

Dynamics of Suppression in Macaque Primary Visual Cortex

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The response of a neuron in primary visual cortex (V1) to an optimal stimulus in its classical receptive field (CRF) can be reduced by the presence of an orthogonal mask, a phenomenon known as cross-orientation suppression. The presence of a parallel stimulus outside the CRF can have a similar effect, in this case known as surround suppression. We used a novel stimulus to probe the time course of cross-orientation suppression and found that it is very fast, starting even before the response to optimal excitatory stimuli. However, it occurs with some delay after the offset response, considered to be a measure of the earliest excitatory signals that reach the CRF. We also examined the time course of response to a stimulus presented outside the CRF and found that cross-orientation suppression begins substantially earlier than surround suppression measured in the same cells. Together, these findings suggest that cross-orientation suppression is attributable to either direct feedforward signal paths to V1 neurons or a circuit involving fast local interneurons within V1. Feedback from higher cortical areas is implicated in surround suppression, but our results make this an implausible mechanism for cross-orientation suppression. We conclude that suppression from inside and outside the CRF occur through different mechanisms.

Key words: cross-orientation suppression; surround suppression; macaque monkey; primary visual cortex; inhibition; synaptic depression

Introduction

The earliest receptive field models of simple cells in primary visual cortex (V1) were based primarily on excitation from afferent LGN fibers (Hubel and Wiesel, 1962), but many researchers have since recognized the importance of inhibition from inside (Benvenuto et al., 1972; Morrone et al., 1982; Bonds, 1989; DeAngelis et al., 1992) and outside (Hubel and Wiesel, 1968; Blakemore and Tobin, 1972; Nelson and Frost, 1978; Knierim and Van Essen, 1992; DeAngelis et al., 1994) the classical receptive field (CRF) in shaping the response properties of these neurons. The response of a neuron to an optimally oriented stimulus can be reduced by superimposing an orthogonal mask stimulus or by placing a parallel stimulus outside the CRF. These phenomena, commonly known as cross-orientation suppression and surround suppression, are two of the most powerful and prevalent forms of suppression in V1.

Cross-orientation suppression has motivated many ideas about cortical computation, including the widely accepted idea of divisive normalization (Bonds, 1989; Heeger, 1992; Carandini et al., 1997). It appears to originate from within the CRF (DeAngelis et al., 1992) and is strongest when the size of the mask is equal to

or smaller than that of the excitatory stimulus. It is broadly tuned for spatial frequency (Bauman and Bonds, 1991; DeAngelis et al., 1992) and temporal frequency (Allison et al., 2001; Freeman et al., 2002) and has little or no selectivity for orientation (Bonds, 1989; DeAngelis et al., 1992; Carandini et al., 1997).

Three mechanisms have been proposed for cross-orientation suppression. The oldest idea is that the suppression is the result of intracortical inhibitory circuits, activated directly by feedforward signals from the LGN, by recurrent activation from nearby cortical neurons, or by feedback from extrastriate cortex (Burr et al., 1981; Morrone et al., 1982; Bonds, 1989; Heeger, 1992; Carandini et al., 1997; Allison et al., 2001; Lauritzen et al., 2001). More recently, Carandini and his colleagues (Carandini et al., 2002; Freeman et al., 2002) have proposed that suppression results from the depression of thalamocortical synapses. Finally, Priebe and Ferster (2006) have shown recently that suppression can result from nonlinearities (contrast saturation and rectification) that reduce the feedforward excitatory signal from the LGN, without either synaptic depression or synaptic inhibition being involved.

These same three sources of suppression (LGN, intracortical, and feedback) have also been proposed as sources of surround suppression. Horizontal intracortical connections within V1 (Nelson and Frost, 1978; Knierim and Van Essen, 1992; DeAngelis et al., 1994) were originally suggested to form the circuitry underlying suppressive signals beyond the CRF. LGN suppressive fields (Levick et al., 1972) can explain several nonlinear response properties (Bonin et al., 2004; Carandini, 2004) and have been postulated to play a role in surround suppression in V1 (Solomon et al., 2002; Ozeki et al., 2004; Wiesel and Sajda, 2005). Finally, feedback from higher cortical areas has been a popular alternative explanation, based on the latency and spatial distribution of signals from the surround (Knierim and Van Essen, 1992; Zipser et

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al., 1996; Cavanaugh et al., 2002; Angelucci et al., 2002; Levitt and Lund, 2002). Recently, the temporal properties of surround suppression have been used to analyze its mechanism: the relatively sluggish dynamics and their modest dependence on cortical distance seem to be most consistent with the feedback hypotheses (Bair et al., 2003).

The common set of proposed origins for signals underlying these two forms of suppression are not the only indication that they may be linked. Heeger (1992) formalized a model in which striate cortical cells normalize their responses to stimulus contrast through mutual inhibition. He further proposed that this pool of inhibition might underlie several suppressive mechanisms within primary visual cortex, including suppression from the surround and from orthogonal masks within the CRF. Others have argued for separate origins for these two suppressive mechanisms (DeAngelis et al., 1992). If these two forms of suppression work through the same mechanism, their timing might reflect this similarity. Alternatively, a difference in time course would indicate distinct mechanisms. Although the timing of surround suppression has been studied, we are not aware of a comparable analysis of the time course of cross-orientation suppression. We report here that cross-orientation suppression is rapid and therefore different in its dynamics from surround suppression, suggesting that it arises from different mechanisms.

Parts of this work have been published previously in abstract form (Smith et al., 2001, 2002).

Materials and Methods

Electrophysiology. We recorded extracellularly from single units in area V1 of 19 Cynomolgus macaques (*Macaca fascicularis*), one Bonnet macaque (*M. radiata*), and two pig-tailed macaques (*M. nemestrina*), ranging in weight from 3.0 to 6.0 kg. The number of animals was large because they were also used for experiments other than those reported here (notably those of Bair et al., 2003). Of 112 complex cells studied, 43 were used for both cross-orientation suppression and surround suppression measurements. A total of 52 other cells were studied for surround suppression, and 17 other cells were studied for cross-orientation suppression.

The techniques used in our laboratory for recording from the visual cortex of anesthetized, paralyzed macaques have been described in detail previously (Cavanaugh et al., 2002). Briefly, animals were premedicated with atropine sulfate (0.05 mg/kg) and diazepam (Valium, 1.5 mg/kg) 30 min before inducing anesthesia with ketamine HCl (10.0 mg/kg). Anesthesia was maintained throughout the experiment by a continuous infusion of sufentanil citrate (typically 4 μ g/kg, adjusted as needed for each animal). To minimize eye movements, the animal was paralyzed with a continuous intravenous infusion of vecuronium bromide (Norcuron, 0.1 mg \cdot kg⁻¹ \cdot hr⁻¹). Vital signs (EEG, electrocardiogram, end-tidal P_{CO₂}, temperature, and lung pressure) were monitored continuously. The pupils were dilated with topical atropine, and the corneas were protected with gas-permeable hard contact lenses. We used supplementary lenses to bring the retinal image into focus by direct ophthalmoscopy. We later adjusted the refraction further to optimize the response of recorded units. Experiments typically lasted 4–5 d. All procedures complied with guidelines approved by the New York University Animal Welfare Committee.

We recorded with quartz–platinum–tungsten microelectrodes (Thomas Recording, Giessen, Germany) advanced with a mechanical microdrive system or with tungsten-in-glass microelectrodes (Merrill and Ainsworth, 1972) advanced with a hydraulic microdrive through a small durotomy made within a craniotomy of \sim 10 mm diameter. The craniotomy was typically centered 4 mm posterior to the lunate sulcus and 10 mm lateral to the midline. The electrode was usually advanced down in the parasagittal plane. We recorded from both the opercular and calcarine segments of V1, in which eccentricities ranged from 1 to 6° and 8 to 20°, respectively. Signals from the microelectrode were amplified and bandpass filtered, and we isolated single units with a dual-window

time-amplitude discriminator (Bak, Germantown, MD). The time of each action potential was recorded with a resolution of 0.25 ms by a CED-1401 Plus laboratory interface (Cambridge Electronic Design, Cambridge, UK).

Visual stimulus generation. We displayed all visual stimuli at a resolution of 1024 \times 731 pixels and a video frame rate of 100 Hz on an Eizo (Cypress, CA) T550 monitor. We used look-up tables to correct for nonlinearities in the relationship between input voltage and phosphor luminance in the monitors. We generated grating stimuli for basic characterization with a Cambridge Research Systems (Kent, UK) VSG 2/2 board running on an Intel x86-based host computer. The cross-orientation suppression stimulus was generated with a Silicon Graphics (Mountain View, CA) workstation. The mean luminance of the display was \sim 33 cd/m². All of the grating stimuli were presented in a circular aperture surrounded by a gray field of the average luminance.

For each isolated neuron, we began by mapping its receptive field for each eye on a tangent screen by hand. We determined the dominant eye to be that which yielded the larger response and occluded the other eye. Using a front surface mirror, we brought the receptive field to the center of a video monitor placed between 80 and 180 cm from the animal's eye, where it subtended between 10 and 22° of visual angle. We then proceeded with experiments under computer control.

The initial characterization experiments consisted of multiple blocks of stimuli, each composed of a randomly ordered group of all of the stimuli in a set. All stimuli within a block were equal in duration and were separated by presentation of a uniform mean gray background for \sim 1.5 s. We characterized the response properties of the cell to gratings in this order: (1) orientation and direction tuning; (2) spatial frequency tuning; (3) temporal frequency tuning; and (4) size tuning. We chose a small patch of optimized grating and adjusted the vertical and horizontal position by hand to obtain the maximal response. This patch was taken to be centered in the receptive field.

Stimuli for the analysis of suppression timing. We used two dynamic stimuli to test the timing of cross-orientation suppression and iso-orientation surround suppression. The cross-orientation stimulus was presented entirely within the CRF. It consisted of two gratings, one parallel and one orthogonal to the preferred orientation, each presented at 50% contrast. This produced four possible states: a blank screen, the preferred grating, an orthogonal grating, or both gratings added to produce a 100% contrast cross-orientation masking stimulus (for examples, see Fig. 1C). Each state lasted for one cycle of drift, typically 80 or 160 ms (range, 80–320 ms), and the entire trial lasted \sim 30 s. Trials were separated by presentation of a uniform mean gray screen for \sim 1.5 s and were repeated to obtain a sufficient number of presentations of each of the four states. The spatial and temporal frequency of the gratings was set to the optimal value for each cell. For temporal frequency, this was either 6.25 or 12.5 Hz. We used a non-optimal temporal frequency only if the peak was $<$ 4 Hz and if increasing the temporal frequency did not cause firing rate to drop below 90% of optimal.

The center-surround stimulus used the CRF and surround apertures that were defined previously. The center and surround gratings could each be oriented either parallel or orthogonal to the preferred orientation of the neuron. This also produced four possible states: a preferred grating with either a parallel or orthogonal surround annulus and a nonpreferred orthogonal grating with either a parallel or orthogonal surround annulus (Bair et al., 2003, their Fig. 2C). Each trial lasted \sim 30 s and was interleaved with a center-alone and surround-alone stimulus. If the surround-alone stimulus produced a substantial response to the transition from orthogonal to parallel, we increased the inner diameter of the annulus to eliminate the response. The temporal frequency of the grating was set at the optimal for each neuron, between 3.12 and 25 Hz (6.25 or 12.5 Hz for most cells). For all cells in which we ran both stimuli, the same temporal frequency was used for both measurements.

Our surround stimulus was designed to explore the phenomenon of iso-orientation surround suppression, which has long been presumed to originate in cortex because of its orientation selectivity. However, it has been suggested that LGN suppressive fields may contribute to the phenomenon of surround suppression in V1 (Solomon et al., 2002; Ozeki et al., 2004; Wiesel and Sajda, 2005). Furthermore, Webb et al. (2005)

proposed that surround suppression may comprise two mechanisms: one that originates in the LGN or V1 input layers and another that is generated through horizontal connections within V1 or feedback from extrastriate cortex. If LGN suppressive fields do play a significant role in surround suppression, then our stimulus should provide a relatively constant level of suppression from these orientation-insensitive neurons (Solomon et al., 2002). In this way, it would isolate the cortical contribution to surround suppression.

Analysis of response latency. We determined response latency using methods detailed previously (Bair et al., 2002, 2003). In brief, we compiled response histograms by segregating spike trains around the time of particular stimulus transitions in each long sequence, adding them, and smoothing them with a Gaussian low-pass filter with an SD of 2 ms. We made latency measurements by comparing the peristimulus time histogram (PSTH) around the chosen transition with the PSTH obtained from “transitions” in which the relevant stimulus did not change. Starting from the maximum value of the difference between the two PSTHs, we searched backward in time to the point at which the difference first fell to 5% of the maximum and took this as the response latency.

For comparison, we also used another method to compute response latency. For each neuron, we found the average PSTH for the transition from a blank to a preferred grating. We then determined the mean and SD in the firing rate over a 50 ms window before the transition (i.e., while the screen was mean gray). The latency was chosen as the time at which the response first exceeded this mean by 2 SDs. Latencies determined with this method were highly correlated with those from the 5% rise method ($r = 0.87$; $n = 58$; $p < 0.0001$) and were not significantly different (mean difference, 1.5 ms; t test, $p = 0.23$). We therefore conclude that our 5% rise method produced a robust estimate of response latency.

Results

We studied the timing of cross-orientation suppression in extracellularly recorded orientation-tuned complex cells from macaque primary visual cortex. In many neurons, we also measured the timing of surround suppression using the methods of Bair et al. (2003) and directly compared this with cross-orientation suppression.

For each recorded neuron, we determined the grating stimulus that was optimal in orientation, direction, and spatial and temporal frequency. We then measured size tuning curves and determined the diameter of the smallest patch of grating that elicited the maximal response (as by Cavanaugh et al., 2002). This defined our optimal CRF stimulus. In general, the response to the optimal stimulus was suppressed when an orthogonal mask was superimposed. On average, the response reduction was 25%, but this was quite variable from cell to cell.

To measure the time course of cross-orientation suppression, we used the general strategy described by Bair et al. (2003) to present a continuous stimulus sequence that randomly combined an optimal grating presented to the CRF with an orthogonal mask. To produce a sustained response to CRF stimulation, we used drifting sinusoidal gratings. We only report the responses of complex cells because the phase-dependent modulation of simple cell responses to drifting gratings prevented us from easily determining response latencies; however, the characteristics of cross-orientation suppression have been found to be similar for simple and complex cells (Morrone et al., 1982; Bonds, 1989).

Each stimulus epoch contained one of four stimulus states: a blank, the optimal stimulus alone, the orthogonal mask alone, or the sum of the mask and the optimal stimulus (for some example stimuli, see Fig. 1). The optimal stimulus and the mask were set to 50% contrast so that their sum was 100% contrast. When present, both the optimal stimulus and the mask were drifting, and each stimulus state lasted for the temporal period of the grating (80 or 160 ms, depending on the temporal frequency). When either the

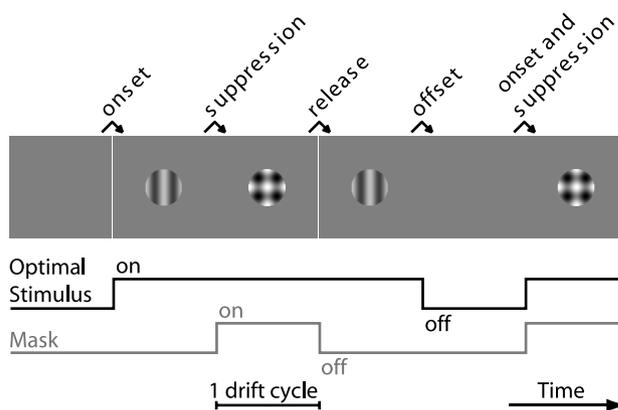


Figure 1. Testing suppression with dynamic stimuli. We used a novel stimulus to test cross-orientation suppression. Each grating was at 50% contrast, smoothly drifting, and could be in either a preferred or an orthogonal orientation. In this case, after each cycle of drift, the optimal and mask grating were randomly chosen to either be present or absent. This created four possible stimuli: a blank screen, a preferred grating or an orthogonal grating at 50% contrast, or a plaid at 100% contrast. We labeled the transitions in which the preferred grating was added or removed while the orthogonal grating was absent as “onset” and “offset.” If the preferred optimal grating was present, the addition or removal of the orthogonal mask were labeled “suppression” and “release.” Changing from a blank to the plaid stimulus was termed “onset and suppression.”

mask or optimal stimulus happened to remain from one state to the next, its motion was seamless across the state transition.

Figure 1 shows an example sequence for six epochs of the stimulus that illustrates the relevant stimulus transitions. In the actual stimulus, the order was random and the stimulus continued for 30 s; multiple 30 s sequences, each with a different random order of states, constitute the full dataset. At the first transition in Figure 1 (bent arrow), the optimal stimulus appeared in the absence of the mask. This “onset” transition typically elicited a strong excitatory response. At the next transition, “suppression,” the mask stimulus appeared while the optimal stimulus continued, and the response typically decreased. When the mask stimulus was removed (“release”), the suppression ended and the response usually increased. When the optimal stimulus disappeared (“offset”), the response returned to baseline. These four transition types, of the possible 16, represent the core conditions for our analysis. We will also later consider a fifth transition (“onset and suppression”), in which the optimal stimulus and mask appeared together after a blank.

Example responses

Figure 2 shows the responses of a V1 neuron to the stimulus transitions just described. Each curve plots the response averaged over all occurrences (Fig. 2A, 441) of the chosen stimulus transition in a window around the time of the transition (set to time 0). The black line shows the response to the transition indicated by the icons, whereas the gray line shows the reference response, which is the response in the absence of a state transition (i.e., the response to two epochs of the stimulus shown by the left icon). We took response latency as the point at which the response to the stimulus transition diverged from the reference response (see Materials and Methods). For this cell, the response onset (Fig. 2A, arrow) is seen in the rapid increase in firing rate ~ 44 ms after the stimulus transition. The response offset (Fig. 2B) occurred at 22 ms, ~ 22 ms earlier than the onset. When the mask turned on or off, the response showed suppression (Fig. 2C) or release from suppression (Fig. 2D), respectively. Both of these responses oc-

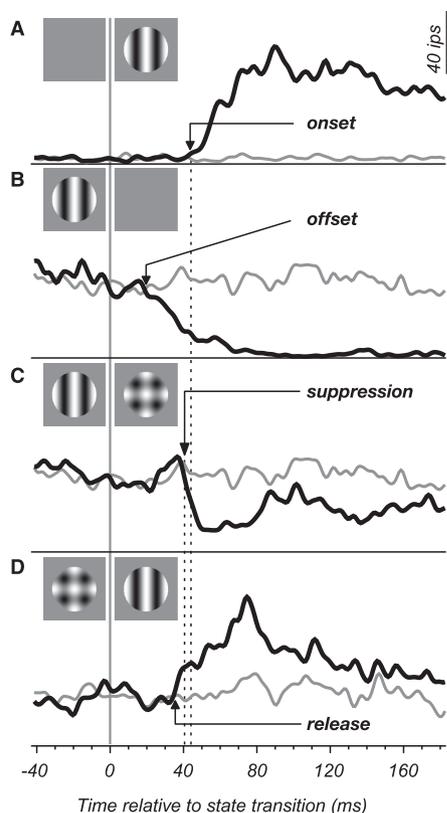


Figure 2. Example responses demonstrating cross-orientation suppression. Here we show the responses of a V1 complex cell to the stimulus transitions shown in Figure 1. The black lines in each panel are average response traces based on a transition at time 0 between the two stimuli indicated with icons. The light gray lines indicate the reference response if the stimulus did not change at time 0. The latencies identified for the four transitions are indicated with arrows, and two vertical dashed lines are drawn to indicate the onset latency and the suppression latency. ips, Impulses per second. **A**, The onset response for this cell occurred 48 ms after the optimal stimulus appeared. **B**, The offset response to the withdrawal of an optimal stimulus tended to precede the onset response, in this case occurring 22 ms after the transition. **C**, The onset of suppression was apparent 41 ms after the mask stimulus was presented. **D**, Release from suppression was apparent 37 ms after the mask stimulus was withdrawn.

occurred a few milliseconds earlier than the onset response but somewhat later than the offset.

Timing statistics

For each cell in our population, we measured the latencies for the four transitions shown in Figure 2. Distributions of these four latencies are shown in Figure 3A–D (arrows indicate means). In a few cases, we could not reliably measure the timing of the transitions because response modulation was too weak (the figure legend gives the numbers of cells included for each transition). The mean offset latency (30.1 ± 9.3 ms) was ~ 20 ms shorter than the mean onset latency (50.0 ± 15.8 ms). This onset delay is consistent with our previous finding that offset tends to precede onset for responses driven from the CRF (Bair et al., 2002; Bair, 2004). Cross-orientation suppression (42.5 ± 11.1 ms) and release (40.9 ± 12.4 ms), however, occurred earlier than response onset. On average, suppression started ~ 6.4 ms before response onset, and this difference was statistically significant (t test, $p < 0.001$). Response suppression and release began at approximately the same time and did not show the asymmetry characteristic of response onset and offset. This is reflected in Figure 3E, in which the data cluster evenly about the identity line. Thus, the raw time course of response and the extracted latency measurements show

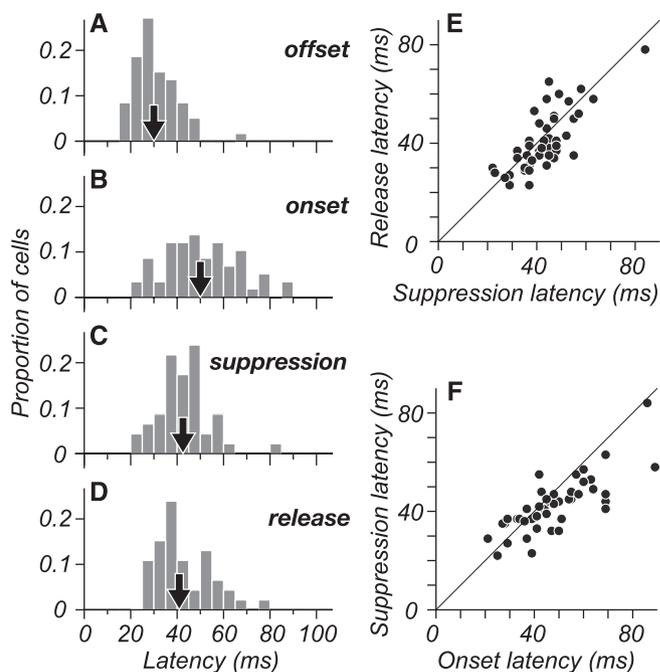


Figure 3. Latency of cross-orientation suppression. **A**, The distribution of offset latency for our population of 60 neurons. The black arrow indicates the mean of the distribution (30.1 ± 9.3 ms; $n = 58$). **B**, The mean onset was ~ 20 ms later than the offset (50.0 ± 15.8 ms; $n = 59$). **C**, Suppression was evident, on average, 6.4 ms before response onset (42.5 ± 11.1 ms; $n = 46$). **D**, Release from suppression occurred at approximately the same time (40.9 ± 12.4 ms; $n = 46$). **E**, As suggested by the similarity of the latencies for suppression and release shown in **C** and **D**, these two values were well correlated. **F**, The relationship between the onset latency of a cell and its suppression latency was also very strong: cells with short-latency onset responses had short-latency suppression and vice versa.

that cross-orientation suppression occurs rapidly. In particular, the suppression usually begins before the response onset to an optimal CRF stimulus.

The basic features of these latencies are similar to those reported by Bair et al. (2002, 2003). The shortest response latency occurred for the offset of the optimal stimulus; the delayed onset response to this stimulus is probably attributable to the integration time required to bring the neuron from a subthreshold to a suprathreshold state. The state transitions involving cross-orientation interactions (suppression and release) occur when the cell is already active, so no integration time elapses before the rate changes. The latencies for these two states are similar, and both are shorter than the latency of the onset response. Note that, if these changes were attributable to the onset and offset of synaptic inhibition, the cells providing the inhibition could not themselves have delayed onset responses, because that would produce an asymmetry between suppression and release timing in the inhibited neuron. However, delayed onset responses are nearly universal in neurons in the LGN and V1 (Bair et al., 2002).

We also examined the relationship across cells between the latencies of response and of cross-orientation suppression (Fig. 3F). It is evident that these latencies were strongly correlated ($r = 0.77$; $n = 44$; $p < 0.001$). This is consistent with the idea that they depend on the same mechanism or arrive at the cell via the same pathway. There was also some trend for neurons with a longer onset latency to have a larger lead time of suppression (i.e., onset latency minus suppression latency). This correlation was statistically significant ($r = 0.70$; $n = 46$; $p < 0.001$). Together, the findings that cross-orientation suppression is very fast and does not exhibit a delayed onset response may be viewed as evidence

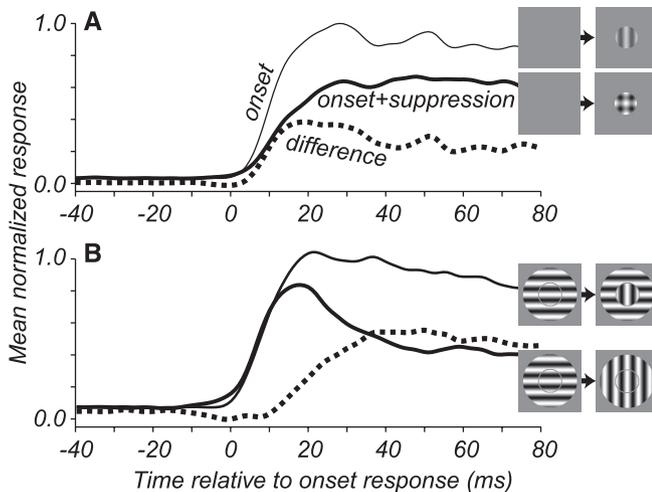


Figure 4. Grand PSTHs showing the average timing of two kinds of suppression across the population. **A**, The timing of cross-orientation suppression. The thin curve shows the average onset response of 59 neurons, elicited by the transition from a blank screen to a preferred grating (icon). The responses were all aligned on the onset latency before being added; this time is taken as 0. The thick curve shows the response of the same neurons to the transition from a blank screen to a plaid combining a preferred and orthogonal grating (“onset + suppression”). The dashed curve shows the difference between the other two traces as a measure of the suppression produced by the orthogonal grating. The curve rises from time 0 and is similar in shape to the onset response, indicating that suppression was present at or before the start of the onset response. **B**, The timing of surround suppression (data from Bair et al., 2003). The thin curve shows the average response of 93 neurons to an orientation transition from orthogonal to preferred (the “onset” response for the surround suppression experiments). As in **A**, the traces were all aligned at the onset latency, which was set to 0. The thick curve shows the average response of the same neurons to a simultaneous transition of a center stimulus from orthogonal to preferred and a surround stimulus from orthogonal to preferred (“onset + suppression”). The dashed curve shows the difference between the other two as a measure of surround suppression. In contrast to the analogous curve in **A**, the surround-suppressive signal was delayed after the onset response and did not stabilize until ~ 50 ms after the onset response began.

that the cross-orientation suppression signals arrive before excitation from the CRF. However, we established previously that it is the offset response, and not the onset, that is the true measure of the earliest excitatory signals that reach the CRF (Bair et al., 2002). Because cross-orientation suppression does not begin at the same time as the offset response, it seems unlikely that the suppressive signal arrives before CRF excitation. One possibility is that it arrives after direct excitation to the CRF but acts before threshold is reached.

To visualize the time course of cross-orientation suppression across our population and to compare it with the timing of CRF excitation and surround suppression, we averaged the PSTHs across all cells for each transition to create a set of grand PSTHs. This method has the advantage that it does not rely on accurately determining all of the individual timing transitions, which are subject to noise. We aligned the PSTHs for all cells to the onset latency and set it to 0 to provide a reference time. The onset is the most accurate latency measurement because the response to the onset of the optimal stimulus almost always has the highest signal-to-noise ratio. In Figure 4A, the grand PSTH for the onset transition is labeled “onset” (thin line). The abrupt upward deflection of this line from the flat baseline at time 0 shows that our onset latencies were aligned with an accuracy of a few milliseconds. The most instructive comparison is with responses to the transition from a blank screen to the combination stimulus containing both the optimal grating and the cross-orientation mask. The time course of the response to this state (thick line) reveals

that firing is suppressed (relative to the response to the optimal stimulus alone) from the moment the rate begins to rise. The difference between the onset and onset/suppression traces (corresponding to the suppressive influence of the mask, dashed line) begins to rise at time 0, indicating that cross-orientation suppression is active at or before the time the onset response begins and continues with a similar time course to the excitation. This is consistent with cross-orientation suppression being present at or before the CRF excitation begins (Figs. 2, 3). The average response for the suppression and release transitions have a time course that is consistent with the example in Figure 2A: they begin before and peak ~ 20 ms after response onset (supplemental Fig. 1A, available at www.jneurosci.org as supplemental material).

This analysis reveals the time course of the cross-orientation suppression signal relative to response onset. However, it is also useful to consider how the population response evolves after the onset of the visual stimulus. We generated a set of grand PSTHs as in Figure 4A, but aligned to stimulus onset, and the responses showed an identical trend (i.e., suppression was evident from the earliest portion of the response). Also, in exploring the response time course of individual neurons, we observed cross-orientation suppression in cases that had both short and long response latencies. This led us to conclude that the grand PSTH in Figure 4A is not biased by a subgroup of neurons that exhibit particularly strong suppression at early response latencies.

Comparison with surround suppression

The pattern of results is distinctly different for surround suppression (Bair et al., 2003). As indicated by the icons in Figure 4, the conditions of surround experiments differed in some details from the cross-orientation experiments. The onset response in the surround case, for example, was elicited by the transition from orthogonal to preferred orientation. The suppression in the surround case was elicited by a similar orientation transition of the surround grating from orthogonal to parallel to the preferred orientation: the orthogonal surround gives little suppression, whereas the parallel surround gives maximal suppression (Cavanaugh et al., 2002; Bair et al., 2003). Using data published previously by Bair et al. (2003), we computed grand PSTHs for conditions analogous to those shown in Figure 4A; the results are shown in Figure 4B. The time course of the onset response for this dataset was very similar to that for the cells in our experiments (thin line). When combined with a transition to the suppressive surround condition, however, the time course was quite different: the suppressed response onset (thick line) follows the unsuppressed response onset for ~ 10 ms before the traces diverge; the suppression then grew in strength for an additional 30 ms before stabilizing at a strongly suppressed value (the average suppression in this condition was 42% compared with 25% for the cross-orientation condition). The dashed line again represents the dynamics of suppression as the difference between the suppressed and unsuppressed conditions, and it shows that surround suppression is much slower than cross-orientation suppression (in Fig. 4A), despite being stronger. The average response for the suppression and release transitions also show that, although some neurons demonstrate early surround suppression, the majority of the effect is evident with some delay after the onset response (supplemental Fig. 1B, available at www.jneurosci.org as supplemental material). Our conclusions from these grand PSTHs are confirmed by comparing the latency statistics for cross-orientation suppression in Figure 3 with those for surround suppression (Bair et al., 2003, their Fig. 4).

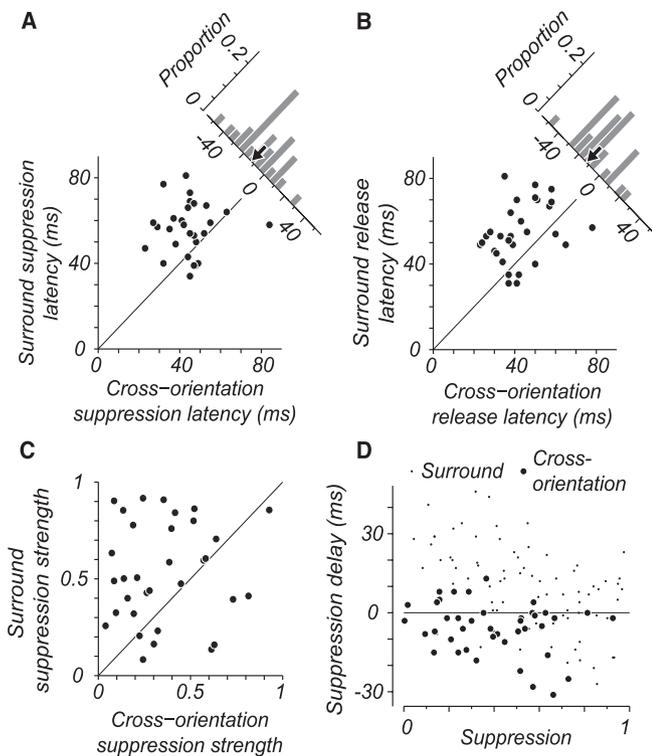


Figure 5. A comparison of the timing of cross-orientation and surround suppression. We compared the suppression and release latencies for the cross-orientation (**A**) and surround (**B**) conditions for each neuron with data from both conditions. There was no statistically significant correlation in either distribution of data. Frequency histograms on each panel show the difference in response timing for suppression at the onset of the suppressive stimulus and its release at its offset. Both distributions are significantly shifted to the left of 0, meaning that, on average, cross-orientation suppression was evident ~ 12 ms before surround suppression, and release from cross-orientation suppression was also earlier by the same amount. **C**, A scatter plot comparing the strength of cross-orientation and surround suppression for 33 cells. No relationship between the strengths of the two types of suppression is evident. Suppression ratio was computed as 1 minus the suppressed response divided by the unsuppressed response (response to plaid divided by response to preferred grating) in a time window equal to one period of the stimulus (typically 160 ms) after response onset (determined separately for each cell). A high value (closer to 1) indicates a large amount of suppression, whereas a low value (closer to 0) indicates a small amount of suppression. **D**, The relationship between suppression delay (“onset” latency minus “suppression” latency) and suppression ratio for both types of suppression. The small symbols (replotted from Bair et al., 2003) represent surround suppression, which is substantially faster when it is strong than when it is weak. The large symbols represent cross-orientation suppression, for which no statistically reliable trend is evident.

To verify that these trends held when tested within the same group of cells, we compared the two forms of suppression using latency measurements collected from individual neurons. Although the grand PSTH has the benefit of viewing the time course without choosing suppression onset or release times that are subject to noise, it also obscures variations in relative timing from cell to cell. In 43 neurons, we collected data on timing for both cross-orientation suppression and surround suppression. For this subset, we are able to perform a within-cell analysis to reveal the absolute difference between the timing of the two types of suppression.

We show an analysis of the paired latency measures from both stimuli in Figure 5, *A* and *B*, for suppression and release, respectively. We observed no significant correlation between the two types of suppression for either the response suppression ($r = 0.05$; $n = 29$; $p = 0.81$) or response release ($r = 0.31$; $n = 30$; $p = 0.09$). The lack of correlation did not result from the different CRF stimuli in the two experiments: there was no significant

latency difference between the two offset conditions (t test, $p = 0.60$) or the onset conditions (t test, $p = 0.63$) among these neurons. There were some neurons in which the latency of surround suppression ($n = 6$ of 29) and release ($n = 8$ of 30) was shorter than cross-orientation suppression and release. This is consistent with our previous finding that some cells do have very fast surround suppression, particularly those in which the suppression is very strong (Bair et al., 2003, their Fig. 5C). Alternatively, these cells might be ones in which the inner radius of the surround stimulus was small enough to elicit suppression from the receptive field center. However, across all cells, suppression and release occurred ~ 12 ms earlier for cross-orientation suppression than for surround suppression (Fig. 5*A,B*, oblique histograms); the difference was highly significant in both cases (t test, $p < 0.001$). We conclude that cross-orientation suppression and surround suppression act with distinctly different time courses.

To further explore the possible relationship between cross-orientation and surround suppression, we examined the correlation between the strength of these forms of suppression in cells that were tested for both (see the legend for the formula used to compute suppression strength). The data in Figure 5*C* show that there was little correlation between the suppression strengths ($r = 0.11$; $n = 33$; $p = 0.53$). Most of the points fall above the identity line, reflecting the fact that surround suppression (mean, 0.42) was usually stronger than the cross-orientation suppression (mean, 0.25).

We showed previously that surround suppression was faster when it was strong than when it was weak (Bair et al., 2003), and we wanted to know whether this relationship held for cross-orientation suppression also. For surround suppression [Fig. 5*D*, small points (replotted from Bair et al., 2003)], we observed a negative correlation between strength and latency (Pearson’s $r = -0.48$; $n = 87$; $p < 0.0001$). Cells with weak suppression (small suppression ratios) show a suppression delay of 20–30 ms on average, whereas cells with strong suppression (large suppression ratios) had little delay on average. The same relationship for cross-orientation suppression is shown by large symbols in Figure 5*D*. In this case, the relationship between strength and latency was in the same direction but much weaker and did not approach statistical significance ($r = -0.25$; $n = 41$; $p = 0.11$). This difference between the two forms of suppression provides additional evidence that they originate from different neural circuits.

Discussion

The timing of suppression by orthogonal masks within the receptive field is very fast and appears to act on the neuron even before the onset response from the CRF (by 6.4 ms on average). However, it occurs significantly after the offset response (by 13.5 ms on average), which is known to be a fast and reliable measure of the earliest latency of a cell (Bair et al., 2002). The early onset of cross-orientation suppression is one feature that clearly distinguishes it from surround suppression, which occurs later by ~ 12 ms on average. A second feature that distinguished these suppressive signals was the relationship between their strength and latency. For surround suppression, strength and latency were strongly anticorrelated, whereas for cross-orientation suppression, they were unrelated. In human observers, Petrov et al. (2005) studied the effects of surround and cross-orientation suppression on contrast sensitivity. Using a double-masking paradigm, they determined that suppression from a cross-orientation grating precedes suppression from a grating in the surround. This result provides additional evidence that the distinction between these two types of suppression is a general one, applicable to both

neural and psychophysical data in primates. Below we will consider the implications of these results for the circuits involved.

Allison et al. (2001) suggested a possible extrastriate origin (area 18) for cross-orientation suppression based on its strength at high temporal frequencies. This hypothesis was based on their results from areas 17 and 18 in the cat, which both receive direct LGN input (Wilson and Cragg, 1967). In the macaque, however, area V2 does not receive a substantial input from the LGN. An alternate candidate for the source of feedback is the middle temporal area (MT), which has short visual response latencies. However, although connections between V1 and extrastriate cortex can be quite fast (Movshon and Newsome, 1996; Nowak and Bullier, 1997; Girard et al., 2001; Hupé et al., 2001), and MT even receives a direct projection from koniocellular neurons in the LGN (Sincich et al., 2004), the latency of MT neurons is longer than the fastest-responding neurons in V1 (Raiguel et al., 1989; Schmolesky et al., 1998; Bair et al., 2002). It seems unlikely that signals could travel to MT and back before the onset of the feedforward response driven directly from the CRF of the V1 neuron. The variation in response latency could possibly mask this circuit delay if the cells with the shortest latencies send signals to extrastriate cortex, which in turn project back to inhibit other cells in V1 with longer response latencies. If such a system were in place, however, we would expect neurons with the shortest response latencies to have some delay for cross-orientation suppression, whereas only those with longer latencies could show no delay or have suppression occur before response onset. This was not the case: cross-orientation suppression was evident before response onset even in cells with the shortest response latencies. Neurons in extrastriate cortex also have receptive field sizes that are much larger than those in V1 at the corresponding eccentricity. If these extrastriate neurons were the source of the suppressive signal, we would expect that it would extend well beyond the CRF. On the contrary, DeAngelis et al. (1992) reported that cross-orientation suppression originates from within the receptive field of cat area 17 neurons and is strongest when the mask is equal to or smaller than the CRF. It therefore seems highly improbable that signals from extrastriate cortex can account for the observed properties of cross-orientation suppression. We suspect that a more direct mechanism may be responsible for this type of suppression.

The mechanism that was originally postulated to account for cross-orientation suppression involves a pooled “normalization” signal that arises from cells within striate cortex (Bonds, 1989; Heeger, 1992; Carandini et al., 1997). This normalization has been suggested to underlie multiple suppressive phenomena within striate cortex, including surround suppression (Heeger, 1992; Cavanaugh et al., 2002). If the same pool of inhibitory neurons were to underlie both types of suppression, their response properties should match, but this does not appear to be the case. Surround suppression is selective for the orientation and spatial frequency of the target in the surround (DeAngelis et al., 1994; Cavanaugh et al., 2002; Müller et al., 2003), whereas cross-orientation suppression seems to lack selectivity (DeAngelis et al., 1992; Carandini et al., 1997). Our results show that the time courses of cross-orientation suppression and surround suppression are quite different. Furthermore, the strength and latency of these two types of suppression are not correlated across our population of cells, and the relationship between strength and timing appears to be different (Fig. 5). We therefore believe that cross-orientation suppression and iso-orientation surround suppression arise from different mechanisms.

Recently, Freeman et al. (2002) proposed that synaptic depression in thalamocortical synapses might underlie cross-

orientation suppression (but see Boudreau and Ferster, 2005). Based on their recordings in cat area 17, they suggest that a cortical basis is unlikely because the suppression is essentially immune to visual adaptation and is engaged by gratings drifting faster than 20 Hz, which exceeds the temporal resolution of most cells in primary visual cortex. These two findings argue against a cortical basis for cross-orientation suppression, unless it is mediated by nonadapting inhibitory interneurons with rapid response dynamics. This is difficult to rule out, because these neurons might exist but be rarely encountered with extracellular electrodes. Another model accounting for cross-orientation suppression was proposed recently by Priebe and Ferster (2006), who showed that suppression can result from nonlinearities that reduce feedforward excitation from LGN inputs. This model invokes neither synaptic depression nor synaptic inhibition, but instead applies contrast saturation and rectification of geniculate relay cells to a linear feedforward system. These two models are related, in that they account for cross-orientation suppression without involving intracortical circuitry. An alternative model using local cortical circuitry has been proposed by Lauritzen et al. (2001). Their model uses strong feedforward inhibition, generated by hypothetical complex inhibitory interneurons in layer 4 that are untuned to orientation, which supplement feedforward excitation by LGN inputs. They find that the addition of synaptic depression to their model does not substantially alter its behavior or change the success of their model in matching cross-orientation suppression data within a cortical inhibition framework.

Historically, almost all research on cross-orientation suppression has been in cat area 17, and there have been only a few studies of this phenomenon in macaque V1 (Carandini et al., 1997, 1998). Although the properties of neurons in cat area 17 and macaque V1 are known to be similar (Hubel and Wiesel, 1962, 1968), we cannot be certain that all of the results will generalize across the species given the known differences in cortical architecture (Wilson and Cragg, 1967). A recent study examined the timing of responses in macaque V1 (Xing et al., 2005) and reported the existence of a fast untuned suppression even in the absence of a cross-orientation stimulus. Xing et al. (2005) did not measure this untuned suppression directly but inferred it by assuming that all sources of suppression are space–time separable, and it remains unclear how it relates to the suppression we measured.

From our data, we can draw some conclusions about what type of mechanism is likely to underlie cross-orientation suppression. A purely excitatory feedforward model would predict that suppression, release, and offset would have the same latency. Alternatively, one might suspect that a model invoking intracortical circuitry would introduce a delay before suppression occurs. We reported that suppression and release occur at the same time, much slower than the offset response but faster than the onset response. If suppression arrived with the CRF excitation, it should arrive near the time of the offset response. However, if we consider the offset response as a measure of the earliest excitatory signals that reach the CRF (Bair et al., 2002), then the 13.5 ms delay before cross-orientation suppression is time enough for intracortical circuitry and inhibition to act before threshold is reached and the onset response occurs. This type of intracortical inhibition might also explain why cross-orientation suppression actually precedes the onset response. If intracortical circuitry is to account for cross-orientation suppression, however, the inhibitory interneurons must be mostly immune to visual adaptation and sensitive to gratings at high temporal frequencies (above the cutoff for most V1 neurons) to account for the results of Freeman

et al. (2002). Furthermore, they must have very short integration times and reach threshold quickly for their inhibition to act before the onset response of their target neuron. Such neurons would have to be rarely or never encountered in typical extracellular recordings, because they have yet to be reported in V1. If synaptic depression is the mechanism underlying cross-orientation suppression, then it must act within only a few milliseconds after response offset and recover with equal speed. The time constant for recovery from synaptic depression *in vitro* is reported to be from 60 to 600 ms (Abbott et al., 1997; Thomson and Deuchars, 1997; Varela et al., 1997), whereas we observed recovery from suppression no more than 20 ms after response onset. Furthermore, Boudreau and Ferster (2005) studied synaptic depression at the thalamocortical synapse in anesthetized cats and concluded that synaptic depression is near saturation at spontaneous levels of activity. These findings that indicate synaptic depression is an unlikely source for cross-orientation suppression.

Therefore, although we can confidently rule out feedback as the source of cross-orientation suppression, the uncertain contribution of a hypothetical population of “fast” interneurons means that we cannot yet distinguish a model based on local inhibition from one based purely on modifications of feedforward excitation by LGN nonlinearities. Nevertheless, our data on the time course of cross-orientation suppression strongly support one of these direct, feedforward models and show that distinct mechanisms produce cross-orientation suppression and surround suppression.

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