performed with a NeuroPhore BH-2 system (Harvard Apparatus) via three-barrel carbon fiber combination electrodes (Carbostar-4; Kation Scientific). Micropipette barrels were filled with gabazine [SR95531, 10 mM, pH 3.0 (Tocris Bioscience), dissolved in 0.9% NaCl]. Ejection currents ranged from 50 to 150 nA, and retention current was −30 nA. Extracellular activity measured with the carbon fiber electrode was amplified, bandpass filtered between 300 Hz and 8 kHz, and digitized at 12 kHz. Estimates of the recording depth were based on micromanipulator readings.

In some experiments (10 of 19 datasets), we implanted a 10 × 10 microelectrode array with an electrode length of 1.5 mm and a grid spacing of 400 μm (Blackrock Microsystems). Methods for these recordings were provided previously (Nauhaus and Ringach, 2007). Spikes were extracted by bandpass filtering between 250 Hz and 7.5 kHz. Signals that crossed an appropriate threshold were saved to disk and defined as multiunit activity. The lateral distance between the carbon fiber electrode and the proximal edge of the array was typically 0.5–1.5 mm. The exact distance between electrode and array depends on relative depth, which we did not control.

Experimental design. Stimuli were generated with the Psychophysics Toolbox (Kleiner et al., 2007) and presented monocularly on a calibrated cathode ray tube monitor positioned 57 cm in front of the animal's eyes (Sony Trinitron 500PS, mean luminance of 32 cd/m^2, refresh rate of 120 Hz). Stimuli lasted 2 or 3 s and were separated by a uniform gray field (~4 s intervals). To measure responses, we averaged firing rate across the entire stimulus duration.

When a single neuron was isolated, we used drifting gratings to characterize its preferences for orientation, direction, spatial frequency, temporal frequency, and size. We then performed predrug control measurements of the following properties: (1) orientation tuning, in which we used drifting sinusoidal gratings at 50% contrast varying in orientation, with optimal spatial frequency (0.1–1.7 cycles/°) and optimal temporal frequency (1–4 Hz); (2) contrast saturation, in which we used drifting sinusoidal gratings varying in contrast, presented at the optimal orientation, spatial frequency, and temporal frequency; and (3) cross-orientation suppression, in which drifting plaids were obtained by summing an optimally oriented test grating and an orthogonal mask grating. The contrast of the mask was 25%. Stimulus diameters varied from 2.0–12.8° except for five experiments, in which we presented full-field gratings. Each of these measurements consisted of 4–10 consecutive blocks of stimulus presentations. Within each block, 5–16 stimuli were presented in random order.

We then applied gabazine at increasing levels of ejection current, while repeatedly measuring neuronal responses. Care was taken not to induce bursting (epileptiform) activity. When neuronal responses were significantly elevated, drug application was terminated. Retention current was applied again and additional measurements were taken until recovery was achieved (usually within 10–45 min). Sites in which spikes could not be held long enough or responses failed to recover were excluded from additional analyses (26 of 45). The effects of iontophoresis were not attributable to the current injection per se: responsiveness either kept increasing or remained significantly elevated in the minutes that followed the end of gabazine ejection.

Descriptive functions. Contrast responses were fitted with the hyperbolic ratio function (Albrecht and Hamilton, 1982):

$$R(c) = R_0 + R_{\max}\frac{c^n}{c_{50}^n + c^n}, \quad (1)$$

where c is stimulus contrast. The function has four parameters: baseline response R_0, responsiveness $R_{\max}$, semisaturation contrast c_{50}, and exponent n. The best fit model parameters were determined by simultaneously fitting the responses in the control and gabazine conditions. To limit the number of free parameters, we took the exponent n to be the same under both conditions. The semisaturation contrast c_{50} was allowed to vary across the two conditions or was forced to be the same across the two conditions ("response gain model").

To study cross-orientation suppression, we varied the test contrast while presenting a mask (25% contrast) and measured two additional contrast responses: one in the control condition and one in the gabazine condition. Data from these conditions were also fitted with a hyperbolic ratio (Eq. 1). For simplicity, we fitted the responses without mask with the response gain model; based on previous work (Freeman et al., 2002), we allowed a mask to affect only the baseline activity R_0 and the semisaturation contrast c_{50}.

We fitted the orientation tuning of responses with a sum of two Gaussians with peaks 180° apart (Carandini and Ferster, 2000):

$$R(\theta) = R_0 + R_p e^{-\frac{(\theta-\theta_p)^2}{2\sigma^2}} + R_n e^{-\frac{(\theta-\theta_p+180)^2}{2\sigma^2}}. \quad (2)$$

In this expression, θ is stimulus orientation (0–360°). The function has five parameters: preferred orientation θ_p, tuning width σ, baseline response R_0, response at the preferred orientation R_p, and response at the null orientation R_n. We took the preferred orientation θ_p to be the same across the control and gabazine conditions.

Simulations based on intracellular data. We considered published measurements of excitatory conductance, inhibitory conductance, membrane potential, and firing rate (Anderson et al., 2000) and simulated the effects of gabazine in those experiments. We chose four cells that were tested in the full 360° range of orientations and directions and that satisfied a criterion for quality of the estimates of excitation and inhibition (namely, that a linear model of the effect of injected current predicted >75% of the variance of the membrane potential).

Model of orientation selectivity. When modeling the effects of gabazine on orientation selectivity, we consider firing rate R to be a rectified version of membrane potential V (Carandini and Ferster, 2000):

$$R(\theta) = \max(0, V(\theta)). \quad (3)$$

We take the membrane potential to be the difference between currents attributable to excitation and inhibition:

$$V(\theta) = V_E(\theta) - V_I(\theta). \quad (4)$$

For simplicity, in these expressions, we take membrane potential and synaptic currents to be all in units of spikes per second and we set spike threshold to zero. Furthermore, we assume that the effect of gabazine is to abolish inhibition [$V_I(\theta) = 0$ under gabazine].

We describe the orientation tuning of excitation and inhibition with a sum of two Gaussians peaking 180° apart (Anderson et al., 2000):

$$V_x(\theta) = a_x\left[\exp\left(-\frac{(\theta-\theta_p)^2}{2\sigma_{x^2}}\right) + d\exp\left(-\frac{(\theta-\theta_p+180)^2}{2\sigma_{x^2}}\right)\right] + b_x, \quad (5)$$

Here, the subscript x can take the values E for excitation and I for inhibition. The shape of this function is determined by three parameters: preferred orientation θ_p, tuning width σ_x, and direction term d. The latter varies between 0 and 1 and is related to the direction index D as $d = (1-D)/(1+D)$. The remaining parameters a_x and b_x are a scaling factor that determines the amplitude of the modulation caused by orientation and a baseline value.

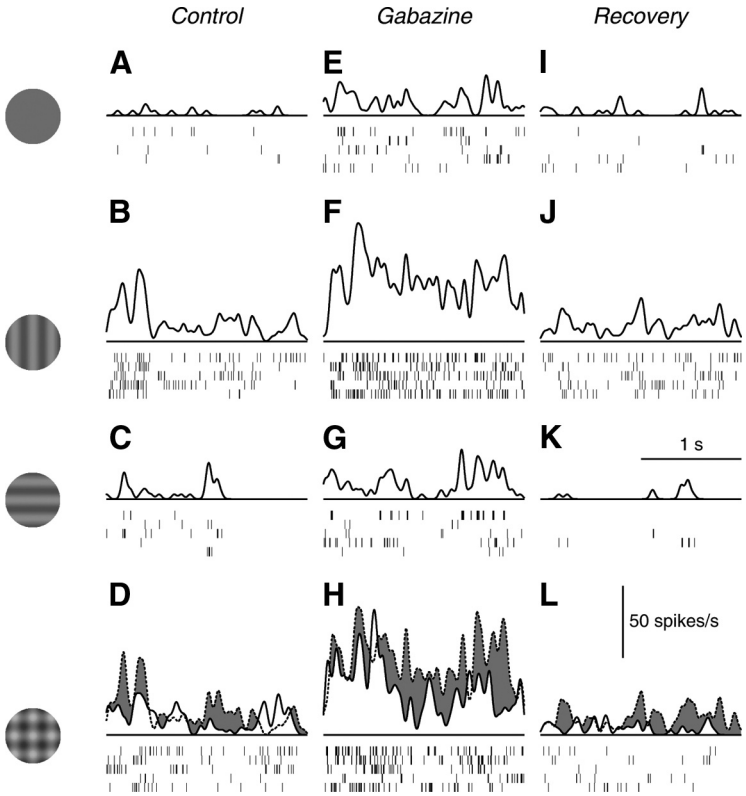

Figure 1. Examples of effects of the $GABA_A$ antagonist gabazine on spike responses. ***A–D,*** Responses of an example neuron (88.3.12-14-18) to a blank screen (***A***), to a grating drifting in the preferred (***B***) and orthogonal (***C***) direction, and to the plaid obtained by adding the two gratings (***D***). Dotted line in ***D*** indicates linear prediction obtained by summing responses in ***B*** and ***C***; gray area indicates suppression. Responses to each stimulus are shown as raster plots and firing rates. ***E–H***, Responses to the same stimuli during gabazine iontophoresis. ***I–L***, Responses in the subsequent control measurement.

The optimal parameters were determined by fitting simultaneously responses in control and gabazine conditions. For simplicity, we imposed that the preferred orientation θ_p and direction term d were the same for excitation and inhibition. For excitation, we allowed all remaining parameters to be free. For inhibition, we considered three possibilities: (1) "free inhibition," in which the tuning width of inhibition σ_I is allowed to differ from that for excitation σ_E; (2) "matching inhibition," in which the two are imposed to be the same ($\sigma_I = \sigma_E$); (3) "untuned inhibition," in which inhibition is imposed to be constant [$V_I(\theta) = b_I$].

We evaluated model performance with bootstrap hypothesis tests (Efron and Tibshirani, 1993). The application of this analysis to neural responses has been detailed previously (Carandini et al., 1997). Briefly, for each model, we tested the null hypothesis that the means of the probability distributions underlying the responses were identical to the predictions of the model. We determined an observed prediction error and computed the probability of observing at least as large an error if the null hypothesis were true. To obtain data that conformed to the null hypothesis, we transformed our measurements by equating their means across trials to the model predictions. We then obtained 1000 bootstrap samples from this transformed dataset and computed the prediction error for each of them. The proportion of bootstrap samples for which the prediction error was larger than the observed prediction error is the achieved significance level (ASL). The smaller the ASL, the stronger is the evidence against the null hypothesis, i.e., against the model.

Results

We recorded from 45 cells in cat V1. We report here on 19 of these cells, which were held long enough to measure their responses before, during, and after gabazine iontophoresis, with the last measurements displaying a full recovery from gabazine. These 19 cells were identified as complex and were mostly located in superficial layers.

As might be expected, the most visible effect of gabazine on V1 responses was to increase firing rates. We illustrate this effect on an example neuron (Fig. 1).The neuron had a low resting firing rate (Fig. 1*A*), responded markedly more to a grating of preferred orientation (Fig. 1*B*) than to an orthogonal grating (Fig. 1*C*), and showed cross-orientation suppression when the two gratings were superimposed (Fig. 1*D*). Applying gabazine increased the firing rate of this neuron both at rest (Fig. 1*E*) and in response to the visual stimuli (Fig. 1*F–H*). Gabazine made the neuron respond more to some stimuli that were previously ineffective (Fig. 1*G*), but it did not abolish selectivity (Fig. 1*F*,*G*) and it did not abolish cross-orientation suppression (Fig. 1*H*). The effects of gabazine were reversible: 30 min after switching off the iontophoresis, the responses returned to the level observed in the control condition (Fig. 1*I–L*).

Other aspects of the responses were not changed. In particular, the variability of the responses across trials remained constant: the ratio of variance to mean measured in 500 ms windows was 1.55 ± 0.06 in the control measurements versus 1.52 ± 0.04 under gabazine (mean ± SE, $n = 19$ neurons, $p = 0.49$). Similarly, the degree to which neurons acted as simple or complex cells remained largely unaffected: the ratio of F1 to DC response component (Skottun et al., 1991) was 0.31 ± 0.04 in control versus 0.36 ± 0.06 under gabazine (an insignificant change, $p = 0.3$).

Role of $GABA_A$ inhibition in contrast sensitivity

We first asked how $GABA_A$ inhibition affects the input–output properties of V1 neurons, i.e., the dependence of their responses on stimulus contrast. $GABA_A$ inhibition could shape the responsiveness of a neuron by controlling the gain at the input, at the output, or at both places.

Pure changes in input gain or in output gain would be particularly simple to describe. If $GABA_A$ inhibition scaled the input, it would effectively multiply the stimulus contrast that reaches the neuron, whereas if it scaled the output, it would multiply responses by the same factor at all contrasts. In the first case, blocking $GABA_A$ synapses with gabazine would shift contrast responses to the left in logarithmic contrast, i.e., change the semisaturation contrast of the neurons. In the second case, it would scale the curves vertically.

We measured the effects of gabazine on contrast responses and found strong evidence in favor of the second scenario: $GABA_A$ inhibition controls response gain but not contrast gain. We illustrate this evidence on four example neurons (Fig. 2*A–D*). Gabazine substantially increased the maximum response in all four neurons, by factors of 3.3, 2.6, 5.3, and 4.0. In two of the neurons (Fig. 2*A*,*D*), it also markedly increased the baseline response. Gabazine, however, did not affect contrast sensitivity: the contrast required to produce half of the saturating response of the

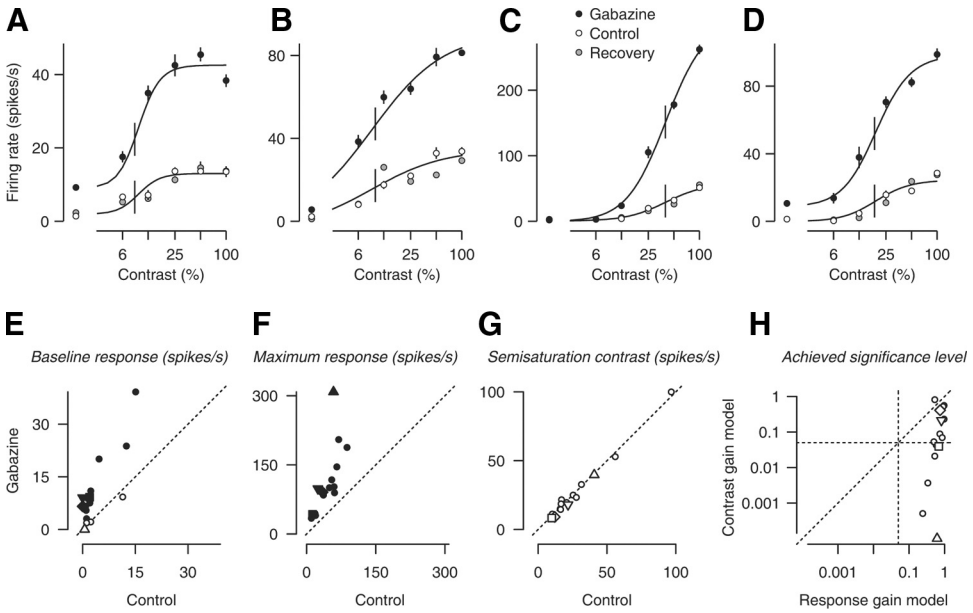

Figure 2. Effects of gabazine on contrast responses. ***A–D***, Contrast response functions of four example cells, measured in control condition (white), under gabazine (black), and in recovery condition (gray). Curves are fits of a response gain model, which has a fixed semisaturation contrast (vertical lines). Neurons 88.3.12-14-18 (***A***, same as in Fig. 1), 87.3.6-18-24, 83.8.15-19-23, and 83.12.6-8-11. ***E***, ***F***, Baseline response r_0 (***E***) and maximum response r_{max} (***F***) for all neurons in the population, in the control and gabazine conditions. Squares, diamonds, upward triangles, and downward triangles represent the neurons in ***A–D***. Filled symbols indicate neurons with significant deviation from the identity line (bootstrap test, $p < 0.05$). ***G***, Estimates of semisaturation contrast c_{50} in the control and gabazine condition, from a more general model in which gabazine was allowed to vary this parameter. ***H***, Comparison of achieved significance level for the response gain model (abscissa) and for a contrast gain model in which gabazine changes semisaturation contrast without affecting responsiveness (ordinate). The latter is markedly inferior to the former and can be rejected in six neurons at $p \leq 0.05$ (horizontal and vertical dashed lines).

cells was the same under control and gabazine conditions (Fig. 2*A–D*, vertical lines).

Indeed, the data from all neurons could be fitted with a simple response gain model, in which gabazine does not affect the contrast gain of the neurons. The model involves two contrast response functions (Eq. 1) having the same semisaturation contrast c_{50} for the control condition and for the gabazine condition. The model provided good fits, as can be judged on the example neurons (Fig. 2*A–D*). It explained a high proportion of the variance (98.7 ± 0.9%, mean ± SD, $n = 15$) and could not be rejected in any neuron based on an ASL of $p < 0.05$ (Fig. 2*H*, abscissa). The parameters of the model can thus be trusted; they indicate that in practically all neurons gabazine increased both baseline response (Fig. 2*E*) and maximum response (Fig. 2*F*). Maximum responses, in particular, increased on average by 167 ± 25% (mean ± SE, $n = 15$). This increase was significant in all cells ($p < 0.001$).

An alternative model, in which gabazine affected only the contrast gain of the neuron, provided markedly inferior fits (Fig. 2*H*). We considered a pure contrast gain model, which allowed gabazine to affect the semisaturation contrast and the baseline response of the neuron but not its maximal response. Compared with the response gain model, the contrast gain model explained a markedly smaller proportion of the variance (94.6 ± 2.8%, mean ± SD, $p = 0.0001$) and could be rejected for 6 of 15 neurons based on an ASL of $p \leq 0.05$ (Fig. 2*H*, ordinate).

Finally, a more general model in which gabazine could affect both response gain and contrast gain did not improve on the excellent performance of the response gain model. The more general model allowed for changes not only in baseline and maximal response but also in semisaturation contrast. This additional parameter, however, provided little advantage over the response gain model: the more general model explained a similar proportion of the variance (99.0 ± 0.9%, mean ± SD, $n = 15$) as the response gain model, with extremely similar values for the ASL. Critically, the values of semisaturation contrast measured by the more general model under gabazine were indistinguishable from those measured in the control condition (Fig. 2*G*). These results, therefore, further indicate that $GABA_A$ inhibition in V1 is a powerful mechanism for the control of response gain but is not involved in the control of contrast gain, i.e., of input gain.

Role of $GABA_A$ inhibition in cross-orientation suppression

We next considered another well-documented signature of contrast gain control or normalization: cross-orientation suppression (Morrone et al., 1982; Bonds, 1989; Bauman and Bonds, 1991; DeAngelis et al., 1992; Sengpiel and Blakemore, 1994; Carandini et al., 1997; Sengpiel et al., 1998; Allison et al., 2001; Busse et al., 2009). Suppression can be observed by superimposing two gratings: one (the test) with the preferred orientation and the other (the mask) with a different orientation (Fig. 1*B*,*C*). The response to the superposition of the stimuli is typically lower than expected from summation (Fig. 1*D*). The strength of this effect depends on the relative contrasts of test and mask (Fig. 3*A*,*B*). When the test is presented alone, V1 responses simply increase with increasing test contrast (Fig. 3*B*, filled circles). Adding a mask to the test reduces these responses, effectively shifting the contrast–response functions to the right (Fig. 3*B*, open circles). Cross-orientation suppression is present with masks of all orientations (DeAngelis et al., 1992); we chose orthogonal masks because they provide the least drive to the neurons, so their effect is almost purely suppressive.

To assess whether cross-orientation suppression relies on $GABA_A$ inhibition, we asked whether its strength is affected by gabazine (Fig. 3*C–J*). We illustrate the results for two example cells (Fig. 3*C–F*). Both cells showed strong cross-orientation sup-

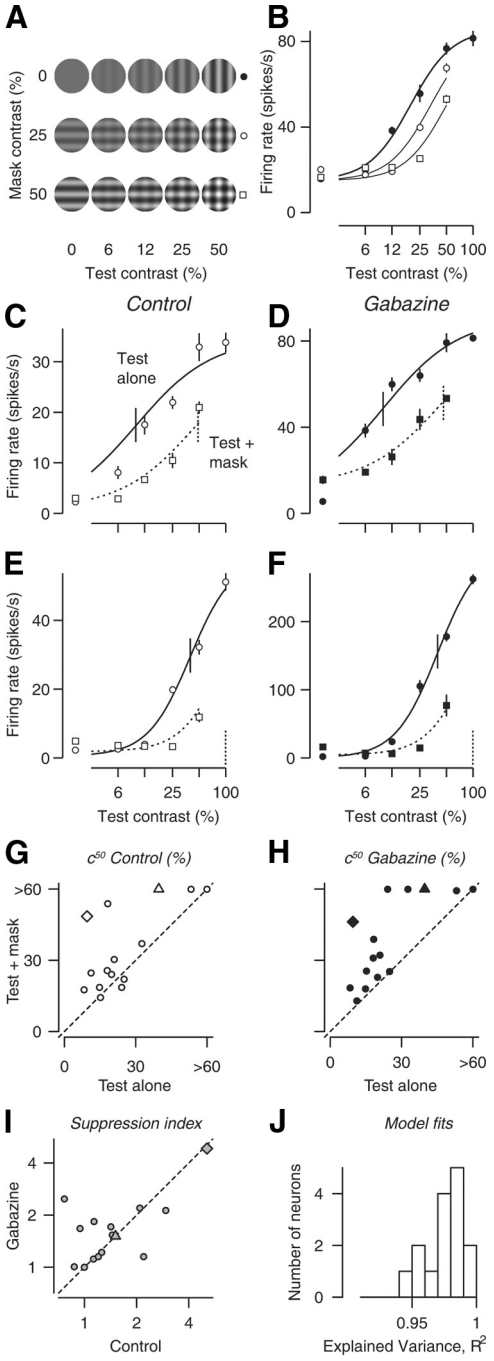

Figure 3. Cross-orientation suppression. ***A***, Stimuli were test gratings at the preferred orientation of the cell (first row), mask gratings at the orthogonal orientation (left column), or plaids obtained by summing the two (remaining columns). ***B***, Contrast response functions for one example cell. Different symbols indicate the contrast of the mask (0, 25, and 50%). Neuron 83.10.15-u42. ***C***, Responses of the neuron shown in Figure 2*B* to a test having a preferred orientation presented alone (circles, solid line) or together with an orthogonal mask (squares, dashed lines). ***D***, Same, under the $GABA_A$ antagonist gabazine. ***E***, ***F***, Same, for the neuron shown in Figure 2*C*. Curves are fits of the response gain model. Vertical lines indicate the value of the semisaturation contrast (c_{50}) in the absence (solid lines) and in the presence (dashed lines) of the mask. ***G***, Suppressive effect of the mask across the population in the control condition. ***H***, Same, under gabazine. ***I***, Gabazine-resistant suppression of responses across the population. Diamonds and triangles represent the neurons in ***C***,***D*** and in ***E***,***F***. ***J***, Fraction of variance explained by this response gain model across the dataset.

pression: adding a mask to the test grating increased the semisaturation contrast c_{50} from 10 to 49% in one cell (Fig. 3*C*) and from 40 to 100% (the upper limit in our fits) in the other cell (Fig. 3*E*). If we define a suppression index as the ratio of semisaturation contrasts measured with and without the mask (Freeman et al., 2002), these two cells showed suppression indices of 5.1 (the largest in our sample) and 2.5. Remarkably, this strong degree of suppression was completely unaffected by blocking $GABA_A$ inhibition with gabazine (Fig. 3*D*,*F*). Gabazine markedly increased the overall firing rates, as expected, but did not affect the semisaturation contrast c_{50} in either the test alone case (as seen in the previous section) or the test plus mask case. Indeed, under gabazine, the suppression indices were 4.9 for the first cell (Fig. 3*D*) and 2.5 for the second cell (Fig. 3*F*), which are essentially the same values as in the control condition.

Very similar results were obtained across the population of recorded cells: gabazine did not reduce cross-orientation suppression. Adding a mask to the test grating suppressed responses for most of the cells not only in the control condition (Fig. 3*G*) but also under gabazine (Fig. 3*H*). Gabazine did not decrease the suppression index; if anything, it increased it (Fig. 3*I*).

Indeed, the data were well fit by a model in which the only effect of gabazine was to increase response gain and baseline response. In this model, there are two semisaturation contrasts: one measured without the mask and one measured with the mask, and the values of these semisaturation contrasts are the same in the control case and under gabazine. This model provided excellent fits to the data. (Fig. 3*J*), explaining on average 98 ± 1% of the variance (mean ± SD, $n = 15$). Cross-orientation suppression, therefore, is not attributable to $GABA_A$ inhibition.

Role of $GABA_A$ inhibition in stimulus selectivity

Having identified a specific role for $GABA_A$ inhibition in response gain control, we now ask whether this effect is the same for all stimulus orientations and directions. In other words, we asked whether $GABA_A$ inhibition also plays a role in shaping the selectivity of a neuron for these attributes. To this end, we measured tuning curves for stimulus orientation and direction of motion. We illustrate the results for four example cells (Fig. 4*A–D*).

Similar to the previous experiments (Fig. 2*F*), we found that the main effect of gabazine was invariably an overall increase in responsiveness. Responsiveness (measured here as the average response across orientations) increased by at least a factor of 2.5 in these four cells and in a dramatic example by almost a factor of 4 (Fig. 4*B*). Across the sample, gabazine increased responsiveness by 242 ± 48% (mean ± SE, $n = 19$) (Fig. 4*E*). The increase was significant in all cells ($p < 0.002$, bootstrap test).

Additional effects were a broadening of tuning width and a reduction in direction selectivity. These effects were strongest in the cells that were initially sharply tuned for orientation (Fig. 4*D*) or that displayed marked direction selectivity (Fig. 4*B*,*D*).

To assess the effects of gabazine on overall orientation selectivity (Fig. 4*F*), we used a global measure of selectivity, the circular variance (Ringach et al., 2002). Circular variance grows with the mean of the response across orientations (the untuned response) and decreases with the amplitude of the modulation seen by changing orientation (the tuned response). Higher values of circular variance, therefore, indicate weaker selectivity. Gabazine affected circular variance significantly in 11 of 19 cells ($p < 0.05$, bootstrap test) (Fig. 4*F*, filled symbols). In these cells, circular variance increased by 52 ± 15% (mean ± SE, $n = 19$). Gabazine, therefore, tended to increase the untuned responses more than the tuned responses.

In neurons that were particularly selective for orientation, gabazine broadened the orientation tuning curves (Fig. 4*G*). Tuning width (the parameter σ in the Gaussian curve fitted to the data) changed significantly under gabazine in 7 of 19 cells ($p <$

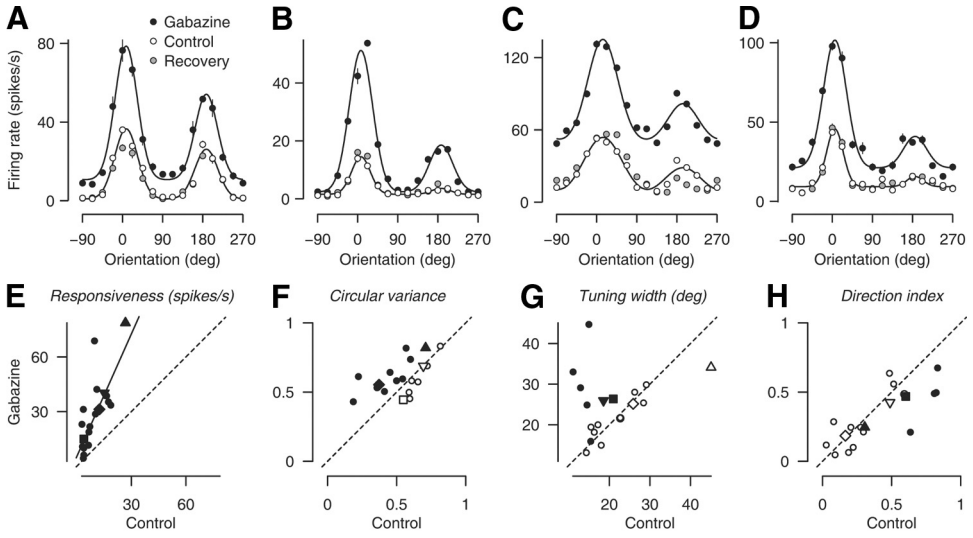

Figure 4. Effects of gabazine on orientation tuning. ***A–D***, Four example cells. Symbols indicate whether tuning curves were measured before, during, or after gabazine iontophoresis. Curves are fits of a descriptive tuning function (sum of Gaussians). Stimulus orientation is expressed relative to preferred orientation. Neurons 86.7.6-10-16, 83.9.9-10-17, 86.3.6-21-28, and 88.5.6-9-13. ***E–H***, Effects of gabazine on tuning parameters across the population of neurons: effects on responsiveness (***E***), circular variance (***F***), orientation tuning width (***G***), and direction selectivity (***H***). In all graphs, black symbols indicate neurons with significant deviation from the identity line (bootstrap test, $p < 0.05$). Diamonds, squares, upward triangles, and downward triangles represent the four cells in ***A–D***.

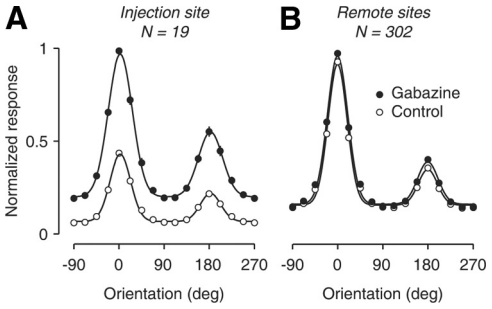

Figure 5. Effects of gabazine are local. ***A***, Average of tuning curves measured at the iontophoresis site in 19 experiments, aligned relative to preferred orientation. ***B***, Average of 302 tuning curves measured with a nearby multielectrode array in 10 of the 19 experiments.

0.05, bootstrap test) (Fig. 4*G*). In these cells, it increased by 95 ± 28% on average (mean ± SE, $n = 19$). Consistent with previous results obtained with bicuculline (Li et al., 2008), the cells in which tuning width increased were among the most highly selective for orientation, with an average σ of 15 ± 1° versus 23 ± 2° for the remaining cells.

Finally, gabazine significantly decreased direction selectivity, especially in those cells that showed significant selectivity to begin with (Fig. 4*H*). We measured direction selectivity through a direction index (Carandini and Ferster, 2000). Gabazine reduced the direction index in 6 of 19 cells ($p < 0.05$, bootstrap test) (Fig. 4*H*). In these cells, the direction index was reduced by 34 ± 7% (mean ± SE, $n = 19$). Similar to the changes in tuning width, the cells whose direction index was reduced tended to be the most direction selective ($D = 0.67 \pm 0.08$ for those 6 cells vs 0.28 ± 0.05 for the remaining ones).

All of these effects were local to the region of iontophoresis, being completely absent in responses measured ~1 mm away (Fig. 5). We compared the effects of gabazine at the site of iontophoresis (Fig. 5*A*) with those measured ~0.5–1.5 mm away with a 10 × 10 array of electrodes (Fig. 5*B*). Whereas the responses of the local sites strongly increased in the presence of gabazine (mean factor of 3.4 ± 0.5, mean ± SE, $p < 0.0001$, $n = 19$), the responses measured from distant sites were unaffected: the average responsiveness increased by an insignificant factor of 1.1 ± 0.1 (mean ± SE, $n = 302$ sites measured in 10 experiments, $p = 0.6$), with no changes in tuning curves (Fig. 5*B*).

Insights from intracellular data

To gain some insight into these results, we asked whether they are consistent with what is known about excitation and inhibition from intracellular measurements (Fig. 6). We considered published measurements of excitatory conductance, inhibitory conductance, membrane potential, and firing rate (Anderson et al., 2000) and simulated the effects of gabazine in those experiments.

We illustrate the results for four cells that were generally well tuned, with three of four giving clear spike responses to gratings of the preferred orientation (Fig. 6*A*, open symbols). The corresponding depolarizations in membrane potential (Fig. 6*B*, gray shading) were accompanied by a concomitant increase in excitatory conductance (Fig. 6*C*) and in inhibitory conductance (Fig. 6*D*), which are typically similarly tuned for orientation (Anderson et al., 2000; Monier et al., 2003; Mariño et al., 2005).

To simulate the effects of gabazine, we set inhibitory conductances to zero and computed the resulting membrane potentials, taking into account the reduced conductance of the neuron; the result is a substantially depolarized potential (Fig. 6*B*, blue shading). Having made a rough estimate of how membrane potentials are transformed into firing rates (Carandini and Ferster, 2000), we could then predict how gabazine would affect the tuning of firing rate (Fig. 6*A*, filled symbols). The main predicted effect is a nonspecific increase in response and a broadening of tuning widths, similar effects to those obtained in our extracellular measurements (Fig. 4).

Excitation, inhibition, and threshold

The exercise performed on intracellular data suggests that the effects of gabazine on the tuning curves for orientation can be explained by known properties of synaptic inhibition. Indeed, it indicates that the effects we have seen under gabazine would be fully expected if the inhibition removed by gabazine has the same

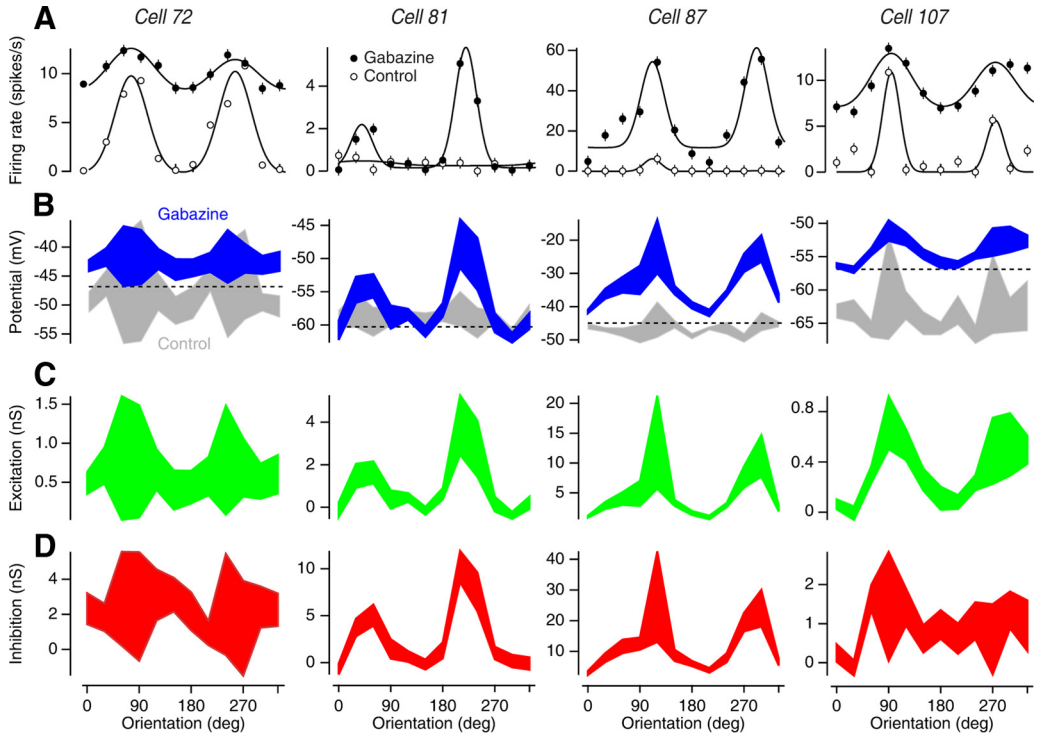

Figure 6. Simulation of effects of gabazine based on actual measurements of excitation and inhibition. Shown are four neurons (columns) from a study using intracellular measurements (Anderson et al., 2000). ***A***, Firing rates measured (white symbols) and predicted if there was no inhibition (black symbols). ***B***, Membrane potentials measured (gray) and predicted if there were no inhibition (blue). The colored regions indicate 90% confidence intervals; the large variability is only minimally attributable to measurement noise and rather reflects the fact that V_m varied over the course of the stimulus (which is to be expected). ***C***, Measured total conductances (increment over the resting condition) for synaptic excitation. ***D***, Same, for synaptic inhibition.

tuning as excitation. A key role in this prediction is played by threshold, which normally prevents spiking responses to most orientations but is no longer able to do so under gabazine.

To test these hypotheses quantitatively, we considered a very simple cellular model (Fig. 7). In the model, the firing rate of the neurons (Fig. 7*A*) depends on an underlying membrane potential response (Fig. 7*B*), and the relation between the two (Fig. 7*B*, shaded area) is described by a simple rectification function, a threshold followed by a linear relationship (Carandini and Ferster, 2000; Priebe et al., 2004; Cardin et al., 2007). The membrane potential response, in turn, is the difference of two sets of synaptic contributions: excitation and inhibition (Fig. 7*C*,*D*). In agreement with intracellular measurements (Fig. 6*C*,*D*), we take excitation and inhibition to have the same preferred orientation (Anderson et al., 2000; Monier et al., 2003; Mariño et al., 2005) and direction (Priebe and Ferster, 2005). Finally, in the model, gabazine abolishes inhibition while leaving excitation unchanged (Fig. 7*G*,*H*), leading to more depolarized membrane potentials and consequently to firing rates that are higher and less tuned (Fig. 7*E*,*F*). The model is specified by few free parameters, which determine the shapes and offsets of Gaussian tuning curves for excitation and inhibition.

This highly simplified cellular model provided an excellent account of the effects of gabazine on the tuning curves (Fig. 8). For the four example cells, the model captured how gabazine increases responsiveness and reduces selectivity for stimulus orientation and direction (Fig. 8*A*–*D*, solid curves). Similar results were obtained in the remaining cells, with the model explaining on average 96 ± 2% (mean ± SD, $n = 19$) of the variance in the responses. This good performance of the model was statistically significant in 15 of 19 cells, in which the model could not be

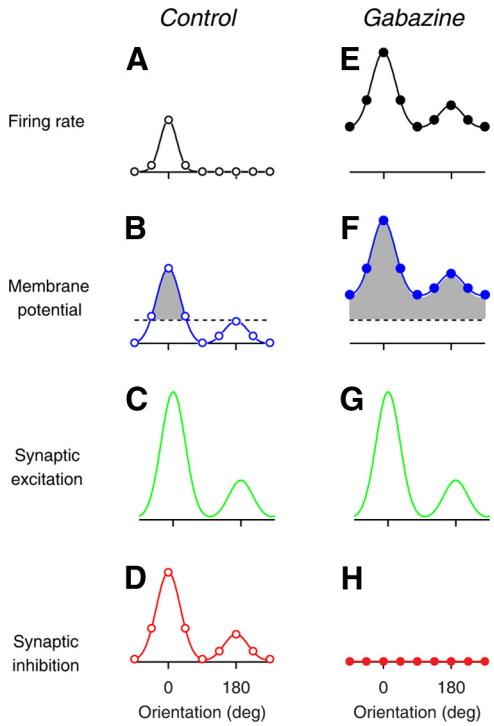

Figure 7. A simple cellular model. ***A***, Tuning of firing rate in control condition. ***B***, Corresponding tuning of membrane potential responses. Dashed line indicates threshold. Shaded area indicates responses that elicit nonzero firing rates. ***C***, Tuning of excitation. ***D***, Tuning of inhibition, under the simplified assumption that inhibition has the same tuning as excitation (matching inhibition). In the untuned inhibition version of the model, this curve would be flat. ***E***–***H***, Same, under gabazine.

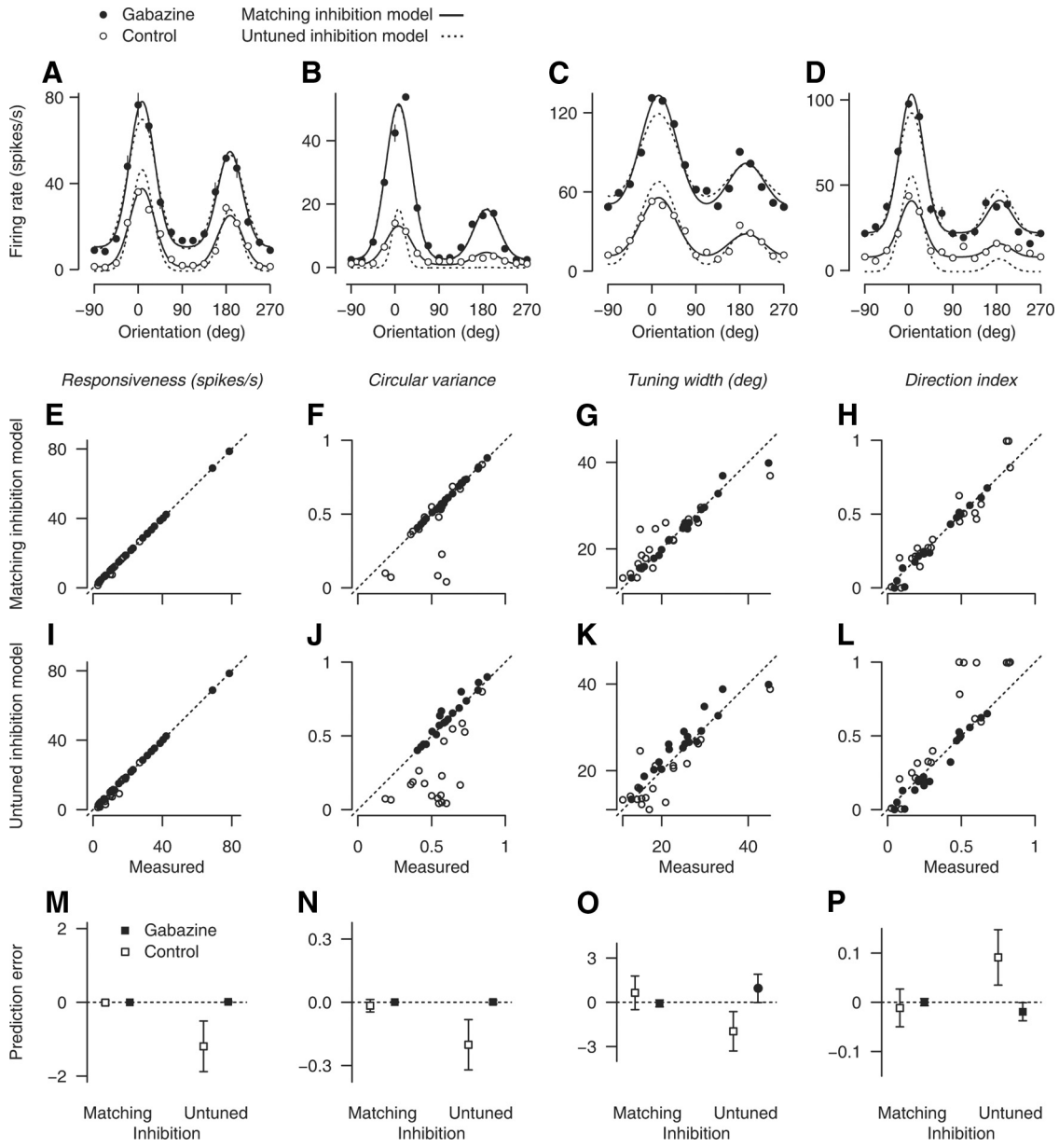

Figure 8. Predictions and performance of the simple cellular model. ***A–D***, Responses of the example neurons of Figure 4, fitted with the simple cellular model (Fig. 7), assuming matching inhibition (solid curves) or untuned inhibition (dashed curves). ***E–H***, Effects of gabazine compared with predictions of the matching inhibition model: responsiveness (***E***), circular variance (***F***), tuning width (***G***), and direction index (***H***). ***I–L***, Same, for the untuned inhibition model. ***M–P***, Comparison of prediction errors made by the matching inhibition model and by the untuned inhibition model. Shown are median deviations from the identity lines in ***E–L***; error bars are 95% confidence intervals.

rejected with an ASL of $p < 0.05$. Specifically, the model was able to capture the main effects of gabazine on responsiveness, circular variance, tuning width, and direction selectivity (Fig. 8*E–H*). The exceptions (values off the identity line) generally involve the fits to the control responses (open symbols). These responses involve lower firing rates, which the fitting procedure tries less hard to capture.

A simpler version of the model, in which inhibition is not tuned for orientation, proved to be inadequate. In this version (untuned inhibition), inhibition is specified by one parameter (offset) rather than two (offset and tuned amplitude). This version of the model provided worse fits (Fig. 8*A–D*, dashed curves). On average, it accounted for only 93 ± 4% (mean ± SD, $n = 19$) of the variance of the responses, which is significantly less than the version with matching inhibition ($p < 0.0001$, paired t test). Throughout, the prediction errors of the untuned inhibition model were larger than those of the matching inhibition model (Fig. 8*M–P*). Accordingly, the fits of the untuned inhibition version of the model provided noticeably worse scores of ASL, and this model could be rejected at the $p < 0.05$ level for 8 of the 19 cells.

Conversely, a more general version of the model, in which excitation and inhibition were not required to match, did not provide any advantages. In this version (free inhibition model), the tuning width of inhibition was free to be narrower or broader from that of excitation. This model includes as a special case the matching inhibition model, in which excitation and inhibition have identical tuning. However, the additional free parameter for the tuning of inhibition did not noticeably improve the fits: for each neuron the ASL score achieved under free inhibition was

almost identical to the ASL score under matching inhibition. Moreover, in those four cases in which we had to reject the model with matching inhibition, we also had to reject the model with free inhibition.

These analyses confirm the impression provided by our initial simulations based on intracellular data. They indicate that the effects of gabazine can be most parsimoniously explained by a loss of an inhibitory drive that has the same tuning as the excitatory drive.

Discussion

Using a combination of pharmacology, electrophysiology, and simple modeling, we have investigated the role of local $GABA_A$ inhibition in shaping the output of neurons in cat primary visual cortex. We have recorded from cells before, during, and after iontophoresis of the highly selective $GABA_A$ antagonist gabazine. The results indicate that $GABA_A$ inhibition contributes in simple ways to the sensitivity and selectivity of V1 neurons.

Our first set of results concerns the sensitivity of neurons: we found that local $GABA_A$ inhibition controls the response gain but not the contrast gain of V1 neurons. These results contradict previous proposals for a key role of $GABA_A$ inhibition in contrast gain control (Carandini and Heeger, 1994; Carandini et al., 1997; Somers et al., 1998), because they indicate that the contrast sensitivity of V1 neurons does not rely on intracortical inhibition. This conclusion may well extend to other cortical areas; for instance, contrast sensitivity in middle temporal area MT of primates is unaffected by blocking inhibition with bicuculline (Thiele et al., 2004).

These results suggest that $GABA_A$ inhibition may be a natural substrate for the control of responsiveness seen during the deployment of visual attention. A recent study, indeed, argues that attention changes the response gain but not the contrast gain of V1 neurons (Lee and Maunsell, 2010). Attention could achieve this goal rather simply if it acted on the strength of $GABA_A$ inhibition.

Our finding that cross-orientation suppression is unaffected by gabazine is direct evidence that this form of suppression does not rely on intracortical inhibition. This finding corroborates previous indirect evidence against a role of inhibition in cross-orientation suppression (Carandini et al., 2002; Freeman et al., 2002; Li et al., 2006; Priebe and Ferster, 2006). In fact, the only data supporting a GABAergic origin of cross-orientation suppression were obtained by blocking inhibition with a diffuse application of bicuculline (Morrone et al., 1987). The interpretation of those data is made difficult by the limitations of bicuculline (Debarbieux et al., 1998).

Contrast saturation and cross-orientation suppression are key pieces of evidence for divisive normalization in V1 (Heeger, 1992; Carandini et al., 1997; Busse et al., 2009). Our results show that they do not rely on $GABA_A$ inhibition and thereby falsify an early proposal for the biophysical substrate of normalization (Carandini and Heeger, 1994; Carandini et al., 1997). Normalization is now thought to rely on alternative mechanisms, at least for phenomena that arise within the receptive field (Carandini et al., 2002; Priebe and Ferster, 2006; Finn et al., 2007). It is currently unclear whether normalization relies on $GABA_A$ inhibition for suppression originating in the surrounding regions (Ozeki et al., 2009; Haider et al., 2010).

Our second set of results concerns stimulus selectivity: we found that local $GABA_A$ inhibition contributes to the selectivity of V1 neurons for stimulus orientation and direction. Inhibition contributes to selectivity simply by matching the selectivity of excitation, thereby keeping the responses to most stimuli below threshold.

The effects of gabazine on tuning curves (increased firing rates, broadened tuning width, and reduced direction selectivity) confirm some but not all of the previous results obtained with bicuculline. Early studies reported very strong effects: bicuculline was seen to broaden markedly the selectivity for orientation or direction of most neurons, in some cells abolishing it altogether (Pettigrew and Daniels, 1973; Rose and Blakemore, 1974; Sillito, 1975, 1979; Tsumoto et al., 1979; Sillito et al., 1980; Eysel and Shevelev, 1994). More recent studies, however, reported subtler effects that are more similar to the ones we observed (Sato et al., 1996; Ozeki et al., 2004; Li et al., 2008). As with gabazine, the size of the effects seen with bicuculline depended on the degree to which neurons are selective in the first place (Li et al., 2008). Overall, the large variability of effects reported in bicuculline studies might be related to the inferior selectivity and non-GABAergic side effects of this drug (Wermuth and Bizière, 1986; Debarbieux et al., 1998; Kurt et al., 2006) or to differences in doses across studies.

To capture the effects of gabazine on orientation tuning curves, we considered a simple cellular model based on a precise match between the tuning of inhibition and excitation. Excitation and inhibition in visual cortex have similar selectivity for orientation (Anderson et al., 2000; Monier et al., 2003; Mariño et al., 2005) although perhaps not for direction (Monier et al., 2003; Priebe and Ferster, 2005) or for stimulus size (Ozeki et al., 2009; Haider et al., 2010). The selectivity of inhibition matches that of excitation also in somatosensory cortex (Okun and Lampl, 2008) and in auditory cortex (Wehr and Zador, 2003). Inhibition and excitation, moreover, are matched not only in sensory-evoked activity but also in the ongoing activity (Haider et al., 2006; Okun and Lampl, 2008; Adesnik and Scanziani, 2010). This match between excitation and inhibition, therefore, may be a fundamental organizing principle of neocortex [but not necessarily all of cortex (Poo and Isaacson, 2009)].

The cellular model that we considered incorporates highly simplified assumptions. First, it assumes that membrane potential is the result of the subtraction of inhibition from excitation. Subtraction is a simplification because inhibition does provide conductance increases at least at some orientations (Borg-Graham et al., 1998; Anderson et al., 2000), which would result in a nonlinear integration of synaptic inputs (a fact that we did include in our simulations based on intracellular data). Second, the model assumes that the relationship between firing rate and the underlying membrane potential is simply a threshold followed by a linear dependence. Intracellular measurements support this notion but also indicate that noise in the membrane potential (which we ignored) smoothes the threshold and turns it into an exponent (Carandini and Ferster, 2000; Carandini, 2004; Priebe and Ferster, 2008). Third, we assumed that the responses observed under gabazine mostly reflect excitatory synaptic inputs, because synaptic inhibition has been essentially abolished. This is oversimplified, because gabazine is likely to have reached the perisomatic region more than the distal dendrites (see below). Also, although $GABA_B$ receptors are unlikely to shape transient visual responses, they may contribute to responses on the scale of seconds. Finally, we assumed that gabazine affected only inhibition, whereas it is likely to have increased (and slightly broadened in tuning) the excitation that the neurons receive from the local network.

Although it was so highly simplified, the model provided a full account of the effects of gabazine on orientation tuning. It predicted the effects of gabazine on overall responsiveness, tuning

width, and direction selectivity. This success suggests that all the effects of gabazine, including those that had previously been ascribed to broadly tuned inhibition, can be explained by inhibition having the same tuning as excitation.

One limitation of our study is that it addresses mostly the inhibition that neurons receive near the soma. Our electrode likely recorded signals near the soma and, given that the ejecting pipette was 20 μm away, the concentration of gabazine is likely to have been largest in the perisomatic region. Concentration at the distal dendrites may have been low, given that gabazine did not affect electrode arrays implanted 0.5–1.5 mm away from the ejecting pipette.

The conclusions that can be drawn from this study, therefore, concern mostly perisomatic inhibition rather than inhibition on distal dendrites. Indeed, this limitation is shared with many other studies on the role of inhibition. Intracellular studies of the orientation tuning of excitation and inhibition, for instance, are primarily based on currents injection at the soma. These currents do not fully spread to distal dendrites (Williams and Mitchell, 2008), so the conductances that are estimated are primarily perisomatic.

Another limitation of our study concerns the specificity of our manipulations. Although we strived to keep the injection of gabazine local, the drug is likely to have spread beyond the neuron under study, potentially altering the function of local microcircuits. Substances applied iontophoretically with similar methods can diffuse as much as 200–600 μm (Candy et al., 1974). Pyramidal neurons in sensory cortex excite one another over comparable distances (Thomson and Lamy, 2007). Therefore, the increase in responsiveness seen with gabazine might be attributable not only to cellular effects (the blockade of perisomatic $GABA_A$ receptors) but also to network effects: an increase in mutual excitation brought about by increased responsiveness in interconnected neurons. We cannot distinguish these two effects and neither can all previous studies that attempted to block inhibition, with the exception of one that blocked inhibition intracellularly (Nelson et al., 1994). The good agreement between our results and those of that study indicates that the main effects that we observed are cellular.

In conclusion, we found that local inhibition mediated by $GABA_A$ receptors controls tuning width and direction selectivity not by being broadly tuned but rather by working hand in hand with an excitatory drive that has the same selectivity. Together, excitation and inhibition exploit the ability of the spike threshold to sharpen orientation tuning, improve direction selectivity, and set the appropriate responsiveness. $GABA_A$ inhibition plays a substantial role in the control of responsiveness: it makes neurons more or less responsive to stimuli, without affecting their sensitivity to contrast. In other words, $GABA_A$ inhibition does not participate in input gain control but rather is a determinant factor in response gain control.

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