Dynamics of extraclassical surround modulation in three types of V1 neurons

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Submitted 4 August 2010; accepted in final form 11 January 2011

NEURONS IN PRIMARY VISUAL CORTEX (V1) are typically composed of a classical receptive field (CRF) center and an extraclassical surround (Albright and Stoner 2002; Allman et al. 1985; Fitzpatrick 2000). Whereas cell responses are driven by center stimulation, the surround plays a more modulatory role that is thought to be important in figure ground segregation and in forming the building blocks of form perception (Seriès et al. 2003; Sillito et al. 1995; Zipser et al. 1996). Previous studies have suggested that the center responses of most V1 cells are suppressed by inclusion of surround stimuli (Jones et al. 2001; Sengpiel et al. 1997; Walker et al. 2000), with maximal suppressive modulation when the center and the surround have the same orientation and spatial frequency (Akasaki et al. 2002; DeAngelis et al. 1994; Knierim and Van Essen 1992; Levitt and Lund 1997; Walker et al. 1999).

However, even under these optimal stimulus conditions, not all V1 cells are suppressed by surround stimuli. Instead, in about one-quarter of the cells, responses will saturate and exhibit a plateau-like tuning profile (DeAngelis et al. 1994; Sengpiel et al. 1997; Walker et al. 2000). In addition, there is a third, more rarely encountered type of V1 cell that shows neither suppression nor saturation of response to increasing stimulus size, but rather increases in firing rate (Cavanaugh et al. 2002a; Gilbert 1977; Li and Li 1994). Thus three types of V1 cells can be characterized, suppressive, plateau, and facilitative, on the basis of their responses to increasing stimulus size beyond their CRF.

Results from previous studies examining the dynamics of surround suppression have helped unravel the underlying mechanisms of surround modulation for suppressive cells. For example, it has been shown that there is an early suppressive component (Alitto and Usrey 2008; Xing et al. 2005) that likely arises through relatively fast feedforward lateral geniculate nucleus (LGN) afferents that already exhibit extraclassical surround suppression (Alitto and Usrey 2008; Ozeki et al. 2004; Sceniak et al. 2006; Solomon et al. 2002; Webb et al. 2005a). In addition, there is a second component that develops later in time (Chen et al. 2005; Xing et al. 2005) and is likely to be mediated instead through cortical mechanisms, which propagate more slowly (Bringuier et al. 1999; Girard et al. 2001; Grinvald et al. 1994; Schwabe et al. 2006).

Previous studies on surround dynamics, however, have not included analyses of nonsuppressive modulation. Therefore, in the present study we have investigated response dynamics of all three types of surround modulation found in V1 (suppressive, plateau, and facilitative) using drifting sinusoidal gratings of various radii. Our results reveal that there are two stages of surround modulation: (1) early surround modulation that is mainly suppressive regardless of cell type and may rely on feedforward mechanisms because of rapid onset, and (2) a secondary surround modulation that evolves later in time, can be suppressive or facilitative depending on the cell type, and may be generated through more slowly propagating cortical circuits.

METHODS

Animal Preparation and Recording

The experiments were performed in 13 adult cats weighing 2.4–5.0 kg and of both sexes. All procedures were approved by the Institutional Animal Care and Use Committee of the University of California, Irvine. Animals were initially anesthetized with a mixture of ketamine (21 mg/kg im) and xylazine (3 mg/kg im). Anesthesia was maintained with isoflurane (0.2–0.6%) in a 67:33 mixture of nitrous oxide and oxygen through artificial respiration. ECG, EEG, and expired CO₂ were monitored throughout the entire experiment to ensure proper level of anesthesia. To prevent eye movements, neuromuscular blockade was induced with an initial bolus of vecuronium bromide (0.6 mg/ml iv) and maintained for the duration of the experiment with 0.15 mg/ml at a flow rate of 2.0 ml/kg⁻¹ h⁻¹ mixed with dexamethasone (0.5 mg·kg⁻¹·h⁻¹·iv) in a solution of 5% dex-
trose and lactated Ringer. Pupils were dilated with 1% atropine sulfate solution, and the nictitating membranes were retracted with 2.5% phenylephrine hydrochloride. Zero-power, air-permeable contact lenses were fitted to each cornea, and 3-mm artificial pupils were placed in front of the eyes. A craniootomy was made above the dorsal surface of area 17 (V1). Extracellular recordings of single cells were made with epoxy-insulated tungsten microelectrodes (5–7 MΩ; FHC, Bowdoin, ME). Electrode penetrations were made perpendicular to the cortical surface, and cells were recorded at all cortical depths. Visually evoked action potentials of single neurons were amplified and isolated by an Xcell-3 four-channel amplifier (FHC) and then fed into a computer running EXPO software (courtesy of Peter Lennie). Spikes were saved at 1-ms resolution for further analysis using custom MATLAB software.

Visual Stimuli

The visual stimuli were generated by a G5 Mac computer with an ATI Radeon 9200 graphics card running EXPO software. Stimuli were displayed on a gamma-calibrated Viewsonic Graphics Series G225f CRT monitor with a mean luminance of 50 cd/m² and at a viewing distance of 37 cm. The refresh rate was set at 100 Hz on the noninterlaced monitor. The locations of the optic disc and the area centralis for each eye were plotted daily using a fiber-optic light source (Pettigrew et al. 1979).

Through visual stimulation of the dominant eye, the receptive field center of each isolated cell was approximated under mouse control with an ~4° diameter aperture of drifting square wave gratings at the approximate preferred orientation. Maximal response was estimated audibly. The exact position of the receptive field center was then determined by reducing aperture size to as small as 1°. Spatial eccentricities of all receptive fields in our experiment were constrained within 2° above and 16° below the area centralis.

Once the receptive field center was established, the CRF properties were tested in detail in the following sequence: First, we reassessed the preferred orientation of each neuron by varying the tilt of the drifting sinusoidal gratings in 22.5° increments. Gratings were shown at 100% contrast with spatial and temporal frequencies of 0.2 cycle/° and 4 Hz, respectively. Next, optimal spatial frequency was determined by presenting ~10° gratings at the preferred orientation while varying spatial period. It is worth noting that although this aperture size did not always match the optimal receptive field size of the cell (see below), it should nevertheless not affect spatial frequency tuning, since this aperture size was more than twice the diameter of the spatial frequency periods used (Mazer et al. 2002). Preferred temporal frequency was then assessed using gratings with the preferred orientation and spatial frequency. The starting phase of all drifting gratings was set to 0°. Finally, the optimal contrast for each cell was determined through contrast-response profiles (10–100%, in 10% steps).

Aperture tuning curves were fitted by a difference of Gaussian (DoG) function

\[ R_s = K_s \int_{-\infty}^{\infty} e^{-(x^2)+i} dx - K_f \int_{-\infty}^{\infty} e^{-i} + R_0 \]  

in which \( R_s \) is the response evoked by different aperture sizes. The free parameters, \( K_s \) and \( r_s \), describe the strength and the size of the excitatory space, respectively; \( K_f \) and \( r_f \) represent the strength and the size of the inhibitory space, respectively; and \( R_0 \) is the spontaneous activity of the cell.

To evaluate how well our experimental data was explained by the model, we calculated the coefficient of determination (\( R^2 \)) using

\[ R^2 = 1 - \frac{\sum_{j=1}^{N} (R_j - F_j)^2}{\sum_{j=1}^{N} (R_j - R_0)^2} \]  

where \( R_j \) is the response to the jth stimulus, \( F_j \) is the predicted value, and \( R_0 \) is the mean response of the actual data (Freeman et al. 2002).

Across the population, the mean \( R^2 \) for 2 s stimuli was 0.86 ± 0.09.

Definition of modulatory cell types and their CRF. In our study, cells with suppressive, plateau, and facilitative extraclassical surounds were defined on the basis of their tuning profiles to a series of gratings drifting within circular apertures of varying diameter. Each aperture was presented for 2 s, and classification of the three modulatory cell types is based on this full time course.

Suppressive cells were defined as those showing a response attenuation >5% to stimuli beyond their CRF (see examples in Figs. 1, A and B, and 2A). The CRF of suppressive cells was determined by parameter \( r_s \) from Eq. 1 (mean \( r_s = 9.3 ± 4.6° \)), which was similar to the aperture size that evoked the maximum response (mean 9.6 ± 3.9°; t-test, \( P = 0.14 \); Sceniak et al. 1999).

Plateau cells were defined as those that either showed <5% suppression or a saturation of response to aperture sizes larger than the CRF (see examples in Figs. 1C and 2B). As described above for suppressive cells, the CRF size of plateau cells was also determined by the parameter \( r_s \) from Eq. 1, consistent with earlier reports describing plateau cells (DeAngelis et al. 1994; Walker et al. 2000).

Facilitative cells were defined as those that exhibited no saturation, but instead showed a monotonic response increase to increases in size of the stimulus aperture (see examples in Figs. 1D and 2C). For such cells, the size of the CRF (center) was determined by locating the annular minimum response field (5% above background; Cavanaugh et al. 2002a) to a series of annuli with variable inner diameters and a fixed 30° outer diameter (see gray trace in Fig. 2C). Thus, although we found that these cells always responded optimally to the largest aperture presented (30°), the CRF of these facilitative cells was much smaller, ranging from 4 to 10° in diameter (see arrow in Fig. 2C). Importantly, if a stimulus was not presented to this small CRF region, the facilitative cell was unresponsive to large stimuli. Overall, the average CRF (7.0 ± 2.5°) was comparable to, although somewhat smaller than, the excitatory space constant derived from Eq. 1 (mean \( r_s = 10.0 ± 3.4° \)).

Simple/complex classification. The mean firing rate and first harmonic component of the accumulated response were computed for each stimulus. V1 neurons were classified as simple or complex by comparing the ratio of the first harmonic to the mean response to drifting grating stimuli (Skottum et al. 1991).

Modulation index. To quantify the extraclassical surround modulation of all three modulatory cell types, we calculated a modulation index (MI) using

\[ MI = (R_{ECS} - R_{CRF}) / \max(R_{ECS}, R_{CRF}) \]  

where \( R_{ECS} \) is the response for maximum aperture size and \( R_{CRF} \) is the response for the CRF. A negative MI indicates suppression, whereas a positive MI indicates facilitation.

Temporal dynamics of the surround modulation. To determine the time course of extraclassical surround modulation, we fitted aperture tuning curves at successive time points using the DoG model in Eq. 1 and calculated MI values for each using Eq. 3. Cumulative time windows were created in steps of 10 ms for the first 200 ms from stimulus onset.
and in steps of 50 ms for the remainder of the 2-s stimulus time period. For a schematic of the cumulative time windows used for each of the aperture tuning curves, see Fig. 1. Figure 1, A and B, represent a simple suppressive cell and a complex suppressive cell, respectively; Fig. 1C represents a complex plateau cell; and Fig. 1D represents a simple facilitative cell.

The reason for using cumulative time windows as opposed to sequential windows of equal size was to improve the signal-to-noise ratio and allow for more reliable aperture fits at each 10-ms bin. For some cells, the use of drifting sine wave gratings led to little or no response in several 10-ms bins (see Fig. 1, A and B). This was especially true for some simple cells that preferred lower temporal frequencies, where several consecutive 10-ms bins would be unresponsive (see example in Fig. 1D). Although the use of cumulative time windows greatly improves fits of the aperture tuning curves, it also sacrifices the precision at which changes in a cell’s response can be pinpointed in time (see DISCUSSION).

Response onset latency of simple cells depends on the initial phase of the stimulus (Movshon et al. 1978; Skottun et al. 1991; Spitzer and Hochstein 1985). The starting phase of our stimuli was always 0°, which was not optimal for a number of our simple cells. As a result, 63% (25/40) of them initiated firing substantially later, especially simple cells preferring low temporal frequencies (see example in Fig. 1D). To compare results of all simple and complex cells, we realigned the onset latency of these delayed simple cells (14/25 suppressive cells, 6/7 plateau cells, 5/8 facilitative cells) to the average onset latency of our complex cells. For this purpose, onset latency was defined as the earliest time that responses to the optimal aperture size (CRF) reached 25% of maximum; the mean latency of our complex cells was 47 ms. Therefore, for each simple cell, the earliest time point that simple cell responses reached 25% of maximum was aligned to 47 ms (see schematic of the cumulative time windows shown in Fig. 1D).

Orientation tuning properties. Responses to drifting gratings varying in orientation (presented at the optimal aperture size and the
preferred spatial and temporal frequencies) were plotted. The orientation tuning curve was fitted using

\[ R_\theta = R_o + R_p e^{-\left(\frac{O_s - O_p}{\sigma}\right)^2} + R_n e^{-\left(\frac{O_s - O_p + 180}{2\sigma}\right)^2} \]  

(4)

where \(O_s\) is the stimulus orientation, \(O_p\) is the preferred orientation, \(R_o\) is the response to different orientations, \(R_p\) and \(R_n\) correspond to the preferred and nonpreferred orientation response, respectively, \(R_o\) is the spontaneous response, and \(\sigma\) is the tuning width. The narrowness of the orientation tuning curve was measured as the half width at half height (HWHH), which equals 1.18\(\sigma\). The orientation selectivity index (OSI), a measure of circular variance, was calculated using

\[ \text{OSI} = \left| \frac{\sum_n R_p \exp(i\theta_n)}{\left(\sum_n |R_n|\right)} \right| \]  

where \(\theta_n\) is the \(n\)th orientation of the stimulus and \(R_n\) is the corresponding response.

Significance tests: Tests for significance were done using one-tailed t-tests or one-way ANOVA.

RESULTS

We recorded from 158 neurons in V1. For each cell, aperture tuning curves were plotted for responses to aperture gratings with increasing diameters, shown drifting for a duration of 2 s (see examples in Figs. 1 and 2). Each curve was then fitted by a DoG function (Eq. 1).

Three Types of Extraclassical Surround Modulation

On the basis of fitted aperture tuning curves, cells could be classified into three types: suppressive, plateau, and facilitative (Fig. 2). The majority of our cells (108/158, 68%) were suppressive, for which responses decreased 5% or greater to aperture diameters beyond optimal. Figure 2A shows a representative suppressive cell. For this cell, the CRF (parameter \(r_c\) from Eq. 1) was 9° (95 spikes/s). The strongest suppression beyond the CRF occurred with the largest aperture diameter presented (30°), reducing spike rate 34% (63 spikes/s).

Effects of the extraclassical surround were not always suppressive. Cells that exhibited no suppression to increasing aperture diameters beyond their CRF were classified into two groups, the more common plateau cells (40/158, 25%) and the rarely encountered facilitative cells (10/158, 6%). Figure 2B shows an example of a plateau cell. In this cell, responses saturated around 10°, and no suppression was observed when larger apertures were presented. This saturation may be caused by a balance between excitatory and inhibitory inputs (Sengpiel et al. 1997). For these plateau cells, their CRF can be represented by the excitatory space constant \(r_c\) in Eq. 1, as described in previous work (DeAngelis et al. 1994; Walker et al. 2000).

Figure 2C shows an example facilitative cell, responses of which continuously increased with increasing aperture size. Importantly, for facilitative cells, we also tested responses to surround annuli and found that increasing the inner diameter led to a marked decrease in firing rate (see gray trace in Fig. 2).

Fig. 2. Three types of extraclassical surround modulation exemplified by different V1 cells. Responses for each cell are plotted against the diameter of stimulus aperture. A: a suppressive cell shows peak response at 10°, which is close to the cell’s classical receptive field (CRF; size of the excitatory space \(r_c = 9°\), indicated by arrow), and then rapidly suppresses in response to further increases in aperture size. B: an example plateau cell shows maximum response to apertures of 10° and larger. Thus the response saturates but is not suppressed by stimuli larger than 10°. The CRF (10°; indicated by arrow) for plateau cells is represented by parameter \(r_c\) extracted from Eq. 1. C: for the example facilitative cell, the response increases with increase in aperture size and does not suppress or saturate (black trace). To identify the CRF, the annular minimum response field was determined through a series of annuli of varying inner diameters (gray trace). The cell has a CRF of 10° (indicated by arrow). The modulation index (MI) is also plotted for each type of cell and equals −0.34 for the suppressive cell in A, +0.07 for the plateau cell in B, and +0.62 for the facilitative cell in C. Error bars are SE.
2C). This means that stimulation of the receptive field center is necessary for the surround to have a facilitative effect. In this way, facilitative cells, like suppressive cells, can also be considered to have a CRF. The inner diameter at which annulus responses dropped to within 5% of the mean background firing rate (the annulus minimum response field; Cavanaugh et al. 2002a) was used to define the CRF of these facilitative cells. For the example shown in Fig. 2C, this corresponded to 10° (indicated by arrow) where the cell response was 10 spikes/s. Center response was then facilitated 62% to 27 spikes/s by presenting the full 30° aperture.

Simple and complex classification of modulatory cell types. In addition to categorizing each neuron based on the type of extraclassical surround modulation, we also classified them as simple or complex by plotting the first harmonic (F1) against the mean response (F0) to the drifting grating stimuli. The results are illustrated in Fig. 3, where cells below the diagonal (F1/F0 > 1) are classified as simple cells. With the use of this criteria, only 40 cells of our entire population were simple cells (25%), whereas the majority were complex cells (n = 118; 75%). Likewise, most of our suppressive (83/108, 77%) and plateau cells (33/40, 83%) were complex as well (open black and filled gray circles located above the diagonal in Fig. 3). Conversely, there was a dramatic difference in the classification of our facilitative cells, because 8 of 10 were simple cells (open black circles falling below the diagonal).

Dynamics of V1 Size Tuning

To determine the time course of extraclassical surround modulation in V1, we segregated responses to different-sized apertures into a series of cumulative time windows (see Fig. 1). For each cell, we plotted size tuning curves for each window and fitted them using Eq. 1.

Figure 4 shows several examples of size tuning curves over time for the different modulatory cell types. For suppressive (Fig. 4, A–C) and plateau cells (Fig. 4, D–F), three examples each are shown, whereas two facilitative cell examples (Fig. 4, G and H) are shown. In addition, Fig. 4I shows the dynamics of annulus response profiles for a facilitative cell. In Fig. 4, for each neuron, the blue curves represent earlier time courses, beginning as early as 30 ms from stimulus onset. Progressively warmer colored curves represent cumulative responses at later time windows up to 2 s (red traces). As a reminder, the classification of each cell as suppressive, plateau, or facilitative is based on the overall response curves to the full 2-s stimulus presentation. All but one of these examples (see description of Fig. 4H below) illustrate that extraclassical surround modulation of responses earlier in time was suppressive regardless of cell type and evolved later into stronger suppression for suppressive cells, no suppression for plateau cells, and facilitation for facilitative cells.

A prime example of the evolution of increasing suppression strength for suppressive cells is illustrated in the traces of the complex cell shown in Fig. 4A. For this cell, the tuning curve at 40 ms (blue trace indicated by arrow) shows a CRF response at 14 spikes/s that was suppressed 64% (MI = −0.64, as determined using Eq. 3) by the largest aperture (30°) to 5 spikes/s. However, at 120 ms (green trace indicated by arrow), the CRF response was 58 spikes/s and responses were suppressed nearly 80%, down to 13 spikes/s, by the largest aperture. Similar increases in suppression strength over time are shown for the two other suppressive cells in Fig. 4, B and C, with the latter of the two being a simple cell example.

The evolution of modulation over time in our plateau cells from suppression to no suppression is best illustrated by the complex cell shown in Fig. 4D. For this cell, from 40 to 70 ms, suppression was quite strong. For example, the response at 40 ms (blue trace indicated by arrow) was 14 spikes/s for the CRF aperture and dropped to only 2 spikes/s for the largest aperture size, yielding 86% suppression (MI = −0.86). However, by 90 ms and beyond, suppression was minimal such that the responses beyond optimal at 150 ms (green trace indicated by arrow) were suppressed only 3% (MI = −0.03): ~31 spikes/s at CRF, down to 30 spikes/s at 30°. At even later cumulative time windows, no suppression was evident. Weakening of suppression strength over time is shown in the other two examples as well; one of these is another complex cell (Fig. 4E) and the other a simple cell (Fig. 4F).

For facilitative cells, one-half (5/10) showed relatively strong suppression early in time followed later by facilitation. For the example complex cell shown in Fig. 4G, the response peaked for a relatively small-sized aperture at 50 ms (blue trace indicated by arrow) and was then suppressed 56% by apertures of 30°. By 120 ms (green trace indicated by arrow), peak response occurred for a larger stimulus and suppression was no longer evident. At most of the subsequent time points, the cell response increased as the size of the stimulus increases, showing neither suppression nor saturation. In some of the facilitative cells (5/10), on the other hand, suppression was not evident at early time points, but rather weak facilitation was observed, such as the blue 50-ms trace shown for the example facilitative cell in Fig. 4H. Nevertheless, as indicated by the green 90-ms trace in Fig. 4H, facilitation also became stronger later in time for these cells.
Figure 4 shows the response profiles over time for annulus testing of an example facilitative cell. In this example, the minimum annulus response field used to define the CRF was very consistent, 8°, across all time points (see arrow in Fig. 4I). This invariance of CRF size over time was found for the population of facilitative cells as well (data not shown).

Dynamics of the Extraclassical Surround Modulation

We next examined detailed dynamics of extraclassical surround modulation for the three cell populations. To do this, we computed a MI for each cumulative time window of each cell (see examples in Dynamics of VI Size Tuning). Actual time windows used for this analysis were in steps of 10 ms for the first 200 ms after stimulus onset and then in steps of 50 ms for the remaining time (see x-axis in Fig. 5).

The resulting evolution of extraclassical surround modulation (MI) over time for the populations is plotted in Fig. 5. The black trace represents facilitative cells, the dark gray trace represents plateau cells, and the light gray trace represents suppressive cells. Consistent with the individual examples shown in Fig. 4, for the three populations, all cell types showed suppression early, even facilitative cells (mean MI < 0; at response onset, ∼30 ms from stimulus onset in Fig. 5A). After this initial period, modulation evolved into facilitation (MI > 0) for facilitative cells 20 ms later (at ∼50 ms from stimulus onset). Similarly, the MI of plateau cells crossed from suppression into facilitation ∼100 ms after stimulus onset. These evolving modulatory effects then stabilized by ∼200 ms for facilitative and plateau cells. For suppressive cells, after the first 30 ms from response onset, surround suppression became even stronger as indicated by an increase in negative MI beginning at the transition from 60 to 70 ms from stimulus onset (see light gray trace in Fig. 5A). Suppression then hit maximum strength at ∼100 ms from stimulus onset, which is mostly consistent with the maximum suppression latency shown for monkey V1 neurons (Bair et al. 2003).

Thus, from our population results, we conclude that two types of extraclassical surround modulation are present over time: an early component that is suppressive even for facilitative and plateau cells, and a later component that is either suppressive or facilitative depending on the cell type. The early suppressive modulation may rely on feedforward mechanisms because of its rapid onset, and the surround modulation that evolves later in time may be generated through different combinations of more slowly propagating cortical circuits.

Receptive Field Size of Different Cell Types Across Cortical Depth

The dynamics of extraclassical surround modulation that we have observed thus far suggest the presence of suppression early in time, followed by either facilitation or increased
suppression depending on the cell type. The early onset of suppression is consistent with a feedforward mechanism from LGN and/or retina (Alitto and Usrey 2008; Nolt et al. 2004; Sceniak et al. 2006), whereas later modulation may be generated through different combinations of cortical circuits. In addition to the more commonly considered cortical sources for extraclassical surround modulation, feedback and long-range lateral connections (Angelucci et al. 2002; Gilbert 1992), another source is through deeper layer neurons within the same cortical column (Allison and Bonds 1994; Bolz and Gilbert 1986). To address this issue, we plotted the diameter of the aperture size eliciting a maximum response for each cell and sorted by cortical depth encountered via the electrode penetration (as shown in Fig. 6A). For facilitative cells, the optimal aperture was always the maximum stimulus diameter (30°). For suppressive cells, the optimal aperture was the aperture that corresponded to the peak response. For plateau cells, the optimal aperture was defined as the point of saturation (size corresponding to 95% of the maximum response).

For each cell, we plotted the aperture size of the maximum response within their respective columns relative to cortical depth (see Fig. 6A). Cells from the same electrode penetration are plotted along the same dashed vertical line. The size of each circle is shown proportionally, with the largest apertures representing 30° of visual angle. As is evident in Fig. 6A, all but one of the facilitative cells (black circles) were located in cortical depths corresponding to the infragranular layers of V1 (>1,200 μm). On the other hand, suppressive (light gray filled circles) and plateau cells (gray open circles) were distributed evenly across all cortical layers. Furthermore, as expected, facilitative cells required larger aperture sizes for maximum response than the other two cell types (see Fig. 6B). Average optimal aperture sizes for suppressive (9.3 ± 3.9°) and plateau cells (10.1 ± 4.1°) were similar and not significantly different (P = 0.30), whereas aperture sizes for facilitative cells were...
significantly larger than those for suppressive ($P < 0.001$) and plateau cells ($P < 0.001$).

It has been proposed that the surround temporal dynamics and visual space covered by the full extraclassical receptive field can only be accounted for through feedback from higher order visual areas where individual neurons have large enough receptive fields with faster propagation speeds than multisynaptic long-range lateral connections (Bullier et al. 2001; Cantone et al. 2005; Cavanaugh et al. 2002a; Schwabe et al. 2006). However, the suppressive surround could arise from local circuits. The large excitatory receptive fields of the deep layer intrinsic facilitative cells may provide an alternative source for the suppressive surround of V1 cells, since the sizes of these receptive fields were comparable to receptive field sizes of neurons found in higher visual areas (see DISCUSSION).

**Spatial Frequency and Orientation Tuning of Suppressive, Plateau, and Facilitative Cells**

Spatial frequency and orientation tuning are related to extraclassical surround modulation in that the maximal suppression occurs when the center and surround are presented with the same orientation and spatial frequency (Akasaki et al. 2002; DeAngelis et al. 1994; Knierim and Van Essen 1992; Levitt and Lund 1997; Walker et al. 1999). We analyzed spatial frequency and orientation properties for all three cell types. Figure 7 shows examples for cells located in the same electrode track (track 3 from Fig. 6A), including four suppressive cells, two facilitative cells, and two plateau cells. As shown in Fig. 7A, the preferred spatial frequency was comparable regardless of modulatory cell type. Likewise, the preferred orientation varied by no more than $22.5^\circ$ from cell to cell (see Fig. 7B). Furthermore, although orientation tuning width did vary, broad and narrow band widths were observed for all three cell types.

Across the population, the spatial frequency distribution shown in Fig. 8A was similar for all three types of modulatory cells (ANOVA, $P = 0.28$). As illustrated in Fig. 8B, the orientation tuning width (HWHH) was linearly related to the OSI of the cells ($R = 0.54$, $P < 0.001$). Among the three types of modulatory cells, the HWHH was not significantly different (ANOVA, $P = 0.14$). On the other hand, the OSI of facilitative cells was significantly higher than that of suppressive and plateau cells (ANOVA, $P = 0.02$). This is perhaps due to most of the facilitative cells being simple cells, and the simple cells had higher average OSI values than our complex cells (Fig. 8D) (Heggelund and Albus, 1978; Leventhal and Hirsch, 1978; Ringach et al. 2002; Schummers et al. 2007). Likewise, the HWHH was generally smaller for simple cells, and the results are statistically significant for suppressive and plateau cells ($P = 0.002$ and $P = 0.003$, respectively; Fig. 8C).

**DISCUSSION**

We found that three different kinds of extraclassical surround modulation exist depending on the type of V1 cell: suppressive, plateau, or facilitative. In addition, our response dynamic analyses showed that these types of surround modulations are not stationary over time. Shortly after stimulus onset, surround modulation is suppressive for all three types of cells. However, this modulation evolves into facilitation for facilitative and plateau cells. On the other hand, suppression does not turn into facilitation at later time points for suppressive...
sive cells, but rather increases in suppressive strength. In this report we discuss our results in light of previous work and consider how they relate to possible underlying mechanisms involved in the evolution of different types of surround modulation over time.

Three Types of Extraclassical Surround Modulation

Stimuli extending beyond the CRF of a V1 neuron will often lead to suppression of the cell’s excitatory center (Allman et al. 1985). It has been well documented that the strength of suppression induced by extraclassical stimuli depends on the relationship between the stimulus represented in the center and the surround. For example, stronger suppression can be obtained when stimulus properties such as orientation, direction, and spatial frequency of the center and the surround match, even when these parameters are not optimal (Akasaki et al. 2002; Cavanaugh et al. 2002b; DeAngelis et al. 1994; Knierim and Van Essen 1992; Levitt and Lund 1997; Walker et al. 1999). The stimuli we employed (full contrast gratings that varied in diameter but always drifted in the preferred orientation and temporal and spatial frequencies) were most likely to lead to maximum suppression. Accordingly, we found that 68% of our V1 cells were suppressed by an extraclassical surround, which is consistent with previous work in both cat and monkey (Jones et al. 2001; Sengpiel et al. 1997; Walker et al. 2000).

Although the majority of our cells were suppressive, 32% (50/158) did not show suppression, since they either reached a plateau in their excitatory response (plateau cells, n = 35) or continued to increase their firing rate with increasing stimulus size (facilitative cells, n = 10). Plateau and facilitative cells have been reported several times before (Cavanaugh et al. 2002a; DeAngelis et al. 1994; Kapadia et al. 1999; Knierim and Van Essen 1992; Li and Li 1994; Polat et al. 1998; Sengpiel et al. 1997; Walker et al. 2000). As such, it has been postulated that responses of plateau cells may be generated by a balance between excitatory and inhibitory inputs (Sengpiel et al. 1997).

Responses of our facilitative cells increased with aperture size and showed no saturation. In our entire experiment, facilitative cells were rarely encountered (10/158, 6%), consistent with the idea that accurate estimation of the receptive field center primarily yields a high incidence of nonfacilitative cells (Cavanaugh et al. 2002a; Fitzpatrick 2000; Walker et al. 2000). Interestingly, most of our facilitative cells were located in infragranular layers of V1 (1,200 μm), and a larger proportion were simple cells (8 of 10). This is consistent with earlier work showing that a majority of neurons in layer 6 of V1 are simple and that some have very large excitatory receptive fields (Bolz and Gilbert 1989; Gilbert 1977; Leventhal and Hirsch 1978). The novel observation in our present work is that we also found deep layer facilitative cells to have a relatively small CRF, ranging from 4–10°, and a facilitative extraclassical surround of at least 30°. Similar results using narrow bars with drifting gratings have been reported by Li and Li (1994) for cat V1, although they were not attributed specifically to deep layer simple cells. More recently, Haider et al. (2010) found that fast-spiking interneurons and regular/thin-spiking pyramidal neurons in cat V1 increased responses to larger natural stimuli than the CRF. This subpopulation of GABAergic and

![Fig. 8. Spatial frequency preference and orientation selectivity distributions for the 3 modulatory cell types. A: the distributions of spatial frequency preference for suppressive, plateau, and facilitative cells are similar (ANOVA, P = 0.28). B: the orientation selectivity index (OSI) for all cells is plotted against the orientation tuning width [half width at half height; (HWHH), shown in radians], and they are linearly related (R = 0.54, P < 0.001). In addition, the OSI of facilitative cells (which are predominantly simple cells) is significantly larger than that of suppressive and plateau cells (ANOVA, P = 0.02). HWHH is similar for the 3 types of cells (ANOVA, P = 0.14). C and D: mean HWHH and OSI, respectively, for the 3 modulatory cell types. Across the population, orientation selectivity and tuning of simple cells (solid bars) is better than that of complex cells (hatched bars). For suppressive cells, these simple/complex differences are significant for both HWHH and OSI, whereas for plateau cells this difference is significant for only the HWHH. For facilitative cells, simple/complex cell differences in HWHH and OSI are not significant, probably due to only having 2 complex cells in the sample.](image-url)
pyramidal cells is consistent with the small population of facilitative cells found in our experiment and indicates that our facilitative cells could be either inhibitory or excitatory. Furthermore, 50% of the facilitative cells in our sample showed suppression early in time, followed later by facilitation, whereas the other 50% of cells showed no evidence of suppression early in time. It could be possible that the inhibitory and excitatory cells with large receptive fields described by Haider et al. (2010) correspond to the two different suppression dynamics we observed.

Mechanisms Underlying Extraclassical Surround Modulation

Across the great majority of the neurons we recorded, extraclassical surround modulation was suppressive at early time points (at response onset) but later diverged into either facilitation or even stronger suppression (Fig. 5). A feedforward mechanism from the LGN may account for this early universal suppression, since LGN neurons already exhibit a suppressive extraclassical surround (Alitto and Usrey 2008; Solomon et al. 2002; Webb et al. 2005b). Furthermore, a feedforward model without lateral inhibition, used to explain suppression for simple cells, could also contribute to the early suppression (Finn et al. 2007). A third possibility is fast suppression arising from nearby cells within V1, especially for cells where suppression comes even before the excitatory input to the CRF reaches spike threshold, as shown in monkeys (Bair et al. 2003). In monkey, faster feedforward propagation of the magnocellular compared with the parvocellular pathway (Alitto and Usrey 2008; Lyon et al. 2010; Schiller and Malpeli 1978; Vidyasagar et al. 2002) may account for such an effect. Likewise, in cat, parallel pathways of feedforward geniculocortical inputs from the slower X and faster Y channels (Cleland et al. 1971; Lennie 1980; Sur et al. 1987) can provide the biological basis for such a scenario.

Although on average early modulation of all the V1 cell types was suppressive, later in time, surround modulations evolved into two types. That is, modulation became positive for facilitative and plateau cells, and for suppressive cells modulation became even more strongly suppressive. These later modulations may be generated through different combinations of cortical circuits. One candidate is long-range lateral connections in V1, which tend to link cells with similar functional properties, such as orientation preference (Buzás et al. 2006; Callaway and Katz 1990; Gilbert and Wiesel 1989; Kisvárday et al. 1997), direction preference (Roerig and Kao 1999), and ocular dominance (Yoshioka et al. 1996). Long-range lateral connections have been demonstrated to account for extraclassical surround modulation, including facilitation and suppression (Mizobe et al. 2001; Polat et al. 1998; Sceniak et al. 2001). Importantly, the speed of horizontal connections covering the extraclassical surround is slow (~0.1–0.2 mm/ms; Bringué et al. 1999; Girard et al. 2001; Grinvald et al. 1994), which may contribute to the later modulation of our results. For instance, as measured through cumulative time windows, the change to stronger suppression for suppressive cells and the transition from suppression to facilitation for facilitative and plateau cells occurs ~20–30 ms after response onset (Fig. 5), which would correspond to long-range connections arising from cells located ~2–3 mm laterally. In addition, suppression strength that peaks ~70 ms after response onset for suppressive cells or facilitation that rises for another ~100 ms is indicative of even longer range lateral connections or possibly multisynaptic lateral circuits. An intriguing possibility for facilitative cells may be the involvement of Meynert cells, which like most of our facilitative cells are found in infragranular layers of cat and monkey V1 (i.e., Gabott et al. 1987; Rockland and Knutson, 2001). Meynert cells are large pyramidal neurons that have been shown to have extremely long-range projecting axons, up to 8 mm (Rockland and Knutson, 2001), and could thus provide excitatory monosynaptic inputs to facilitative cells that arrive as late as 80 ms after response onset.

As explained in METHODS, the reason for using cumulative time windows was to improve the signal-to-noise ratio and allow for more reliable fits at each 10-ms bin. However, it is important to note that the cumulative time point at which suppression strength increases for suppressive cells or when suppression switches to facilitation for the population of our facilitative cells (20–30 ms as shown in Fig. 5) is not the exact point at which this signal begins to affect the cell’s response; rather, it is when this influence has outweighed the influence of an early suppressed response. Therefore, the true latencies for these components are likely to be modestly shorter, by some amount that is difficult to estimate.

Another likely contributor to extraclassical surround modulation is feedback from extrastriate visual cortex, which can cover large regions of visual field corresponding to the extraclassical surround of V1 neurons (Angelucci et al. 2002; Bair et al. 2003; Bullier et al. 2001; Cantone et al. 2005; Cavanaugh et al. 2002a; Chen et al. 2005; Levitt and Lund 2002; Xing et al. 2005) and usually targets excitatory neurons (Johnson and Burkharter 1996; Salin and Bullier 1995; Shao and Burkharter 1996). In this way, feedback connections arising from a large region of the visual field may contribute to the larger facilitative surround modulation that occurs later in time for facilitative and plateau cells. Feedback may also contribute to the later increase in strength of suppression for suppressive cells via intrinsic V1 relays onto local inhibitory cells (Schwabe et al. 2006). Because feedback axons are myelinated, these inputs are likely to arrive similarly in time, if not sooner, to the typical ~2-mm long-range lateral connections described above (Angelucci et al. 2002; Bair et al. 2003; Schwabe et al. 2006). Therefore, the effects of feedback projections should occur within the first 20 ms beyond response onset (Xing et al. 2005). In our experiments this time frame corresponds to the change from suppression to facilitation for our facilitative cell population and the point where suppression strength begins to increase for our suppressive cells (Fig. 5).

In addition to long-range lateral and feedback connections, another possibility for later extraclassical surround modulation is through connections within columns. Most of our facilitative cells were located in deeper layers of V1 and were simple cells, consistent with previous results showing that such cells are found in layer 6 (Gilbert 1977). End inhibition of layer 4 cells will disappear after inactivating layer 6 with GABA, indicating that layer 6 cells account, at least partly, for surround suppression of cells in layer 4 (Bolz and Gilbert 1986; Bolz et al. 1989). Moreover, the inhibitory effects mediated by infragranular layers could be propagated throughout the column (see Allison and Bonds 1994). In this regard, our dynamic
surround modulation results (Fig. 5) show that the evolutions of stronger suppression and stronger facilitation occur over a similar time course. Probably the most noteworthy feature of these rarely encountered facilitative cells is that they have very large excitatory receptive fields, far bigger than the excitatory fields of other cells in V1, even within the same column (Fig. 6). Most critically, however, these large facilitative receptive fields match the diameter of the extracellular suppressive surrounds for the more commonly encountered suppressive cells. As such, they are capable of contributing to the more distal surround effects. Because facilitation develops later in time and coincides with the onset and continued development of the stronger suppression observed for suppressive cells, we suggest that facilitative cells may play a key role, perhaps directly as GABAergic interneurons for suppressive cells, we suggest that facilitative cells may play a key role, perhaps directly as GABAergic interneurons or through excitatory synapses onto inhibitory neurons within the same cortical column.

Overall, our present results suggest that mechanisms underlying surround modulation combine a number of different sources, including feedforward, intracolumnar, long-range horizontal, and feedback connections, and that these sources differ depending not only on the cumulative time relative to stimulus onset but also on the type of V1 cell.

ACKNOWLEDGMENTS

We thank Emily Grossman for helpful comments on this manuscript.

REFERENCES


Li CY, Li W. Extensive integration field beyond the classical receptive field of cat’s striate cortical neurons-classification and tuning properties. Vis Neurosci 34: 2337–2355, 1994.


