

Cellular Mechanisms Underlying Stimulus-Dependent Gain Modulation in Primary Visual Cortex Neurons In Vivo

Jessica A. Cardin,¹ Larry A. Palmer,¹ and Diego Contreras^{1,*}

¹Department of Neuroscience, University of Pennsylvania School of Medicine, 215 Stemmler Hall, Philadelphia, PA 19106, USA

*Correspondence: diegoc@mail.med.upenn.edu

DOI 10.1016/j.neuron.2008.05.002

SUMMARY

Gain modulation is a widespread neuronal phenomenon that modifies response amplitude without changing selectivity. Computational and in vitro studies have proposed cellular mechanisms of gain modulation based on the postsynaptic effects of background synaptic activation, but these mechanisms have not been studied in vivo. Here, we used intracellular recordings from cat primary visual cortex to measure neuronal gain while changing background synaptic activity with visual stimulation. We found that increases in the membrane fluctuations associated with increases in synaptic input do not obligatorily result in gain modulation in vivo. However, visual stimuli that evoked sustained changes in resting membrane potential, input resistance, and membrane fluctuations robustly modulated neuronal gain. The magnitude of gain modulation depended critically on the spatiotemporal properties of the visual stimulus. Gain modulation in vivo may thus be determined on a moment-to-moment basis by sensory context and the consequent dynamics of synaptic activation.

INTRODUCTION

Modulation of the sensitivity, or gain, of neurons to specific inputs without concomitant alteration of selectivity is a fundamental property observed throughout the nervous system and a defining element of the contribution of single neurons to network operations. Gain modulation has been shown in humans and other species in association with sensory, motor, and cognitive functions. Gaze direction signals regulate neuronal response gain in primary visual cortex (Trotter and Celebrini, 1999; Weyand and Malpeli, 1993), posterior parietal cortex (Andersen and Mountcastle, 1983), and V4 (Moore and Armstrong, 2003) and modulate the gain of midbrain auditory responses (Winkowski and Knudsen, 2006). Similarly, focused spatial attention enhances the gain of neuronal responses in both primary visual cortex (McAdams and Reid, 2005) and V4 (Connor et al., 1996, 1997; McAdams and Maunsell, 1999; Williford and Maunsell, 2006). Recent evidence suggests that spatial attention also increases

the response gain of visual evoked potentials in humans (Kim et al., 2007). In addition to these regulatory effects, neuronal response gain for one sensory parameter can be modulated by changes in another parameter. In primary visual cortex, contrast gain modulation allows receptive field properties and orientation selectivity to remain constant, regardless of contrast-dependent changes in the overall magnitude of neuronal responses (Alitto and Usrey, 2004; Anderson et al., 2000b; Ferster and Miller, 2000; Miller, 2003; Sclar and Freeman, 1982; Skottun et al., 1987).

At the level of single neurons, gain is defined as the slope of the relationship between input amplitude and spike output. Large-scale neural processes, such as sensory perception, are ultimately dependent on the conversion of input to output by the individual cells that make up neuronal networks. Changes in these neuronal input-output functions permit scaling of network functions according to sensory context. Neurons in vivo are embedded in constantly active networks (Steriade, 2001) and receive a continuous stream of synaptic input that modifies their integrative properties (Destexhe and Paré, 1999). Indeed, studies in vitro and computational models have suggested that a key functional consequence of this ongoing synaptic activity is the modulation of the response sensitivity of single neurons.

Despite extensive phenomenological characterization of gain modulation, the underlying cellular mechanisms remain unclear. Computational and in vitro studies have found that changes in the level of synaptically driven Vm fluctuations, also called synaptic noise, may change the gain of the input-output curve (Chance et al., 2002; Ho and Destexhe, 2000; Prescott and De Koninck, 2003; Shu et al., 2003), suggesting that these fluctuations are a critical element of gain modulation. Synaptic noise smoothes the transformation of Vm activity to spike output and may contribute to contrast-invariant orientation tuning in visual cortex (Anderson et al., 2000b; Hansel and van Vreeswijk, 2002; Miller and Troyer, 2002; Finn et al., 2007). In contrast, changes in membrane conductance and mean membrane potential (Vm) cause lateral shifts in a neuron's input-output curve (additive) without changes in gain (multiplicative) (Chance et al., 2002; Fellous et al., 2003; Ho and Destexhe, 2000; Shu et al., 2003). However, shunting inhibition coupled with variable excitatory drive can modulate gain (Mitchell and Silver, 2003), and small excitatory or inhibitory inputs may cause modulation of response gain for a larger nonlinear input (Murphy and Miller, 2003). Despite these efforts, the contributions of these cellular mechanisms to neuronal gain modulation have not been directly tested in vivo.

Here, we used intracellular recordings in primary visual cortex to explore the cellular mechanisms by which sensory-driven network activity modulates neuronal gain. We used two types of visual stimulus to evoke distinct regimes of synaptic input to cortical cells. Our results show that neuronal response gain in vivo is regulated by ongoing variations in the composition and temporal organization of synaptic input. Visually evoked Vm fluctuations alone failed to significantly modulate neuronal gain but did affect spike timing. In contrast, Vm fluctuations in combination with changes in mean Vm and mean input resistance consistently resulted in gain modulation. Under normal behavioral conditions, the spatiotemporal properties of the visual scene are continuously changing (Dong and Atick, 1995; Krieger et al., 2000). The resulting variation in network synaptic activity may act rapidly to enhance or diminish the sensitivity of cortical neurons to inputs, providing an adaptive mechanism by which cortical networks adjust to sensory context.

RESULTS

The goal of these experiments was to test, in vivo, the hypothesis that changes in the amount or pattern of synaptic input to visual cortical neurons result in predictable changes in the slope, or gain, of their input-output functions. To modify the ongoing pattern of synaptic activation, we used two types of visual stimulus: sinusoidal drifting gratings and spatiotemporally broadband stimuli. To construct input-output functions and measure gain, we injected current pulses of different intensities and measured the resulting spike response. The results described here are based on intracellular recordings from 72 cells in layers 2–6 of cat primary visual cortex.

Two Modes of Network Synaptic Activity

We chose two types of visual stimulus (Figure 1A) because they represent extremes in a range of spatiotemporal properties but evoke spike responses of comparable magnitudes. Drifting gratings contain a single temporal and spatial frequency and produce a slow (1–2 Hz) and repeatable modulation of synaptic input (Anderson et al., 2000a). In contrast, the broadband stimuli contain a broad and variable range of temporal and spatial frequencies (see *Experimental Procedures*) and produce an irregular pattern of synaptic input. We will first describe the neuronal responses to the two stimuli as a function of contrast and identify their impact on the three main postsynaptic parameters previously implicated in gain modulation by computational and in vitro studies: mean Vm depolarization (VmDC), Vm fluctuations (quantified as the standard deviation of the Vm, VmSD), and changes in input resistance (R_{in}). To facilitate comparisons across cells, all measurements were made relative to activity in the absence of visual stimuli. Across the population of cells, the mean Vm was -66.3 ± 3.4 mV, the mean VmSD in the absence of visual stimuli was 2.4 ± 0.6 mV, and the mean R_{in} was 67.4 ± 5.2 M Ω . We quantified the F1 component of the visual responses (Skottun et al., 1991) but did not include it in the analysis because only changes in VmDC have been demonstrated to affect neuronal gain (Shu et al., 2003).

The characteristic Vm and spike responses evoked by the two visual stimuli are illustrated by the layer 2/3 complex regular spik-

ing (RS) cell shown in Figure 1. An optimal drifting sinusoidal grating of 8% (low) contrast evoked a small depolarizing VmDC from rest and an increase in VmSD (Figure 1B, left). Increasing the contrast to 64% (high) resulted in a larger depolarizing VmDC and VmSD (Figure 1C, left) and a significantly different Vm distribution (two-sample Kolmogorov-Smirnov test; $p < 0.05$). These changes were visible as a rightward shift and a broadening of the distribution of Vm values (Figure 1D, left). In comparison, the broadband stimulus of 20% (low) contrast evoked a small increase in VmSD but no change in VmDC (Figure 1B, right). Increasing the contrast to 90% (high) resulted in a larger increase in the magnitude of the VmSD in the continued absence of any change in VmDC (Figure 1C, right). Thus, in contrast to the grating, the broadband stimulus evoked a broadening of the distribution of Vm values without a significant shift in mean Vm ($p > 0.05$; Figure 1D, right). The Vm distributions evoked by the high-contrast grating and broadband stimuli were significantly different (two-sample Kolmogorov-Smirnov test; $p < 0.01$). Quantification of the responses of this cell to the two stimuli at varying contrasts is shown in Figure S1 available online.

The population averages for these two Vm parameters as a function of contrast are shown in Figure 2 ($n = 66$ drifting grating, 48 broadband). The VmDC and the spike response for both simple and complex cells in response to drifting grating stimuli of increasing contrast were well fit by hyperbolic ratio functions (Vm: $R_{max} = 5.9$ mV, $C_{50} = 21.2\%$, $exp = 2.1$; spikes: $R_{max} = 26.2$ Hz, $C_{50} = 18.1\%$, $exp = 1.7$) (Figure 2A). In contrast, in response to broadband stimuli, the VmDC did not change, but the spike response increased linearly, reaching firing rates comparable to those elicited by gratings (slope = 0.31 Hz/%, $r^2 = 0.99$) (Figure 2B). As reported in previous studies, fast spiking (FS) cells demonstrated greater response firing rates than RS cells (Contreras and Palmer, 2003; Nowak et al., 2003; Figure S2). However, because the results were similar for the two cell types, the data have been combined here for clarity.

The two types of visual stimulus also evoked differing changes in Vm fluctuations. Drifting gratings elicited a contrast-dependent increase in VmSD that was well fit by a hyperbolic ratio function ($R_{max} = 2.5$ mV, $C_{50} = 8.9\%$, $n = 1.8$). In comparison, broadband stimuli elicited a linear increase in VmSD that did not saturate (slope = 0.04 ± 0.01 mV/%, $r^2 = 0.99$), reaching a maximum value of 3.5 ± 0.9 mV (Figure 2C). Together, these results suggest that the contrast-dependent elevation in firing rate evoked by broadband stimuli is driven entirely by Vm fluctuations rather than sustained Vm depolarization (VmDC).

Drifting gratings and broadband stimuli also had different impacts on cellular input resistance (R_{in}). We injected a series of hyperpolarizing pulses (100 ms) of varying amplitudes before and during visual stimulation and measured R_{in} from the slope of the linear portion of the voltage-current (V-I) relationship (see *Experimental Procedures*). Drifting gratings evoked a mean ($n = 44$) contrast-dependent decrease in R_{in} of $18.9\% \pm 1.7\%$ ($24.0\% \pm 0.2\%$ increase in input conductance) at 64% contrast (one-sample t test; $p < 0.001$; Figure 2D). In comparison, broadband stimuli did not lead to a significant reduction in mean R_{in} ($n = 21$), even at a contrast of 90% ($p > 0.05$; Figure 2D).

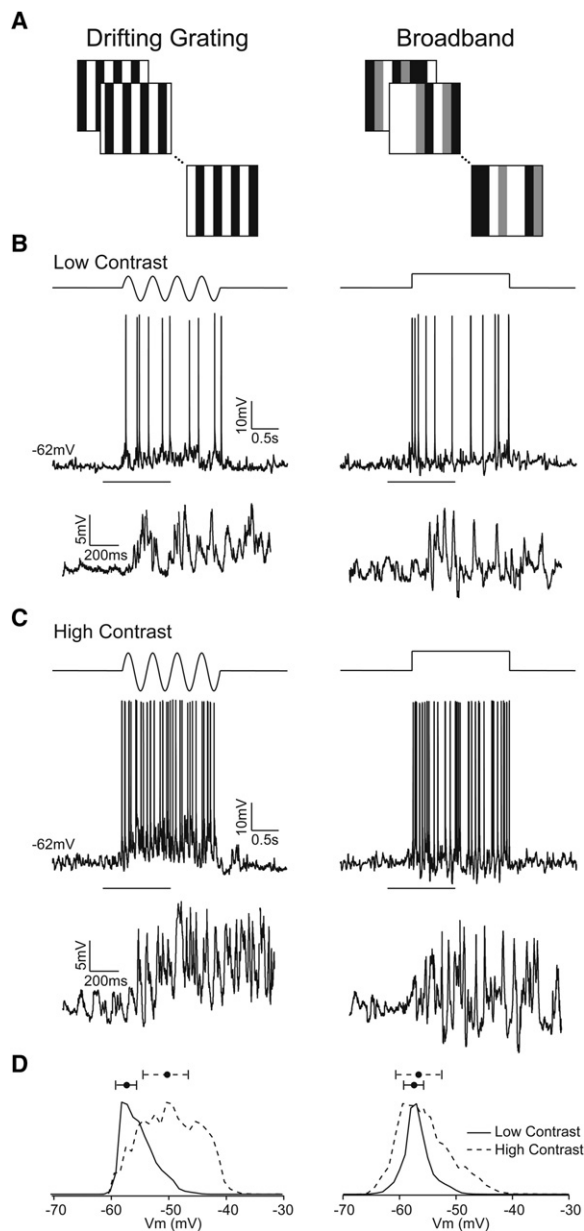


Figure 1. Drifting Grating and Spatiotemporally Broadband Stimuli Evoke Distinct Regimes of Synaptic Activity with Differing Postsynaptic Impacts

In each case, the portion denoted by the line is expanded as an inset trace.

(A) Schematics of the drifting grating (left) and broadband (right) stimuli.

(B) In this example complex layer 2/3 RS cell, a drifting sinusoidal grating of 8% contrast (left) evoked increased firing, a small Vm depolarization, and increased synaptically driven Vm fluctuations (inset trace). A spatiotemporally broadband stimulus of 20% contrast (right) evoked increased Vm fluctuations (inset trace) and firing but no net Vm depolarization.

(C) At 64% contrast, the drifting grating stimulus evoked a greater increase in firing rate, coupled with a sustained Vm depolarization and larger Vm fluctuations (left). In comparison, at 90% contrast, the broadband stimulus evoked a similar increase in firing rate and Vm fluctuations without a sustained Vm depolarization (right). The firing pattern evoked by the broadband stimulus was more irregular than that evoked by the drifting grating.

Stimulus-Dependent Gain Modulation

The distinct postsynaptic effects of the two types of visual stimulus allowed us to address, *in vivo*, the fundamental question of whether changes in synaptically driven Vm fluctuations function as a gain modulation mechanism. To measure input-output gain, we used depolarizing current pulses (100 ms) and constructed a plot of mean firing frequency versus current intensity (F-I) for each cell. We compared the F-I curve obtained in the absence of visual stimuli to those obtained during visual stimulation with drifting gratings and broadband stimuli of increasing contrast. We quantified gain for each cell by measuring the instantaneous slope at the I_{50} midpoint of a sigmoid fitted to each F-I curve and expressed that value relative to the midpoint gain of the F-I curve in the absence of visual stimuli. Data from an example layer 5 complex RS cell are shown in Figure 3. In the absence of visual stimulation, this cell had a sigmoidal F-I curve with the steepest slope (i.e., highest gain) between 0.25 and 0.4 nA and saturation at 0.5 nA (Figure 3A, left). Drifting gratings of increasing contrast (for clarity, only 0%, 16%, and 64% are shown) predominantly caused an increase in the magnitude of the responses to small current pulses, resulting in a concomitant decrease in the slope of the F-I curve. In addition, drifting grating stimuli caused a contrast-dependent leftward shift of 0.08 nA in the midpoint (I_{50}) of the F-I curve.

To further illustrate the effect of the visual stimulus, we plotted the derivative of the F-I curve as a function of firing rate, which represents a continuous measurement of gain for each stimulus contrast (Figure 3B, left). Stimulation with drifting gratings caused a contrast-dependent decrease in gain across the full range of firing rates. As shown in Figure 3C (left), the gain of the F-I curve decreased with increasing contrast, with the ratio of gain during visual stimulation to gain in the absence of visual stimuli falling to 0.47 during presentation of a drifting grating of 64% contrast. Thus, the combined postsynaptic effects of the drifting grating stimulus resulted in both a lateral shift in the F-I curve and an overall decrease in gain.

Broadband visual stimulation had a markedly different impact on the cell's input-output relationship. Despite evoking an increase in firing rate at resting Vm and during low-amplitude (0–0.2 nA) current pulses, the broadband stimulus failed to change the mean firing rate in response to larger current pulses over most of the range used to obtain the F-I plot. As a result, neither the overall slope nor the lateral position of the F-I curve was affected (Figure 3A, right). The overlapping plots of gain versus firing rate (Figure 3B, right) demonstrate the lack of gain modulation across the range of firing rates. Indeed, the gain ratio was 0.99 during presentation of a broadband stimulus of 90% (Figure 3C, left).

Population averages for the changes in gain induced by drifting gratings ($n = 32$) and broadband stimuli ($n = 26$) as a function of contrast are shown in Figure 3C (right). Increasing the duration

(D) Plots of Vm distributions during stimulation with drifting gratings (left) or broadband stimuli (right). At high contrasts, the drifting grating stimulus caused a significant rightward shift ($p < 0.05$) and a broadening of the Vm distribution. In comparison, the broadband stimulus caused a broadening of the Vm distribution but no lateral shift. Distributions have been normalized to the maximum value. Error bars denote mean $\pm$ SEM.

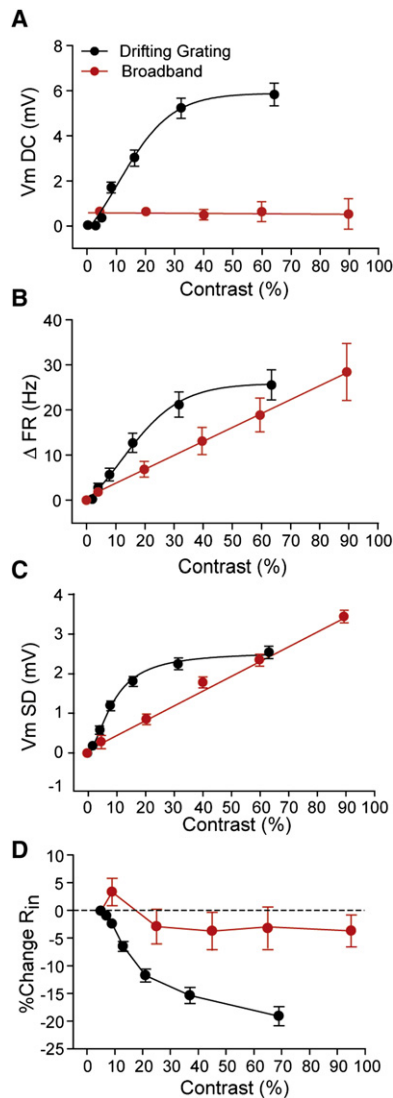


Figure 2. Cellular Impact of Drifting Gratings and Broadband Stimuli

(A) Population Vm contrast response curves of VmDC for drifting gratings (black) were well fit by a hyperbolic ratio curve. In comparison, broadband stimuli evoked no significant VmDC (red).

(B) Population firing rate (FR) contrast response curves for drifting gratings were also well fit by a hyperbolic ratio curve and saturated at high contrasts. Broadband stimuli evoked a linear relationship between contrast and firing rate without saturation.

(C) Similarly, population averages of Vm fluctuations (VmSD) in response to drifting gratings were well fit by hyperbolic ratio curves. Population VmSD contrast responses to broadband stimuli showed a linear relationship with stimulus contrast.

(D) Population averages demonstrated a mean R_{in} decrease $23.2\% \pm 5.7\%$ during presentation of a 64% contrast drifting grating ($n = 15$ cells; 53.4 ± 7.2 to 41.0 ± 5.7 M Ω ; $p < 0.0001$). In comparison, a 90% contrast broadband stimulus did not evoke a change in mean R_{in} (53.6 ± 6.1 to 53.9 ± 16.0 M Ω ; $p > 0.05$).

of the injected current pulses did not alter the observed results ($n = 7$ cells; Figure S3). Drifting gratings caused a significant, contrast-dependent decrease in the gain ratio at 64% ($p < 0.0001$). Despite a significant increase in Vm fluctuations, broadband

stimuli did not evoke significant gain modulation, even at 90% contrast ($p > 0.05$). These results suggest that, in vivo, Vm fluctuations alone do not obligatorily modulate gain.

Why did the broadband stimulus fail to modulate gain, while the drifting grating stimulus was highly effective? An important clue is provided by activity at depolarized Vm levels (Figure 4). To understand the different patterns of visually evoked spike output and their effects on mean firing rates, we examined the instantaneous frequencies of the spike responses during the current pulses used to obtain the mean firing rate values for the F-I plots. Instantaneous firing rates for one cell are shown in Figure 4A (same cell as Figure 3). Small amplitude pulses (0.12 nA) in the absence of visual stimuli caused a variable output with a mean frequency of 19.8 ± 2.6 Hz. Concomitant presentation of a drifting grating increased both the variability and the mean (35.6 ± 4.5 Hz) of the instantaneous frequencies in the response. The broadband stimulus evoked a comparable increase in the mean output and a much larger increase in variability (32.2 ± 9.6 Hz), including many instances of high-frequency bursts and suppressed firing. In the middle range of the F-I plot, current pulses (0.32 nA) without visual stimulation evoked similar variability but consistently higher instantaneous frequencies (37.5 ± 3.2 Hz). The drifting grating again increased both the variability and resulting mean firing rate (52.4 ± 4.8 Hz). The broadband stimulus caused a much larger increase in the variability of the instantaneous firing frequencies but failed to change the mean firing rate (38.4 ± 13.3 Hz). Cumulative distribution plots of instantaneous firing frequencies for each condition are shown in the inset panels in Figure 4A. At both current pulse levels, the drifting grating- and broadband-evoked distributions of instantaneous firing rates were significantly different (two-sample Kolmogorov-Smirnov test; $p < 0.01$). These results were consistent across the population of cells for which both drifting grating and broadband measurements were made ($n = 26$; $p < 0.05$ in each case).

The above results suggest that the broadband stimulus redistributes spikes in time, with bouts of high firing rates interspersed with an absence of firing, but the drifting grating stimulus evokes a sustained increase in spike output. To capture these differences, we measured the coefficient of variation of the interspike interval (CV_{ISI}) in a subset of cells ($n = 15$) during each stimulus condition. During drifting grating stimulation, the CV_{ISI} increased for low-contrast stimuli, reaching a maximum of 1.60 ± 0.2 at 16% contrast, and decreased toward 1 for high-contrast stimuli. However, the CV_{ISI} during broadband stimulation increased monotonically to a maximum of 1.64 ± 0.2 at 90%. Since CV_{ISI} is affected by firing rate, we plotted the CV_{ISI} data against the mean firing rate (Figure 4B). Differences at low firing rates were negligible, but at high firing rates, the mean CV_{ISI} of the broadband stimulus responses was significantly greater than that of the drifting grating responses (paired t test; $p < 0.01$). The large CV_{ISI} shown here in response to broadband stimuli suggests a high level of transient epochs of synchronization in the synaptic input (Stevens and Zador, 1998). In comparison, the decreased CV_{ISI} in response to high-contrast drifting grating stimuli suggests a sustained synaptic input more similar to a current pulse (Tateno and Robinson, 2006). Further analysis of stimulus-specific spike patterns suggests that the broadband stimulus dynamically modulates firing probability over short time intervals

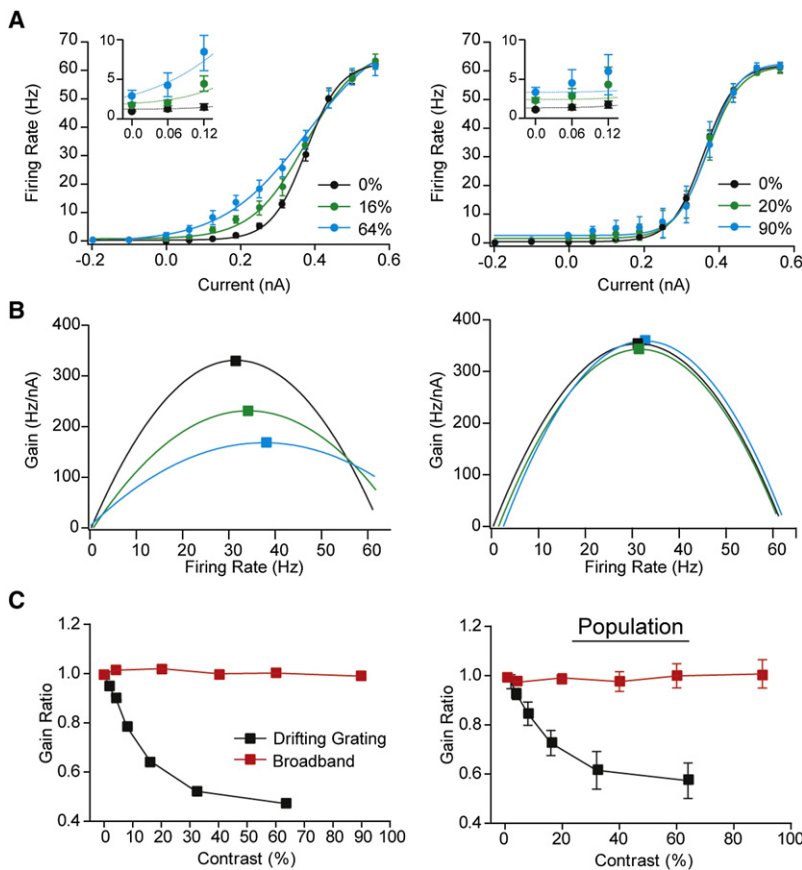


Figure 3. Stimulus-Dependent Gain Modulation

(A) Current pulse injections of varying magnitudes were given to an example complex layer 5 RS cell during stimulation with either drifting gratings (left) or broadband stimuli (right). Note that the firing rate evoked by high-contrast drifting gratings at V_{rest} in this RS cell example is lower than the population average shown in Figure 2B, which includes both RS and FS cells. Drifting gratings caused a leftward shift in the position of the F-I curve and a decrease in the slope, or gain, of the curve. Broadband stimuli increased firing rates within a limited Vm range close to V_{rest} but did not change the position or the overall slope of the F-I curve, regardless of contrast. Insets show expansions of the portion of the F-I curve near V_{rest} . Gain was measured as the instantaneous slope of the F-I curve at the midpoint, or I_{50} , of a fitted sigmoid.

(B) Instantaneous gain was measured from the sigmoid fits to the F-I curves shown in (A) and plotted against mean firing rate. Squares denote gain at the I_{50} midpoint of the curve. Drifting gratings caused a contrast-dependent decrease in gain across a wide range of firing rates (left), while broadband stimuli did not modulate gain at any firing rate (right).

(C) Gain measurements were calculated as the ratio of gain during visual stimulation to gain in the absence of visual stimuli. The example cell shown in (A) and (B) demonstrated a decreased gain ratio with increasing drifting grating contrast, but the ratio was largely unaffected by broadband stimuli (left). Average gain ratio measurements for the population of cells (right) showed a significant, contrast-dependent decrease in gain in response to drifting grating stimuli (black). In contrast, broadband stimuli (red) did not significantly affect gain, suggesting that increased Vm fluctuations alone do not obligatorily lead to gain modulation in vivo.

(Figure S4), despite a lack of impact on gain as measured by mean firing rates.

Cellular Mechanisms of Visually Evoked Gain Modulation

The distinct postsynaptic effects of the two types of visual stimulus provide additional insight into the cellular mechanisms underlying gain modulation in vivo. To assess the contribution of changes in VmDC, we measured the gain of the F-I curve in each cell while introducing a change in VmDC by tonically injecting low levels of current. As shown by the example complex layer 2/3 RS cell in Figure 5, neither hyperpolarizing nor depolarizing shifts in VmDC from rest significantly changed the slope of the F-I curve in the absence of visual stimulation (gain [in Hz/nA]: V_{rest} 178.1, V_{Dep} 167.1, V_{Hyp} 173.9; Figure 5A). Similarly, VmDC changes did not affect the degree of gain modulation evoked by a drifting grating of 64% contrast, as shown by the similar slopes of the F-I curves in Figure 5B (gain: V_{rest} 118.3, V_{Dep} 114.6, V_{Hyp} 115.7 Hz/nA). Likewise, introduction of a change in VmDC did not affect the lack of gain modulation evoked by a broadband stimulus of 90% contrast (gain [in Hz/nA]: V_{rest} 189.9, V_{Dep} 189.0, V_{Hyp} 181.1; Figure 5C). Overall, in agreement with previous in vitro data (Shu et al., 2003), sustained changes in Vm led only to additive or subtractive shifts in the F-I plot, rather than changes in the slope (Figure 5D; $n = 8$ cells; mean gain ratio: no visual stimulation 1.02 ± 0.02 , drifting grating 0.91 ± 0.08 ,

broadband 0.94 ± 0.07 ; $p > 0.05$ in all cases). These results suggest that the leftward shift, but not the change in slope, in the F-I curve in response to drifting grating stimuli is due to the visually evoked change in VmDC. In addition, the combination of VmSD evoked by the broadband stimulus and depolarizing VmDC was not sufficient to induce gain modulation.

Previous work has suggested that Vm depolarization and R_{in} decrease cause opposing left- and rightward lateral shifts in the position of the F-I curve, respectively (Chance et al., 2002; Ho and Destexhe, 2000; Shu et al., 2003). The drifting grating stimulus evoked both increased VmDC and decreased R_{in} , suggesting two competing influences on the lateral position of the F-I curve. If so, the observed leftward F-I curve shift evoked by the drifting grating should be smaller than that predicted from the magnitude of the evoked change in VmDC. Using the observed lateral shift in the I_{50} point of the F-I curve during sustained depolarizing current injection (as in Figure 5A), we calculated the magnitude of lateral shift expected for a given change in VmDC. We then estimated the visually evoked leftward shift of the F-I plot expected for each cell, given the change in VmDC induced by a 64% drifting grating. The mean predicted lateral I_{50} shift (-0.12 ± 0.1 nA) was 66.8% greater than the mean observed shift (-0.05 ± 0.03 nA; $n = 8$ cells; $p < 0.01$). Because increased VmSD alone does not cause lateral F-I curve shifts (Chance et al., 2002; Ho and Destexhe, 2000; Shu et al., 2003), these results suggest that the leftward shift in the F-I curve due to visually

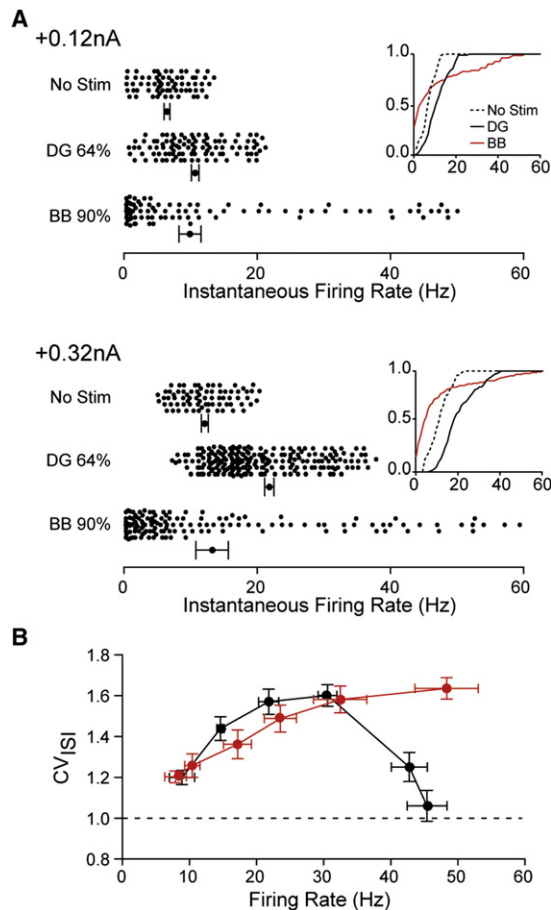


Figure 4. Two Modes of Visually Evoked Spike Output

(A) Distribution of instantaneous firing rates drawn from the F-I curves in Figure 3A. In each case, the instantaneous firing frequencies are shown in the absence of visual stimuli, in response to a 64% drifting grating, and in response to a 90% broadband stimulus. Under a low level of depolarization (top), both stimuli caused an increase in mean instantaneous firing rate and firing variability. Under a higher level of depolarization (bottom), the grating continued to increase the mean firing frequency but the broadband stimulus greatly increased firing rate variability without further changing the mean. Cumulative distributions of instantaneous firing rates for each condition are shown in the inset panels. In each case, the drifting grating and broadband distributions were significantly different ($p < 0.01$).

(B) The CV_{ISI} of the spike responses to drifting gratings (black) was high for low contrasts and decreased toward 1 at high contrasts. The CV_{ISI} for broadband responses (red) showed a continual, contrast-dependent increase. The CV_{ISI} for the two stimulus conditions was similar at low firing rates and diverged significantly at high firing rates ($n = 15$ cells; $p < 0.01$).

evoked depolarization is partially countered by a competing rightward shift due to R_{in} decrease.

The different levels of spike response variability evoked by the two stimuli suggested that measurements of mean R_{in} (Figure 2D) might conceal dynamic changes during the rapidly varying response to the broadband stimulus. To reveal changes in R_{in} on a moment-to-moment basis, we used hyperpolarizing pulses of -0.5 nA injected at 3 Hz before and during the presentation of visual stimuli (Figure 6A) and estimated R_{in} from the amplitude of each voltage response (Figure 6B). The drifting grating

evoked an immediate and sustained R_{in} decrease, but the broadband stimulus elicited a significant, contrast-dependent increase in the moment-to-moment variability of R_{in} in the continued absence of a sustained change in mean R_{in} (unpaired t test; $p < 0.01$; Figure 6B). This variability included epochs when the visually evoked R_{in} exceeded the baseline R_{in} . Across the population of cells ($n = 18$ drifting grating and 15 broadband), the broadband stimulus evoked significantly greater maximum R_{in} variability, measured as the SD of the R_{in} , than did the drifting grating stimulus (unpaired t test; $p < 0.01$; Figure 6C). The rapidly varying R_{in} evoked by the broadband stimulus suggests interspersed epochs of highly synchronized synaptic events and withdrawal of input. In each case, the temporal dynamics of R_{in} changes matched the temporal properties of the two visual stimuli.

A summary of the differences between the effects of the two visual stimuli on neuronal gain is shown in the population plots in Figure 7. The contrast-dependent changes in VmDC (Figure 7A), VmSD (Figure 7B), and R_{in} (Figure 7C) evoked by drifting grating stimuli were each linearly related to the change in gain. In contrast, the broadband stimulus evoked similar changes in VmSD in the absence of any change in gain (Figure 7B). Furthermore, the increased VmSD evoked by the broadband stimuli, when combined with Vm depolarization by current injection (mean $\Delta VmDC = 5.6 \pm 0.7$ mV; mean gain ratio = 0.94 ± 0.07) (Figures 5C and 5D; replotted with population mean in Figure 7A), also failed to cause gain modulation. These results suggest that engagement of multiple cellular mechanisms is necessary for gain modulation to be observed in vivo.

DISCUSSION

Gain modulation matches the limited output range of individual target neurons to the dynamic range of network synaptic inputs. This adaptive scaling of neuronal input-output relationships provides a flexible mechanism by which cells can integrate and respond to highly variable synaptic inputs while maintaining effective information encoding. In addition, gain changes allow single neurons to represent more than one parameter in their spike trains without loss of selectivity (Salinas and Sejnowski, 2001).

Neurons in vivo receive an ongoing barrage of synaptic inputs from the surrounding network, and several studies using in vitro and computational methods have explored the role of this background synaptic activity as a cellular mechanism of gain modulation. These studies agree that changes in the level of sustained synaptic activation can modify the relationship between input amplitude and spike output via changes in three main postsynaptic mechanisms: the amplitude of Vm fluctuations (VmSD), the neuronal R_{in} , and the resting Vm (VmDC). However, the exact role of these three mechanisms in the modulation of input-output gain is not fully understood, in part due to the differing methods and measurements used in previous work. Furthermore, the impact of ongoing synaptic activation on gain modulation in vivo has not been studied in detail. In the current study, we changed the levels of network synaptic input by varying the contrast of two types of visual stimulus with different spatiotemporal properties. We found that changes in the level of sensory-driven synaptic input to single neurons in primary visual cortex in vivo lead to

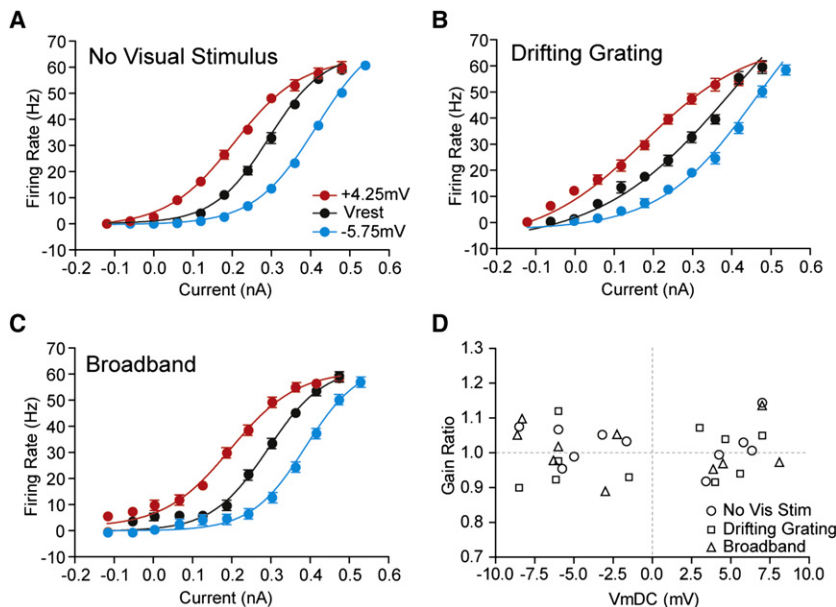


Figure 5. Vm Depolarization Alone Does Not Modulate Neuronal Gain

(A) F-I curves were calculated for this example complex layer 2/3 RS cell at hyperpolarized (-5.75 mV, blue), resting (black), and depolarized ($+4.25$ mV, red) Vm levels in the absence of visual stimuli. Vm depolarization (VmDC) caused a lateral shift in the position of the F-I curve but did not affect the slope (gain) of the curve.

(B) F-I curves for the cell were repeated at the same Vm levels in the presence of a drifting grating of 64% contrast. The drifting grating evoked a decrease in the slope of the F-I curve in comparison with the curves shown in (A). Sustained VmDC again caused a lateral shift but no change in the F-I curve slope.

(C) F-I curves were repeated at the same Vm levels in the presence of a broadband stimulus of 90% contrast. The broadband stimulus did not affect the slope of the F-I curve, regardless of VmDC.

(D) Plot of data from cells in which current injection was used to change Vm in the absence of a visual stimulus (circles), during drifting grating stimuli (squares), and during broadband stimuli (triangles). In each case, the measured change in VmDC is plotted against the measured gain ratio.

changes in the slope, or gain, of their input-output function in a stimulus-dependent manner.

Cellular Mechanisms of Gain Modulation In Vivo

We found that sinusoidal drifting gratings caused a sustained increase in VmDC and VmSD and a sustained decrease in R_{in} in all cells. The magnitude of each of these three postsynaptic effects was contrast dependent and linearly correlated with a visually evoked decrease in gain. In addition, drifting gratings caused a leftward shift in the cell's response curve. Previous work in vitro found that a balanced increase in excitatory and inhibitory input caused both decreased gain and a decrease in neuronal response magnitudes to all inputs (Chance et al., 2002). In contrast, we found that the synaptic activity evoked in vivo by the grating stimulus caused a decrease in gain but an increase in neuronal response magnitude. This increase in response magnitude was caused by the leftward curve shift, likely the result of an increase in excitatory drive.

In agreement with previous results in vitro (Chance et al., 2002; Shu et al., 2003) and predictions from computational models (Ho and Destexhe, 2000; Holt and Koch, 1997; Murphy and Miller, 2003), we found in vivo that changing the VmDC with current injection shifts the F-I plot laterally without changing the slope. Murphy and Miller (2003) found that a small (~ 50 pA) current injection could cause roughly multiplicative gain changes in the tuning curve of a model neuron for a larger nonlinear input. However, our VmDC results are derived from large somatic current injections (~ 0.2 nA) in the context of a relatively linear series of current pulse inputs. In addition, small gain changes due to current injection may be difficult to detect in vivo.

Using the lateral F-I curve shift imposed by VmDC changes, we estimated the impact of the drop in R_{in} on the lateral position of the F-I curve. Even though our experiments in vivo did not allow us to directly manipulate neuronal R_{in} in isolation, we were able to identify a rightward shift in the F-I curve that was caused

by the visually evoked decrease in R_{in} . These findings agree well with predictions made by previous studies that a drop in R_{in} , or shunt, causes rightward displacement of the response curve without changing the slope (Chance et al., 2002; Shu et al., 2003). However, this rightward shift was countered by the larger leftward shift induced by VmDC, resulting in the overall enhancement of response magnitudes. Our results support the possibility of a contribution of R_{in} change to gain modulation, as neither increased VmSD alone nor VmSD combined with VmDC evoked gain modulation. Computational results suggest that a decrease in neuronal R_{in} due to shunting inhibition may cause changes in gain under some conditions (Murphy and Miller, 2003). This can occur in the context of spike output driven by variable excitatory synaptic input to the soma (Mitchell and Silver, 2003) or by intense synaptic input to the dendrites, causing dendritic saturation (Prescott and De Koninck, 2003). In agreement with the predictions of several previous studies in vitro (Chance et al., 2002; Shu et al., 2003), our results suggest that the observed regulation of the neuronal input-output function by visually evoked synaptic input is due to the combined impact of changes in Vm fluctuations, input resistance, and depolarization.

Relationship between Vm Fluctuations and Gain

To directly test the hypothesis that increased Vm fluctuations modulate neuronal gain in vivo, we used a broadband visual stimulus that increased VmSD alone. Indeed, the broadband stimulus evoked rapid depolarizing and hyperpolarizing events that were balanced around the resting Vm and associated with transient changes in R_{in} both above and below the baseline value, leaving the VmDC and the mean R_{in} unchanged. Increases in R_{in} above baseline indicate that at least some of the hyperpolarizations characteristic of the response to the broadband stimulus are caused by withdrawal of synaptic input, something never observed during the response to drifting gratings.

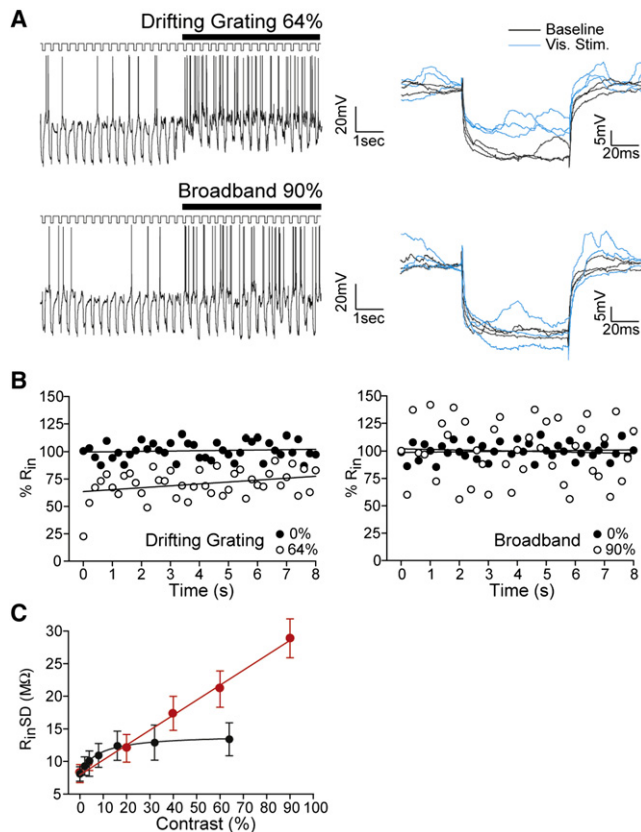


Figure 6. Spatiotemporally Distinct Visual Stimuli Evoke Different Levels of Moment-to-Moment R_{in} Variability

(A) Example traces from a complex RS cell showing a series of hyperpolarizing current pulses (100 ms at 3 Hz) before and during presentation of a drifting grating or broadband stimulus. Mean input resistance (R_{in}) showed a rapid and sustained decrease upon presentation of the drifting grating but did not change during the broadband stimulus. Overlaid baseline (black) and visual stimulus (blue) pulses are shown to the right.

(B) Moment-to-moment measurements of the change in R_{in} during stimulation with drifting gratings (left) and broadband stimuli (right) in the cell shown in (A). Despite a lack of impact on mean R_{in} , broadband stimuli evoked both momentary decreases and increases in R_{in} .

(C) Population averages of the variability of the R_{in} measurements at each contrast level, measured as R_{inSD} . Broadband stimuli evoked significantly greater R_{inSD} than did drifting gratings at high contrasts ($p < 0.01$).

The increased VmSD evoked by the broadband stimulus drove a spike response at resting Vm but failed to modulate the overall gain of the F-I curve. Because cells at rest in vivo sit slightly below spike threshold, the broadband stimulus produced a floor effect in which depolarizing events bring the cell above spike threshold but hyperpolarizing events have little obvious impact (Azouz and Gray, 2003; Chance et al., 2002). At higher levels of current injection, this floor effect dissipated, and any increase in spike events caused by depolarizing synaptic events was countered by spikes lost due to hyperpolarizing events. Thus, at higher levels of injected current, when the cell was firing at a sustained rate, the increased VmSD evoked by the broadband stimulus increased firing rate variability but did not provide enough drive to increase overall spike output. This diminished

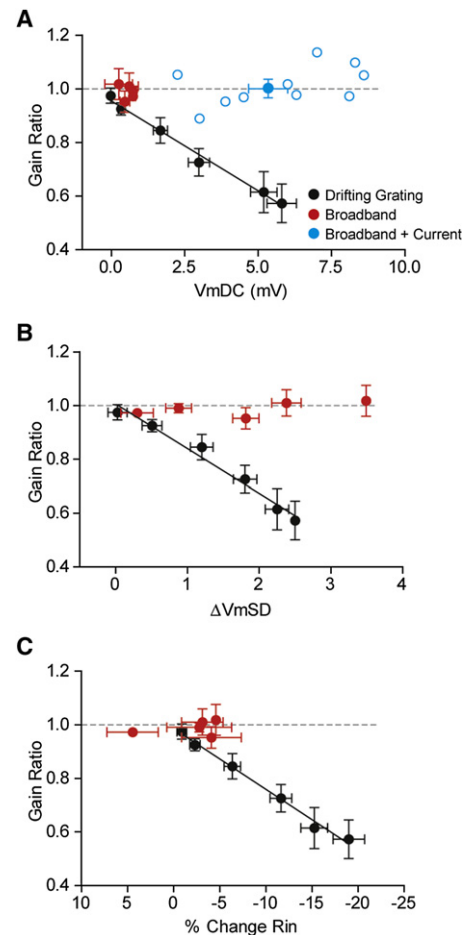


Figure 7. Cellular Mechanisms of Gain Modulation

(A) The sustained Vm depolarization (VmDC) evoked by drifting grating stimuli was linearly related to the observed degree of gain modulation (black). In contrast, broadband stimuli evoked neither depolarization nor gain modulation (red). However, pairing broadband stimuli with VmDC induced by sustained injection of low levels of current also failed to evoke gain modulation (blue).

(B) The increased Vm fluctuations (VmSD) evoked by drifting gratings were also linearly correlated with the observed gain modulation. However, broadband stimuli evoked comparable magnitudes of VmSD in the absence of gain modulation.

(C) The sustained R_{in} decrease associated with drifting grating stimulation was linearly correlated with the degree of visually evoked gain modulation. In contrast, the broadband stimulus evoked greater R_{in} variability, as shown by the larger error bars, but no change in mean R_{in} or gain.

impact of the broadband stimulus at high firing rates is in agreement with previous findings that the effects of synaptic noise decrease significantly with increasing firing rates (Chance et al., 2002; Shu et al., 2003).

These results suggest that transient epochs of synaptic input with high variance are not sufficient to produce gain modulation in vivo. One possibility is that gain control may require a consistent level of synaptic input associated with a sustained increase in excitatory or inhibitory conductances, such as those observed in response to drifting grating stimuli. The differences in postsynaptic effects discussed above indicate that the two visual stimuli

used here generate distinct regimes of synaptic input. Both the balance of excitatory and inhibitory conductances and the synchrony of synaptic inputs determine the magnitude and temporal dynamics of Vm fluctuations and thus mediate the extent to which synaptic noise may modulate neuronal response gain (Fellous et al., 2003; Ho and Destexhe, 2000). Thus, a second possibility is that differences in the balance and precise timing of excitatory and inhibitory synaptic inputs may play a role in generating the different magnitudes of gain modulation observed here.

The VmSD evoked by the broadband stimulus had a much smaller impact *in vivo* than would be expected from previous results *in vitro*, suggesting a potential nonlinear relationship between Vm fluctuations and neuronal gain. In contrast with results *in vitro*, the large VmSD under baseline conditions *in vivo* may limit the amount of modulation exerted by synaptically driven Vm fluctuations. In the present study, baseline Vm fluctuations in the absence of visual stimuli (2.4 ± 0.6 mV) were already equivalent in magnitude to the maximum network-driven fluctuations associated with gain modulation *in vitro* (Shu et al., 2003). Additional increases in VmSD may therefore have less significant impact on neuronal gain *in vivo* than under quiet *in vitro* conditions.

Temporal Dynamics and Gain Control

Despite having a minimal impact on neuronal gain, the broadband stimulus had a significant effect on the pattern of spike output. The high CV_{ISI} values associated with the broadband stimulus are almost never obtained in computational models or *in vitro* experiments and indicate a large degree of transient synchrony in the visually evoked synaptic inputs (Stevens and Zador, 1998). Previous work has suggested that increases in uncorrelated background synaptic activity may regulate neuronal gain without affecting spike output variability (Chance et al., 2002). We found that increases in Vm fluctuations *in vivo* may occur independently of increases in spike variability and still be associated with powerful modulatory effects on neuronal gain, as shown by the relatively low CV_{ISI}, high VmSD, and significant gain modulation introduced by the high-contrast grating stimulus.

The two temporal profiles of network synaptic activity we observed likely result from the very distinct spatiotemporal dynamics of the two stimuli, which may lead to differences in the types of cells activated (Cardin et al., 2007), their degree of synchronization (Kohn and Smith, 2005; Nase et al., 2003), and the short-term plasticity processes that engage to enhance or depress different elements of the local network (Boudreau and Ferster, 2005; Nowak et al., 2005). However, additional temporal constraints are superimposed on the structure of the incoming synaptic volleys evoked by the visual stimulus. These include the membrane time constant of the cell, which is affected by the visually evoked change in R_{in} and the synchrony between synaptic inputs (Bernander et al., 1991; Fellous et al., 2003). In addition, the distribution of active inputs over the dendritic tree, which may be different between the two stimulus conditions, affects the time course of synaptic integration. Intrinsic electrophysiological properties, such as active dendritic conductances (Gasparini and Magee, 2006; Oviedo and Reyes, 2005) and firing properties (Contreras and Palmer, 2003; Llinas, 1988; Nowak et al., 2003), also contribute to resonant phenomena and the neuronal spike frequency profile (Thomson et al., 2002).

Conclusions

Other cellular mechanisms of gain modulation have been proposed, such as activation of dendritic NMDA receptors (Fox et al., 1992) and modulation of intrinsic currents that shape the spike after hyperpolarization and the interspike interval (Higgs et al., 2006; Smith et al., 2002). More recently, a role for neuromodulators has been suggested in mediating contrast gain control in visual cortex (Disney et al., 2007). In the current study, our emphasis was on global cellular mechanisms of gain modulation, and we did not attempt to distinguish specific ways in which these mechanisms might be engaged. However, the three elements of sensory-evoked gain regulation identified here are core mechanisms by which network synaptic activity impacts individual neurons, and they may play key roles in gain modulation under a wide range of conditions.

The availability of multiple modes of neuronal gain may allow cortical networks to rapidly adapt the ongoing gain state to fit the current regime of sensory input. Indeed, the two modes of activity described here represent one condition in which gain is robustly modulated over long periods and a second condition in which neuronal gain is stable, regardless of visual contrast. Such variations in gain state have the potential to affect important aspects of cortical visual processing, such as contrast-invariant orientation tuning. This potential impact is highlighted by the striking linear contrast response function evoked by the broadband stimulus, without the nonlinear contrast gain that is a hallmark of the well-characterized response to drifting grating stimuli. The relationship between regulation of the magnitude and time course of cortical gain and the context-dependent nature of visual responses remains to be explored.

EXPERIMENTAL PROCEDURES

Surgical Protocol

Experiments were conducted in accordance with the ethical guidelines of the National Institutes of Health and with the approval of the Institutional Animal Care and Use Committee of the University of Pennsylvania. Surgical and recording methods were as reported previously (Cardin et al., 2005; Contreras and Palmer, 2003). Briefly, adult cats (2.5–3.5 kg) were anesthetized with an initial intraperitoneal injection of thiopental (25 mg/kg) and supplementary halothane (2%–4% in a 70:30 mixture of N₂O and O₂). Subsequently, the animal was paralyzed with gallamine triethiodide (Flaxedil) and anesthesia was maintained during surgery with intravenous thiopental as needed for the duration of the experiment (14–16 hr) with a continuous infusion (3–10 mg/kg/hr). Heart rate, blood pressure, and EEG were monitored throughout the experiment. The end-tidal CO₂ concentration was kept at $3.7\% \pm 0.2\%$, and the rectal temperature was kept at $37^{\circ}\text{C} - 38^{\circ}\text{C}$ with a heating pad.

The surface of the visual cortex was exposed with a craniotomy centered at Horsley Clarke posterior 4.0, lateral 2.0. The stability of the recordings was improved by performing a bilateral pneumothorax, drainage of the cisterna magna, hip suspension, and by filling the cranial defect with a solution of 4% agar. Intracellular recordings were performed with glass micropipettes (50–80 M Ω) filled with 3 M potassium acetate. All cells had a stable resting V_m more negative than -60 mV coupled with overshooting action potentials.

Visual Stimulation

The corneas were protected with contact lenses after dilating the pupils with 1% ophthalmic atropine and retracting the nictitating membranes with phenylephrine (Neosynephrine). Spectacle lenses were chosen by the tapetal reflection technique to optimize the focus of stimuli on the retina. The position of the monitor was adjusted with an x-y-stage so that the area centralae were centered on the screen.

Stimuli were presented on an Image Systems (Minnetonka, MN) model M09LV monochrome monitor operating at 125 frames/s at a spatial resolution of 1024×786 pixels and a mean luminance of 47 cd/m^2 . Custom software allowed for stimulus control, online displays of acquired signals (V_m and spikes), and a graphical user interface for controlling all stimulus parameters. In addition to this online control, all data were stored on a Nicolet Vision (LDS, Middleton, WI) for offline analyses. V_m and stimulus marks were sampled at 10 kHz with 16 bit analog-to-digital converters. Computer-assisted hand plotting routines were used with every cell to provide initial estimates of the optimal orientation and spatial and temporal frequencies and to determine the receptive field dimensions. Tuning curves for orientation and spatial frequency were determined online with a series of drifting sinusoidal gratings spanning the initial estimates.

We used two types of visual stimuli: drifting gratings and broadband stimuli. Drifting gratings of optimal parameters were presented at contrasts of 0%, 2%, 4%, 8%, 16%, 32%, and 64%. Broadband stimuli were presented at contrasts of 0%, 4%, 20%, 40%, 60%, and 90%. Broadband stimuli were generated by dividing the width of the receptive field into eight equal bars of the optimal orientation. Each bar varied randomly every 8 ms between bright, dark, and mean luminance. The bars were uncorrelated in space and time, resulting in variable temporal frequencies with a maximum of 125 Hz and variable spatial frequencies with a maximum of 4/receptive field width. In some cases, short current pulses were given repeatedly during the visual stimulus (see below).

Both F1 and DC changes in visually evoked spike output and the underlying V_m response to drifting gratings were measured for simple and complex cortical cells. However, only the DC components were used. The spike and V_m responses to broadband stimuli were measured as the DC component. Similar results for the experiments outlined here were observed in both simple and complex cells, and the two groups were therefore combined for analysis. Both the V_m and spike responses to drifting gratings of increasing contrast were well fit by the hyperbolic ratio function: $R(C) = R_{\max} \times C^n / (C_{50}^n + C^n)$.

Cells were classified as simple or complex based on two criteria. First, the relative modulation of spike trains evoked by an optimized patch of drifting sinusoidal grating was measured. If the response at the fundamental temporal frequency of the stimulus (F1) exceeded the average (DC) response, the cell was classified as simple. Otherwise, the cell was classified as complex (Skottun et al., 1991). Second, we estimated the one-dimensional spatiotemporal weighting function by averaging membrane potential and spike responses to bright and dark bars ($n = 16$) distributed across the receptive field at the optimal orientation. Cells exhibiting nonoverlapping regions excited by bright and dark stimuli were classified as simple. Cells showing excitation to bright and dark stimuli throughout their receptive fields were classified as complex. These two measures yielded the same functional classification in every case.

Vm Fluctuations and Firing Rate Variability

V_m fluctuations evoked by visual stimuli were measured as the standard deviation of the V_m after spike removal (Fellous et al., 2003; Ho and Destexhe, 2000; Shu et al., 2003) and are referred to as $V_m\text{SD}$. To facilitate comparisons across cells, $V_m\text{SD}$ during visual stimulation was measured relative to the $V_m\text{SD}$ observed in the absence of visual stimuli. For simple cell responses to drifting gratings, the F1 component of the V_m response was removed by subtracting a fitted sinusoid before measuring $V_m\text{SD}$. For complex cells, the DC component, calculated as the mean V_m during the response, was similarly subtracted prior to measuring $V_m\text{SD}$. Spikes were removed by detecting the spike threshold at the base of the action potential and extrapolating the V_m values from the start to the end of the spike, followed by smoothing with a three point running average. For F-I plot calculations, firing rate was measured as the mean firing rate during each set of current pulses. Instantaneous firing rate was measured as one/interspike interval. Measurements of the coefficient of variation of the interspike interval (CV_{ISI}) were made from randomly interleaved presentations of stimuli of varying contrasts. Each presentation lasted 2 s, and each contrast was presented a minimum of ten times. Cells whose firing rates were too low to reliably calculate the CV_{ISI} were not used for this analysis.

Input Resistance

To measure mean input resistance during visual stimulation, we gave interleaved current pulses (100 ms) of varying magnitudes during presentation of

visual stimuli of varying contrast. All parameters were varied pseudorandomly. Each pairing of current level and contrast was repeated 10 to 15 times. We then constructed a voltage-current (V-I) plot from the injected current pulses and calculated mean R_{in} as the slope of a line fit to the linear portion of the V-I plot for each contrast level. To estimate input resistance on a moment-to-moment basis, a series of current pulses of uniform amplitude were given at 3 Hz during presentations of visual stimuli at varying contrasts. For these calculations, R_{in} was estimated from each pulse. Variability of input resistance was calculated as the SD of the R_{in} values from these pulses.

Gain Quantification

To quantify visually evoked modulation of the gain of the neuronal response to current injection, we gave hyperpolarizing and depolarizing current pulses (100 ms) of varying amplitudes and generated F-I plots. Each pulse amplitude was repeated a minimum of ten times. We first fitted a sigmoid to each F-I curve. Gain was then measured as the instantaneous slope at the midpoint, or I_{50} , of the sigmoid. To obtain F-I plots during visual stimulation at varying contrast levels, current pulse amplitude and stimulus contrast were simultaneously interleaved in pseudorandom order until all possible combinations had been presented a minimum of ten times. In a subset of cells, F-I gain was measured from two sets of curves obtained with pulses of differing durations (100 or 500 ms; see Figure S3). In another subset of cells, F-I curves were calculated from pulses given while holding the cell at varying levels of V_m depolarization with current injection. In all cases, gain was expressed as the ratio of the F-I gain during visual stimulation to the F-I gain in the absence of visual stimulation.

Statistical Analysis

Statistical tests were used as noted in the main text. Significance was set at $p < 0.05$. Unless otherwise noted, error bars denote SEM.

SUPPLEMENTAL DATA

Supplemental Data for this article, which include Supplemental Figures, can be found online at <http://www.neuron.org/cgi/content/full/59/1/150/DC1/>.

ACKNOWLEDGMENTS

Sponsored by NIH-NEI R01 EY013984 (D.C.), R01 EY016430 (L.A.P.), F32 EY017501 (J.A.C.), and K99 EY018407 (J.A.C.). The authors thank M.J. Higley for helpful discussions and comments on this manuscript.

Received: December 18, 2007

Revised: March 20, 2008

Accepted: May 1, 2008

Published: July 9, 2008

REFERENCES

- Alitto, H.J., and Usrey, W.M. (2004). Influence of contrast on orientation and temporal frequency tuning in ferret primary visual cortex. *J. Neurophysiol.* 91, 2797–2808.
- Andersen, R.A., and Mountcastle, V.B. (1983). The influence of the angle of gaze upon the excitability of the light-sensitive neurons of the posterior parietal cortex. *J. Neurosci.* 3, 532–548.
- Anderson, J.S., Carandini, M., and Ferster, D. (2000a). Orientation tuning of input conductance, excitation, and inhibition in cat primary visual cortex. *J. Neurophysiol.* 84, 909–926.
- Anderson, J.S., Lampl, I., Gillespie, D.C., and Ferster, D. (2000b). The contribution of noise to contrast invariance of orientation tuning in cat visual cortex. *Science* 290, 1968–1972.
- Azouz, R., and Gray, C.M. (2003). Adaptive coincidence detection and dynamic gain control in visual cortical neurons in vivo. *Neuron* 37, 513–523.
- Bernander, O., Douglas, R.J., Martin, K.A., and Koch, C. (1991). Synaptic background activity influences spatiotemporal integration in single pyramidal cells. *Proc. Natl. Acad. Sci. USA* 88, 11569–11573.

- Boudreau, C.E., and Ferster, D. (2005). Short-term depression in thalamocortical synapses of cat primary visual cortex. *J. Neurosci.* 25, 7179–7190.
- Cardin, J.A., Palmer, L.A., and Contreras, D. (2005). Stimulus-dependent gamma (30–50 Hz) oscillations in simple and complex fast rhythmic bursting cells in primary visual cortex. *J. Neurosci.* 25, 5339–5350.
- Cardin, J.A., Palmer, L.A., and Contreras, D. (2007). Stimulus feature selectivity in excitatory and inhibitory neurons in primary visual cortex. *J. Neurosci.* 27, 10333–10344.
- Chance, F.S., Abbott, L.F., and Reyes, A.D. (2002). Gain modulation from background synaptic input. *Neuron* 35, 773–782.
- Connor, C.E., Gallant, J.L., Preddie, D.C., and Van Essen, D.C. (1996). Responses in area V4 depend on the spatial relationship between stimulus and attention. *J. Neurophysiol.* 75, 1306–1308.
- Connor, C.E., Preddie, D.C., Gallant, J.L., and Van Essen, D.C. (1997). Spatial attention effects in macaque area V4. *J. Neurosci.* 17, 3201–3214.
- Contreras, D., and Palmer, L. (2003). Response to contrast of electrophysiologically defined cell classes in primary visual cortex. *J. Neurosci.* 23, 6936–6945.
- Dong, D.W., and Atick, J.J. (1995). Statistics of natural time-varying images. *Network. Computation in Neural Systems* 6, 345–358.
- Destexhe, A., and Paré, D. (1999). Impact of network activity on the integrative properties of neocortical pyramidal neurons in vivo. *J. Neurophysiol.* 81, 1531–1547.
- Disney, A.A., Aoki, C., and Hawken, M.J. (2007). Gain modulation by nicotine in macaque v1. *Neuron* 56, 701–713.
- Fellous, J.M., Rudolph, M., Destexhe, A., and Sejnowski, T.J. (2003). Synaptic background noise controls the input/output characteristics of single cells in an in vitro model of in vivo activity. *Neuroscience* 122, 811–829.
- Ferster, D., and Miller, K.D. (2000). Neural mechanisms of orientation selectivity in the visual cortex. *Annu. Rev. Neurosci.* 23, 441–471.
- Finn, I.M., Priebe, N.J., and Ferster, D. (2007). The emergence of contrast-invariant orientation tuning in simple cells of cat visual cortex. *Neuron* 54, 137–152.
- Fox, K., Daw, N., Sato, H., and Czeplita, D. (1992). The effect of visual experience on development of NMDA receptor synaptic transmission in kitten visual cortex. *J. Neurosci.* 12, 2672–2684.
- Gasparini, S., and Magee, J.C. (2006). State-dependent dendritic computation in hippocampal CA1 pyramidal neurons. *J. Neurosci.* 26, 2088–2100.
- Hansel, D., and van Vreeswijk, C. (2002). How noise contributes to contrast invariance of orientation tuning in cat visual cortex. *J. Neurosci.* 22, 5118–5128.
- Higgs, M.H., Slee, S.J., and Spain, W.J. (2006). Diversity of gain modulation by noise in neocortical neurons: regulation by the slow afterhyperpolarization conductance. *J. Neurosci.* 26, 8787–8799.
- Ho, N., and Destexhe, A. (2000). Synaptic background activity enhances the responsiveness of neocortical pyramidal neurons. *J. Neurophysiol.* 84, 1488–1496.
- Holt, G.R., and Koch, C. (1997). Shunting inhibition does not have a divisive effect on firing rates. *Neural Comput.* 9, 1001–1013.
- Kim, Y.J., Grabowecky, M., Paller, K.A., Muthu, K., and Suzuki, S. (2007). Attention induces synchronization-based response gain in steady-state visual evoked potentials. *Nat. Neurosci.* 10, 117–125.
- Kohn, A., and Smith, M.A. (2005). Stimulus dependence of neuronal correlation in primary visual cortex of the macaque. *J. Neurosci.* 25, 3661–3673.
- Krieger, G., Rentschler, I., Hauske, G., Schill, K., and Zetsche, C. (2000). Object and scene analysis by saccadic eye-movements: and investigation with higher-order statistics. *Spat. Vis.* 13, 201–214.
- Linias, R.R. (1988). The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science* 242, 1654–1664.
- McAdams, C.J., and Maunsell, J.H. (1999). Effects of attention on orientation-tuning functions of single neurons in macaque cortical area V4. *J. Neurosci.* 19, 431–441.
- McAdams, C.J., and Reid, R.C. (2005). Attention modulates the responses of simple cells in monkey primary visual cortex. *J. Neurosci.* 25, 11023–11033.
- Miller, K.D. (2003). Understanding layer 4 of the cortical circuit: a model based on cat V1. *Cereb. Cortex* 13, 73–82.
- Miller, K.D., and Troyer, T.W. (2002). Neural noise can explain expansive, power-law nonlinearities in neural response functions. *J. Neurophysiol.* 87, 653–659.
- Mitchell, S.J., and Silver, R.A. (2003). Shunting inhibition modulates neuronal gain during synaptic excitation. *Neuron* 38, 433–445.
- Moore, T., and Armstrong, K.M. (2003). Selective gating of visual signals by microstimulation of frontal cortex. *Nature* 421, 370–373.
- Murphy, B.K., and Miller, K.D. (2003). Multiplicative gain changes are induced by excitation or inhibition alone. *J. Neurosci.* 23, 10040–10051.
- Nase, G., Singer, W., Monyer, H., and Engel, A.K. (2003). Features of neuronal synchrony in mouse visual cortex. *J. Neurophysiol.* 90, 1115–1123.
- Nowak, L.G., Azouz, R., Sanchez-Vives, M.V., Gray, C.M., and McCormick, D.A. (2003). Electrophysiological classes of cat primary visual cortical neurons in vivo as revealed by quantitative analyses. *J. Neurophysiol.* 89, 1541–1566.
- Nowak, L.G., Sanchez-Vives, M.V., and McCormick, D.A. (2005). Role of synaptic and intrinsic membrane properties in short-term receptive field dynamics in cat area 17. *J. Neurosci.* 25, 1866–1880.
- Oviedo, H., and Reyes, A.D. (2005). Variation of input-output properties along the somatodendritic axis of pyramidal neurons. *J. Neurosci.* 25, 4985–4995.
- Prescott, S.A., and De Koninck, Y. (2003). Gain control of firing rate by shunting inhibition: roles of synaptic noise and dendritic saturation. *Proc. Natl. Acad. Sci. USA* 100, 2076–2081.
- Salinas, E., and Sejnowski, T.J. (2001). Gain modulation in the central nervous system: where behavior, neurophysiology, and computation meet. *Neuroscientist* 7, 430–440.
- Scal, G., and Freeman, R.D. (1982). Orientation selectivity in the cat's striate cortex is invariant with stimulus contrast. *Exp. Brain Res.* 46, 457–461.
- Shu, Y., Hasenstaub, A., Badoual, M., Bal, T., and McCormick, D.A. (2003). Barrages of synaptic activity control the gain and sensitivity of cortical neurons. *J. Neurosci.* 23, 10388–10401.
- Skottun, B.C., Bradley, A., Scal, G., Ohzawa, I., and Freeman, R.D. (1987). The effects of contrast on visual orientation and spatial frequency discrimination: a comparison of single cells and behavior. *J. Neurophysiol.* 57, 773–786.
- Skottun, B.C., De Valois, R.L., Grosof, D.H., Movshon, J.A., Albrecht, D.G., and Bonds, A.B. (1991). Classifying simple and complex cells on the basis of response modulation. *Vision Res.* 31, 1079–1086.
- Smith, M.R., Nelson, A.B., and Du Lac, S. (2002). Regulation of firing response gain by calcium-dependent mechanisms in vestibular nucleus neurons. *J. Neurophysiol.* 87, 2031–2042.
- Steriade, M. (2001). Impact of network activities on neuronal properties in corticothalamic systems. *J. Neurophysiol.* 86, 1–39.
- Stevens, C.F., and Zador, A.M. (1998). Input synchrony and the irregular firing of cortical neurons. *Nat. Neurosci.* 1, 210–217.
- Tateno, T., and Robinson, H.P. (2006). Rate coding and spike-time variability in cortical neurons with two types of threshold dynamics. *J. Neurophysiol.* 95, 2650–2663.
- Thomson, A.M., Bannister, A.P., Mercer, A., and Morris, O.T. (2002). Target and temporal pattern selection at neocortical synapses. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 357, 1781–1791.
- Trotter, Y., and Celebrini, S. (1999). Gaze direction controls response gain in primary visual-cortex neurons. *Nature* 398, 239–242.
- Weyand, T.G., and Malpeli, J.G. (1993). Responses of neurons in primary visual cortex are modulated by eye position. *J. Neurophysiol.* 69, 2258–2260.
- Williford, T., and Maunsell, J.H. (2006). Effects of spatial attention on contrast response functions in macaque area V4. *J. Neurophysiol.* 96, 40–54.
- Winkowski, D.E., and Knudsen, E.I. (2006). Top-down gain control of the auditory space map by gaze control circuitry in the barn owl. *Nature* 439, 336–339.