

Nonlocal origin of response suppression from stimulation outside the classic receptive field in area 17 of the cat

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Abstract

A stimulus located outside the classic receptive field (CRF) of a striate cortical neuron can markedly influence its behavior. To study this phenomenon, we recorded from two cortical sites, recorded and peripheral, with separate electrodes in cats anesthetized with Propofol and nitrous oxide. The receptive fields of each site were discrete (2–7.3 deg between centers). A control orientation tuning (OT) curve was measured for a single recorded cell with a drifting grating. The OT curve was then remeasured while stimulating simultaneously the cell's CRF as well as the peripheral site with a stimulus optimized for that location. For 22/60 cells, the peripheral stimulus suppressed the peak response and/or shifted the center of mass of the OT curve. For 19 of these 22 cells, we then reversibly blocked stimulus-driven activity at the peripheral site by iontophoretic application of GABA (0.5 M). For 6/19 cells, the response returned to control levels, implying that for these cells the inhibitory influence arose from the blocked site. The responses of nine cells remained reduced during inactivation of the peripheral site, suggesting that influence was generated outside the region of local block in area 17. This is consistent with earlier findings suggesting that modulatory influences can originate from higher cortical areas. Three cells had mixed results, suggesting multiple origins of influence. The response of each cell returned to suppressed levels after dissipation of the GABA and returned to baseline values when the peripheral stimulus was removed. These findings support a cortical model in which a cell's response is modulated by an inhibitory network originating from beyond the receptive field that supplants convergence of excitatory lateral geniculate neurons. The existence of cells that exhibit no change in peripherally inhibited responses during the GABA application suggests that peripheral influences may arise from outside area 17, presumably from other cortical areas (e.g. area 18).

Keywords: Visual cortex, Surround suppression, Receptive field, Orientation tuning

Introduction

A striate cortical neuron's receptive field (RF) is traditionally thought of as a static structure because the presence of a spatially optimal stimulus within the RF produces a reliable and repeatable response (e.g. an orientation tuning curve). Although a stimulus placed outside the RF does not excite action potentials, it can modulate the neuron's response to an excitatory stimulus within the RF. Therefore, in addition to directly monitoring its own RF, a neuron indirectly conveys information from a large portion of the surrounding visual field (Nelson & Frost, 1985; Allman et al., 1985; Gilbert & Wiesel, 1990; Knierim & Van Essen, 1992; Li & Li, 1994; Levitt & Lund, 1997; Sengpiel et al., 1997). The classic receptive field (CRF) is the region that when stimulated evokes an excitatory response from a cell. Here we define the extended receptive field (ERF) as the portion of the visual field external to the CRF that when stimulated modulates an excitatory response to

a stimulus within the CRF. Extracellular (Li & Li, 1994) and intracellular (Binguier et al., 1999) recordings show that the integration of the ERF can extend more than 11 deg into the periphery. The influence that stimulation of the ERF has on the CRF response can be classified as iso-orientation suppressive (Blakemore & Tobin, 1972; Nelson & Frost, 1978; Orban et al., 1979), globally suppressive (i.e. independent of surround orientation) (Bishop et al., 1973; Maffei & Fiorentini, 1976; Sillito et al., 1995), as well as facilitatory (Maffei & Fiorentini, 1976; Li & Li, 1994; Crook et al., 2002). The magnitude of modulation from the ERF can vary depending on the relative contrast levels of stimuli located in the CRF and ERF (Levitt & Lund, 1997; Polat et al., 1998). Cells in area 17 thus appear to have the computational power to integrate across large portions of the visual field.

The origins and pathways of the signals integrated over such large areas are not yet identified. A common presumption is that the modulatory neural activity coming from outside the CRF arises from direct communication between cells within area 17. Long-range horizontal connections of pyramidal cells extend 5 mm (Kisvarday & Eysel, 1990) to 8 mm (Hirsch & Gilbert, 1991)

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parallel to the cortical surface and could provide the pathway necessary for stimuli outside a neuron's CRF to influence its activity. Optical imaging studies show that a minimal stimulus activates a much larger region than would be predicted by the retinotopic bounds of the CRF. A small stimulus activates spike activity in neurons across approximately 750 μm of cortex while optical imaging indicates slow-potential influence up to 4 mm distant from the center of stimulation (Grinvald et al., 1994; Das & Gilbert, 1995). Interneuronal communication from within area 17 may not entirely account for the large spatial integration found there. Cortico-cortical projections may also play a role in the spatial organization of the ERF. Alonso et al. (1993) and Martinez-Conde et al. (1999) report that inactivating neural activity in area 18 can modulate the orientation and velocity tuning of cells in retinotopically matched regions within area 17. Temporal frequencies higher than those typically preferred by area 17 cells suppress a cell's response to an excitatory stimulus, and the temporal frequencies that modulate the area 17 cell's responses most effectively are those primarily preferred by area 18 neurons (Allison et al., 2001). These data suggest that feedback from area 18 can modulate a neuron's response to a stimulus within the CRF, implying that the properties of the CRF are not constructed just from activity within area 17, but rely on higher order feedback as well. Most recently, Angelucci et al. (2002) used histological techniques in macaques to suggest that area 17 long-range connections are involved in the construction of the CRF at low contrasts, while ERF properties arise from area 18 feedback.

We investigated the origin of peripherally induced suppression that influenced the orientation tuning of area 17 neurons by testing the hypothesis that activity arising within area 17 alone is responsible for observed peripheral influences. If this is true, then local inactivation at the site responding to the peripheral stimulus would eliminate its effect on the response of the recorded neuron. To this end, we isolated single cortical cells in area 17 of the cat that showed modulated response properties when a discrete portion (which we will call the peripheral receptive field, PRF) of the ERF was stimulated simultaneously. After characterizing this change, we reversibly blocked the region in visual cortex that retinotopically corresponded to the PRF with iontophoretic injection of GABA and remeasured the tuning curve in the presence of both stimuli. In 9/19 cases, we observed a persistent modulation in the presence of the peripheral stimulus despite the local blockade in area 17. We conclude that influences from the ERF may arise from outside area 17, presumably from higher cortical areas such as area 18.

Methods

Surgical preparation

We prepared 12 adult cats (2.0–4.0 kg) for electrophysiological recording in accordance with the guidelines established by the American Physiological Society, the Society for Neuroscience, and Vanderbilt University's Animal Care and Use Committee. Each cat received an injection of 0.5 ml atropine sulfate (Elkins-Sinn, Cherry Hill, NJ) and 0.5 ml acepromazine maleate (TechAmerica, Elwood, KS) prior to inducing general anesthesia by inhalation of 5% halothane (Fluothane, Ayerst, Philadelphia, PA) in O_2 . A forelimb vein was cannulated for intravenous (i.v.) injection of 1% Propofol (Baxter, Irvine, CA) to maintain anesthesia and the gas was discontinued. A tracheal cannula was inserted, the head was mounted in a stereotaxic device, and the scalp was reflected along

the midline. A 2×5 mm craniotomy was performed over the representation of *area centralis* in area 17 (Horsley-Clarke coordinates P4–L2). After positioning of microelectrodes the hole was sealed with agar and melted Tackiwax (Cenco, Chicago, IL).

Recording conditions and iontophoresis

To suppress eye movements during recording, the cats were paralyzed with an i.v. (intravenous) injection of pancuronium bromide (Pavulon 2 mg/ml, Baxter, Irvine, CA) and respired at 30 breaths/min with a mixture of $\text{N}_2\text{O}:\text{O}_2:\text{CO}_2$ (75:23.5:1.5) at a stroke volume adjusted to maintain expired pCO_2 at 3.9%. Anesthesia was maintained with the combined N_2O and Propofol (2 mg/kg-h) and monitored by observation of the electroencephalogram (EEG) and electrocardiogram (EKG). Boluses of Propofol were given for changes in heart rate or absence of sleep spindles and the injection pump was adjusted appropriately to ensure adequate anesthesia. Rectal temperature was maintained at 37.5°C with a servo-controlled heat pad. Phenylephrine hydrochloride (10%) was dropped into each eye to retract the nictitating membranes, the pupils were dilated with drops of atropine sulfate (1%), and contact lenses with 4-mm artificial pupils were inserted. Auxiliary lenses were mounted to ensure that the eyes were focused on the stimulus plane at a distance of 57 cm. The optic disk and *area centralis* were plotted using a reversible ophthalmoscope.

Separate electrodes recorded extracellular activity from two cortical sites with discrete receptive fields (referred to as *recorded* and *peripheral*) in area 17. Control recordings were taken from isolated cortical cells at the recorded site using tungsten-in-glass microelectrodes (Levick, 1972) with uninsulated tips 18–20 μm long and 2 μm wide. The second electrode consisted of a pipette electrode for recording glued onto a three-barrel pipette (tip separation < 50 μm) for iontophoretic injection. Two barrels of the pipette contained 0.5 M GABA (pH 3.5) for local inactivation. The third barrel was filled with 0.9% saline (pH 3.5) for balancing the current during injection from the other barrels. A –30 nA retaining current was used to prevent leakage of GABA. The GABA electrode was placed 2–3 mm anterior to the first electrode and manipulated with a manual microdrive until multiunit activity from a cell cluster with a receptive field (defining the peripheral locus) that did not overlap the recorded cell's receptive field was isolated. The electrodes within the recorded and peripheral sites were lowered so that their relative depths did not exceed 300 μm during the experiment. We confirmed that iontophoretic application of GABA reversibly suppressed stimulus driven activity at the peripheral site.

Stimulation

Receptive fields were plotted using a manually controlled projection system and all were located within 7 deg of the *area centralis*. Each cell was categorized as simple or complex and ocular dominance was rated on a five-point scale (Hubel & Wiesel, 1962). A Sony Multiscan 400PS display was positioned to present a monocular stimulus to the dominant eye. Sine-wave gratings (windowed within a 4–10 deg circular field) were created with a Cambridge Research Systems CRS2/3 pattern generator. The grating centered on the peripheral site was windowed to the smallest circular field that elicited a response, typically 3–5 deg. Separate gratings were centered on the recorded and peripheral receptive fields. We measured the recorded cell's tuning curves for orientation, spatial frequency, and temporal frequency by varying each

parameter. The spatial and temporal frequencies were then fixed at the optimal parameter. Likewise, the peripheral receptive field was evaluated with a separate stimulus and each parameter was fixed to drive the multiunit activity maximally. Stimulus contrast was set at 0.56 with a mean luminance of 49 cd/m².

Experimental protocol

Our experimental sequence consisted of three measuring periods followed by two recovery periods. First, an orientation tuning curve was measured for the recorded cell's CRF by presenting nine stimulus orientation at 10-deg intervals centered on the preferred angle. The orientation tuning curve was then reassessed while simultaneously stimulating the CRF and the PRF. (As described above, the peripheral stimulus was fixed at the spatiotemporal optimum for the group of cells in that area. Systematic variation of the spatial properties in the periphery was beyond the scope of these experiments. It would also reduce the probability that local GABA injection would effectively silence peripheral activity, since different spatial configurations would excite cells a greater distance from the injection electrode array.) In cases where the peripheral stimulation modulated the recorded cell's response, a third orientation tuning curve was measured while stimulating both sites and iontophoretically applying GABA (two barrels, 90–150 nA per barrel) to suppress locally the activity of the peripheral cell cluster. Iontophoresis of GABA was then discontinued and a 20-min interval (or longer as necessary) was allowed for GABA reuptake to occur. The orientation tuning curve was reevaluated in the presence of the peripheral stimulus to confirm the reversibility of the GABA injection. A final measurement was made without the peripheral stimulus to validate the influence of the peripheral stimulus and confirm a return to control values. Full recovery at each stage was a prerequisite for acceptance of the data set.

Data acquisition and statistical analysis

Data acquisition was managed by a computer which relayed stimulus criteria to the pattern generator, logged the time of occurrence of each spike, and displayed the data as it was collected. Action potentials were recorded during a 4-s period and accumulated in 2 s, 128 bin/s poststimulus time histograms (PSTHs). Ten sweeps of each orientation were presented to collect an averaged response over a 40-s duration. The set of stimuli were interleaved and pseudorandomized to compensate for the inherent nonstationarity of the visual cortex. In a presentation sequence, individual stimuli were displayed once, with 1 s of mean luminance between presentations, until the set was depleted. Each set was then cycled in different random order for ten total presentations of each condition. A null condition (uniform field at the mean luminance of the gratings) was included in each set to evaluate the spontaneous discharge of the cell.

To establish whether the tuning curve measured during peripheral stimulation differed from the control curve, the 95% confidence interval was calculated from the averaged control response via a sweep-by-sweep analysis at each stimulus orientation. The upper and lower confidence intervals delimit the averaged control response, effectively creating two additional curves. By definition, of the collection of all possible 95% confidence intervals that could be constructed based on any given sample from the population, 95% will contain the population mean. To ensure that differences in firing rates were due to the peripheral stimulus or administration of GABA rather than fluctuations in brain activity

or loss of the extracellular field potentials, all cell responses were required to recover within these bounds when the peripheral stimulus or GABA was removed.

We compared both the peak response of the curve and the center of mass (CoM) (Kabara & Bonds, 2001) to assess quantitatively the influence of the peripheral stimulus and subsequent administration of GABA. To determine the exact peak location, we smoothed the tuning curves with a cubic interpolation at a resolution of 0.5 deg. The peak is characterized by the stimulus orientation at which the maximum response occurs. The amount of suppression or facilitation was calculated by dividing the difference of the peak control and modulated response rates by the control value. For cases in which the peak rate shifted in the presence of the peripheral stimulus, the percent modulation was calculated between maximum responses, regardless of peak orientation.

The CoM represents the generic shape of the curve as a weighted average of the responses at each stimulus. All CoM calculations were determined relative to the peak orientation across the -40- to +40-deg interval, so that a perfectly symmetrical response function would have a CoM equal to 0 deg. This measurement is useful because it reflects the contribution of nonoptimal stimuli. For example, a negative CoM signifies a more heavily weighted response to orientations left (along the abscissa) of the peak orientation, while a positive value indicates a curve with more activity in response to orientations to the right of the peak.

In Fig. 1, a theoretical control orientation curve is compared with four possible changes that could occur when the peripheral site is stimulated. A neuron's response (spikes/s) is plotted as a function of stimulus orientation across a 90-deg abscissa (nine angles at 10-deg intervals). The vertical bars designate the limits of the 95% confidence interval (CI). Based on these bounds, all four curves are statistically different from the control. Curve 1 illustrates a suppressed response without a significant shift in CoM or peak orientation. The peripheral stimulus reduces the neuron's response at each orientation uniformly so that the general shape of the curve remains unchanged. A shift in both CoM and peak orientation coinciding with a suppressed response are shown in curve 2. Such a change in the tuning curve indicates that the suppression induced by the peripheral stimulus is not uniform across the cell's orientation domain, but is stronger for orientations along the left portion of the curve. Curve 3 shows that although the response rate is not suppressed, a shift of the peak response to a nonoptimal orientation can pull a curve outside the confidence limits. This shift in peak orientation is classified by a leftward shift in CoM. Curve 4 shows an example of a shift in CoM although the peak orientation itself does not change. A rightward shift in the CoM is found in the skewed profile of this response because the neuron's responses to nonoptimal angles to the right of the peak are facilitated, while its responses to orientations left of the peak are suppressed.

Results

Characteristics of suppression by localized peripheral stimulation

The response of a cortical cell is in general suppressed by stimulation of the area outside the CRF (Blakemore & Tobin, 1972; Maffei & Fiorentini, 1976; Nelson & Frost, 1978; Li & Li, 1994; Levitt & Lund, 1997). In these earlier studies, an annular stimulus was presented outside the CRF in conjunction with an excitatory

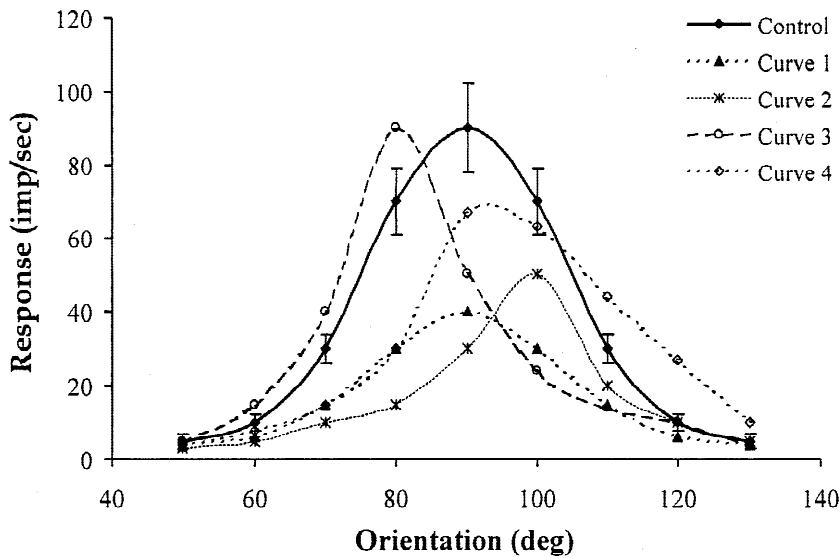


Fig. 1. Prototypical orientation tuning curve and examples of modulation. The control curve (*solid lines*) exemplifies the response (spikes/s) of a cell to a base grating presented at nine orientations in 10-degree increments. The vertical bars designate the 95% confidence interval used to distinguish the uniqueness of each curve. Curves 1–4 demonstrate the modulation of the response when a peripheral grating is displayed simultaneously with the base grating. Curve 1 (*filled triangles*) shows proportional suppression where the shape of the tuning curve does not change. Curve 2 (*asterisks*) shows both suppression and a shift in tuning. The peak response shifts from 90 deg to 100 deg resulting in a rightward shift of the CoM. Curve 3 (*open circles*) shows a shift in tuning without suppression. The 10-deg shift in peak orientation would be quantified by a leftward shift in CoM. Curve 4 (*open diamonds*) shows more heavily weighted suppression at orientations to the left of the tuning peak. Although the peak does not change, the response to nonoptimal stimuli to the right of the curve is higher than to those orientations to the left. This shift would be reflected in a rightward shift in CoM.

stimulus over the CRF. Our method differed in that we mapped and stimulated small (2–6 deg diameter) discrete portions of the ERF, here called the PRF, to determine the contributions from individual regions of the surround rather than the impact of the surround as a whole. We examined 60 cells using this technique and found that in 29 cases stimulation of the PRF modulated the response of the recorded cell beyond its 95% confidence limits. The perturbation was characterized by a change in the peak response rate and/or a shift in the CoM. For our experiments, in order to minimize the cortical region excited by the peripheral stimulus, we limited its area to the smallest circular field that significantly suppressed a neuron's excitatory response to a stimulus within the CRF.

The orientation tuning curves in Fig. 2 illustrate two examples of the response modulation patterns we observed during stimulation of the PRF. The control curve (*circles*) represents the orientation tuning of the recorded cell when a single stimulus was presented within its CRF. Each point indicates the average response across ten trials with vertical bars designating the 95% CI. The peripheral curve (*squares*) indicates the response of the same cell when the two discrete receptive fields (CRF & PRF) were stimulated simultaneously. Neither the peak orientation nor the CoM shifted for the cell shown in Fig. 2A, but the maximum response rate was reduced by 28%, falling below the limits of the control CI (cf. curve 1 in Fig. 1). When the peripheral stimulus was removed and the orientation tuning was reassessed with a single stimulus over the CRF, the response function returned to within the control CI denoted by the recovery curve (*asterisks*).

The cell shown in Fig. 2B shows that the peripheral stimulation may also change the tuning of a recorded cell. This cell exhibited a peak response of 45 spikes/s to a stimulus orientation of 140 deg. The addition of the peripheral stimulus not only suppressed the peak response to 24 spikes/s, but also shifted the preferred orientation by 28 deg to the right. The alteration of the response profile is reflected by a 6.2-deg rightward shift in the CoM. The response in the presence of the peripheral stimulus is clearly a unique curve in that every point in the tuning curve except one along the flank falls below the CI of the control. Again, the recovery response returned to levels statistically similar to the control values.

Of the 29/60 cells in our sample whose response profiles were significantly altered by stimulation of the PRF, seven cells appeared to be affected by the peripheral stimulus, but were excluded from the final set of data points because pretest and posttest control values did not overlap. Fig. 3A summarizes the change in the peak response that occurred for the remaining population of recorded cells during stimulation of the PRF. The abscissa is the percent change of response magnitude and the ordinate indicates the shift in peak orientation in degrees. The cells exhibiting no significant peripheral influence (*open circles*) are plotted against those cells that were influenced by the peripheral stimulus (*filled diamonds*), indicated by responses distinct from the 95% CI of the control curve. The cells categorized as uninfluenced had an average peak response modulation of $6.8 (\pm 4.1)\%$ and showed minimal shifts in peak orientation (mean = 2.0 ± 2.0 deg). Slight variations in the response occurred within the 95% CI limits. For instance, the peak response of one cell shifted 8.5 deg when the peripheral stimulus was presented. However, because the cell had a broad response peak, the peripheral response remained within the 95% CI. Cells influenced by the peripheral stimulus were suppressed on average by $44.3 (\pm 18.7)\%$ with shifts in the peak orientations up to 30 deg (mean = 10.6 ± 9.6 deg). Although facilitation from stimulation outside the CRF has been reported in some cases (Maffei & Fiorentini, 1976; Nelson & Frost, 1985; Sillito et al., 1995; Crook et al., 2002), our results revealed a generally suppressive influence from peripheral stimulation. However, due to tuning shifts, we occasionally saw response facilitation at certain orientations. Cells lying near the horizontal axis (10/22) had suppressed responses without shifts in the tuning peak. These cells include five cases where the response was suppressed uniformly across all orientations (cf. curve 1, Fig. 1) and five cases where, although the peak response did not shift, the responses at nonoptimal orientations were modulated at differing levels to cause a CoM shift (cf. curve 4, Fig. 1). The datum lying above the origin near the vertical axis represents a cell that displayed a less common type of modulation. Although the response was not suppressed, the orientation preference moved 21 deg (cf. curve 3, Fig. 1). Eleven cells affected by the peripheral stimulus showed both strong declines in the maxi-

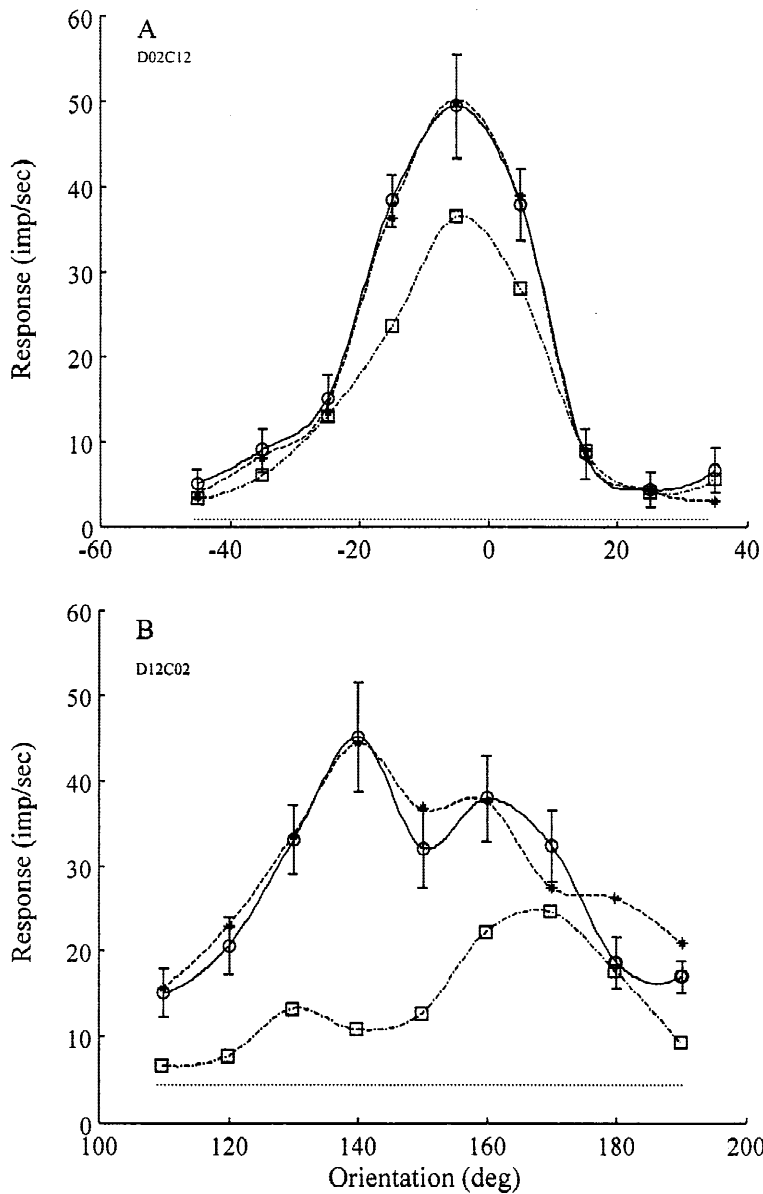


Fig. 2. Examples of peripheral modulation. In A, the control curve (*open circles*) shows the response (spikes/s) of a cell plotted as a function of the orientation of a stimulus presented within the CRF. The vertical bars designate the 95% confidence interval (CI) used to distinguish the uniqueness of each curve. When a secondary stimulus is presented simultaneously outside the CRF, the response (*open squares*) to the preferred orientation is suppressed by 28%. When the peripheral stimulus is removed, the response returns to values within the 95% CI of the control curve (recovery, *asterisks*). In B, the control has a bimodal peak with the highest response occurring at 140-deg. The peripheral modulation suppresses the response to the orientations on the left more so than the right, resulting in shift in the tuning of the cell. This change in activity is quantified with a 6.2-deg rightward shift in the CoM. The response during the recovery phase again resumes control values. In each figure, the dashed horizontal line illustrates the maintained discharge level.

num response rate as well as shifts in peak orientation. The magnitude of the influences from the PRF is surprising considering the small size (2–6 deg) and distance [mean = 5.97 ± 1.49 deg] of the second stimulus from the CRF of the recorded cell.

Changes in the CoM from the same population of cells are presented in Fig. 3B. The abscissa is the CoM of the recorded cell's orientation tuning function relative to its orientation peak during control stimulation. Again, the CoM was calculated across a -40 - to $+40$ -deg interval so that a perfectly symmetric response would have a CoM of zero. The ordinate is the CoM of the cell's orientation tuning function when the peripheral stimulus was simultaneously presented. As in the top panel, cells statistically unaffected by peripheral stimulation are plotted as *open circles*. A linear regression analysis of the data from these cells (slope = 0.9944, $R^2 = 0.989$) confirms the CoM did not shift significantly between stimulus conditions (mean = 0.3 ± 0.2 deg). Some of the cells that were influenced by the peripheral stimulus (*filled diamonds*) also lie on or near the diagonal. This result occurs when all

orientations were suppressed uniformly and the CoM did not change. However, if some orientations were suppressed more than others, a change in the CoM reflects the shift in activity. Cells plotted below the diagonal indicate a leftward shift of response levels in the tuning curve and cells plotted above the diagonal represent a rightward shift. The majority of data points (17/22) from cells affected by peripheral stimulation are located off the diagonal indicating that nonoptimal orientations were asymmetrically modulated or that a distinct shift in the entire tuning of the curve offset the peak location. In addition to changes in the peak response, modulations at nonoptimal orientations alter the overall response characteristics of the cell.

Relationships between CRF and PRF tuning properties

Previously observed relationships between the stimulus orientations in the CRF and ERF range from nonorientation-selective inhibition (Bishop et al., 1973) to orientation-selective inhibition

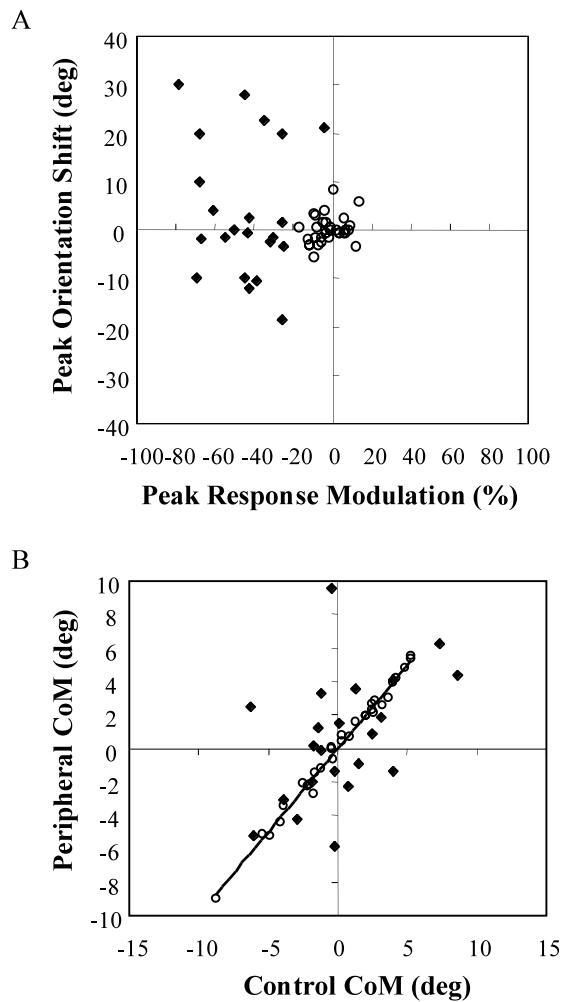


Fig. 3. Characteristics of peripheral modulation. Two scatter plots quantify the modulation caused by peripheral stimulation in our sample of cells ($N = 53$). *Filled diamonds* represent cells that were peripherally modulated, and *open circles* represent cells that were not influenced by peripheral stimulation. In A, the cell's response amplitude at its preferred stimulus orientation is analyzed. The ordinate shows the magnitude of shift between the control tuning peak and the tuning peak during peripheral stimulation. Data points above zero indicate a rightward shift in the peak, while those below zero illustrate a leftward shift. The abscissa shows the change in response amplitude at the tuning peak during peripheral stimulation. Data points to the left of zero indicate suppression, while points to the right show facilitation. Clearly, all cells influenced by the peripheral stimulus were suppressed. Some showed both decreased responses as well as shifts in tuning (i.e. cells not lying on either axis). One cell had a 21-deg shift in activity without suppression (lying near y axis above origin). All the cells not influenced by the peripheral stimulus are clustered around the origin. In B, the response at all orientations is examined by comparing the CoMs of the control curve and curve measured during peripheral stimulation. The diagonal axis is unity. Some of the peripherally influenced cells lie on the diagonal indicating that the modulation was proportional at all orientations. Cells falling above the diagonal show leftward shifts in the CoM (i.e. the response at nonoptimal orientations to the right were more heavily suppressed), while cells below the diagonal show rightward shifts in CoM. All cells not peripherally modulated lie on the diagonal axis.

(Maffei & Fiorentini, 1976), and even directionally selective inhibition (Nelson & Frost, 1978). In our experiment, the peripheral electrode array was positioned more or less randomly with respect

to the recorded cell until a nonoverlapping PRF was isolated. We examined the peripheral stimulus orientation relative to the CRF optimal orientation on a cell-by-cell basis for the cases when the peripheral stimulus modulated the recorded cell's tuning curve. Fig. 4A shows the pattern of peripheral influence as a function of the orientation difference between the CRF and PRF stimuli. The abscissa describes the differences in angles between the peripheral stimulus orientation (optimized to the response from that region) and recorded cell's optimal orientation. The ordinate is the percent of cells within each group that were peripherally suppressed. CRF response suppression was found for all relative orientations, though the pattern was not uniform. Peripheral stimuli oriented 10–30 deg from the optimal orientation suppressed the recorded cell in 54% cells ($N = 24$). These orientations are the angles flanking the optimal orientation within the tuning curve. Similar results have been documented elsewhere (Bonds, 1989; Levitt & Lund, 1997; Sengpiel et al., 1997) suggesting that stimuli oriented at modestly nonoptimal angles are more likely to influence a cell.

We then compared the magnitude of suppression occurring within each range of orientation differences (Fig. 4B). The ab-

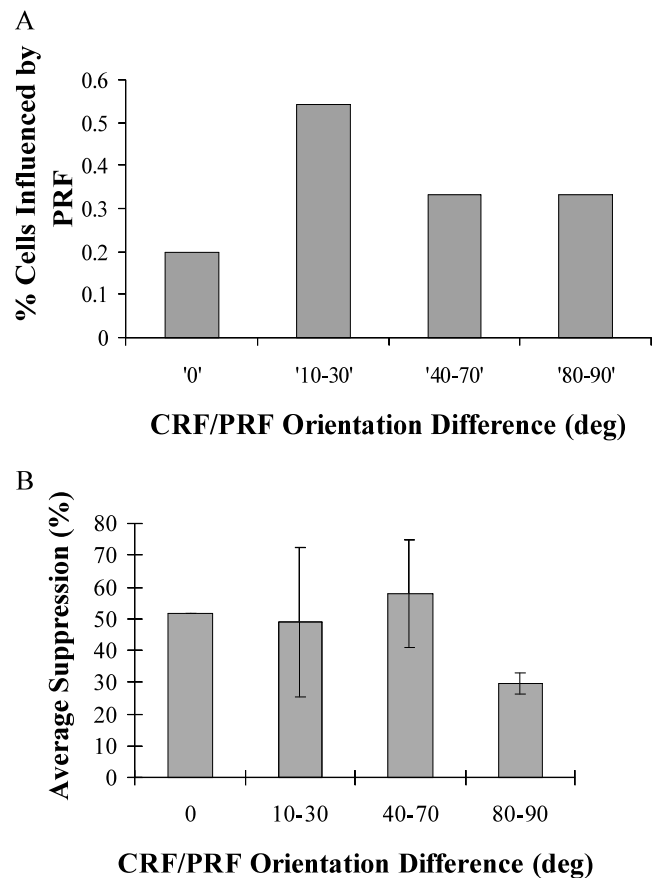


Fig. 4. Comparison of tuning peak and peripheral stimulus orientation. In A, the percentage of cells that were influenced by peripheral stimulation is shown according to the relative difference between CRF tuning peak and PRF stimulus orientation. The peripheral stimuli oriented 10–30 deg from the tuning peak most frequently modulated the response. In B, the magnitude of suppression for those cells that were influenced by the peripheral stimulus is averaged in each group. Vertical bars denote the standard deviation. The amount of suppression does not depend on the orientation of the peripheral stimulus.

scissa again describes the differences in angles between the PRF and CRF stimulus orientations. The ordinate indicates the average response suppression for the number of cells within each range with error bars showing the standard deviation. These levels of suppression from small patches (mean = 46.9%, ranging from 23.2% to 91.6%) are comparable with results of stimulating the ERF with an annular stimulus surrounding the entire CRF (Li & Li, 1994; Sengpiel et al., 1997; Levitt & Lund, 1997). The first group (0 deg) does not have error bars because only one cell was suppressed (52%) by the peripheral stimulation at the optimal orientation of the recorded cell. The second group (10–30 deg) suppressed the recorded cell on average 49%. The peripheral stimuli oriented at oblique (40–70 deg) and orthogonal (80–90 deg) angles relative to the CRF stimulus caused 58% and 30% suppression, respectively. Notably, while a peripheral stimulus oriented near the CRF orientation affected a larger percentage of neurons than the other orientations (Fig. 4A), when suppression occurred the magnitude of suppression did not correlate significantly with the orientation difference between recorded and peripheral regions. As with other reports (Kabara & Bonds, 2001), we find less suppression at other angles, but our differences are not as extreme.

Evidence that surround stimuli have a repulsive effect on a neuron's preferred orientation (Dragoi & Sur, 2000; Kabara & Bonds, 2001) led us to compare the directional shifts of the peak response and CoM to the orientation of the peripheral stimulus (Table 1). An *attractive* response denotes a tuning curve where the peak orientation shifts along the abscissa toward the peripheral stimulus orientation. A *repulsive* shift indicates a shift away from the peripheral stimulus orientation. We observed no apparent correlation between the orientation of the peripheral stimulus and the direction of the response peak shift. Of the 22 cells that proved to be peripherally modulated, ten of the peak orientations did not shift when the peripheral region was stimulated ($CI_{95\%} = 4.09$ deg). For six cells, the orientation tuning curve recorded during peripheral stimulation shifted from the control curve toward the orientation of the peripheral region (i.e. attraction). In two of these cases, the orientation tuning curve peak shifted to match the orientation of the peripheral stimulus. The peaks of the remaining six peripherally influenced responses shifted repulsively away from the peripheral stimulus orientation.

Table 1. Relative shifts in peak response and CoM during peripheral stimulation^a

	Peak	CoM
None	10 (45%)	5 (23%)
Attractive	6 (27%)	6 (27%)
Repulsive	6 (27%)	11 (50%)

^aOf those cells that were peripherally modulate, the tuning peak shift was quantified as none, attractive, or repulsive. Attractive indicates a shift towards the orientation of the peripheral stimulus. Repulsive indicates a shift in the opposite direction from the peripheral stimulus orientation. Nearly half (45%) of the cells did not show a change in tuning peak, while those that did show a shift were likely to occur in either direction. In the CoM analysis, 50% of the cells showed a repulsive shift away from the peripheral stimulus orientation. These results indicate that the peripheral stimuli consistently suppress the responses at nonoptimal orientations similar to the PRF orientation (i.e. the activity shifts away from the PRF orientation).

The CoM of the tuning curve is a useful measure that differs from simple shifts of the peak orientation because it is sensitive to response changes at all orientations of the tuning curve and therefore reveals less obvious modulations in activity. We performed an attractive/repulsive shift analysis on the CoM location. Of the 22 cells that were modulated by the peripheral stimulus, five revealed no significant change in the CoM between the control curve and the curve with peripheral stimulation ($CI_{95\%} = 0.88$ deg). Almost twice as many cells (11/22) showed a repulsive CoM shift away from the peripheral stimulus orientation than those with an attractive shift toward the peripheral stimulus orientation (6/22). A shift in the CoM away from the peripheral stimulus orientation suggests that the peripheral stimulus more strongly suppresses the cell's response to orientations near that of the peripheral stimulus. By reducing the response amplitude at the matching orientation, the CoM shifts away from the PRF orientation. The fact that the CoM shifted more frequently than the response peak demonstrates that the influence of the peripheral stimulus does not simply suppress the cell as in gain control, but reshapes its response function.

Influence of local PRF blockade

We determined that the peripheral stimulus influenced the response of the recorded cell in 22 cases by modulating the peak activity and/or altering the shape of the orientation tuning function. Presumably, if the modulation resulted from neural activity at the peripheral site in area 17 that was driven by the peripheral stimulus, then inactivating the peripheral activity by iontophoretic application of GABA should cause the orientation tuning curve to resume (or at least approach) control levels despite the presence of the peripheral stimulus. Fig. 5 illustrates three different results observed during the iontophoretic block of neural activity at the peripheral site. For the cell in Fig. 5A, application of GABA produced disinhibition. The solid line with *open circles* indicates the control curve for the recorded cell, with the vertical bars describing the 95% CI. The peak of the curve occurred at 259.5 deg with a response rate of 20.6 spikes/s. The peripheral stimulus caused a 9.5-deg leftward shift (*squares*) and suppressed the peak response amplitude by 34%. After applying GABA and remeasuring the orientation tuning curve in the presence of the peripheral stimulus (*asterisks*), the curve recovered to within the 95% CI of the control curve. This result is consistent with the idea that neural activity at the site of the peripheral electrode influences the response of the recorded cell during stimulation with the peripheral stimulus. After the iontophoresis of GABA was discontinued and a 20-min period was allowed for reuptake, the coupled stimuli were presented again and the orientation tuning curve returned to suppressed levels. Finally, the single excitatory stimulus was presented over the CRF and the curve recovered to within the 95% CI of the control measurement.

Iontophoretic application of GABA did not affect all cells similarly. In some instances, the GABA injection did not completely eliminate the peripheral modulation, as shown in Fig. 5B. The broad control curve had a double-peaked response at 45 spikes/s. Response suppression occurred at all orientations in the presence of the peripheral stimulus. Injection of GABA slightly elevated the curve from the peripherally suppressed response, but the values did not recover to the levels of the control curve. We verified that the GABA was silencing the peripheral site (discussed further in next section). After discontinuing the iontophoresis and allowing for reuptake, recovery measurements confirmed that the cell resumed the appropriate response levels. This result suggests

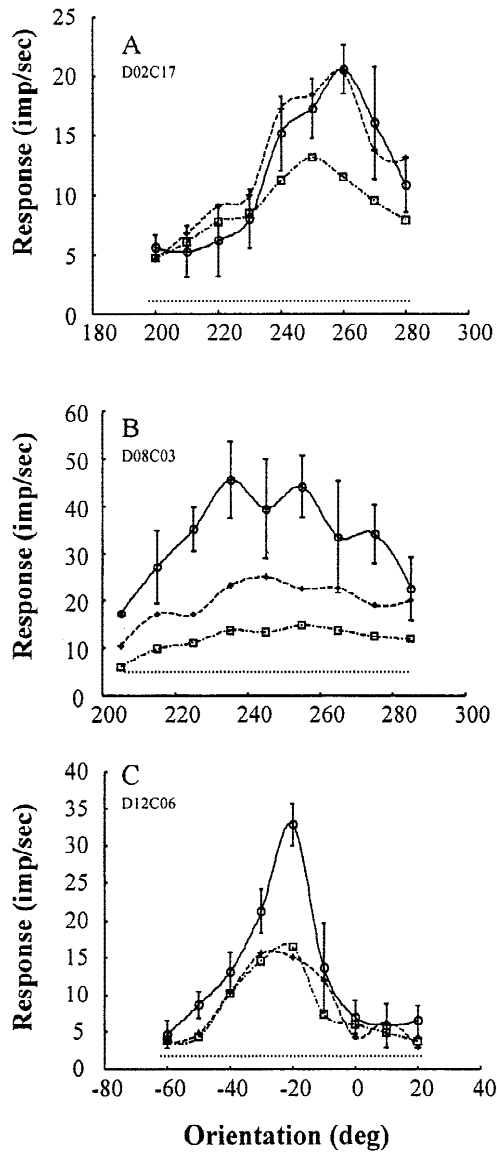


Fig. 5. Examples of GABA blockade results. In cases where a peripheral influence was demonstrated, the peripheral site in area 17 was blocked with GABA. Three different results were recorded. In A, the response during peripheral stimulation is suppressed and shifts to the right (*open squares*). During the GABA blockade, the response to both stimuli is remeasured (*asterisks*) and falls within the 95% CI of the control curve indicating that the peripheral modulation is arising from within area 17. In B, the response is substantially suppressed during peripheral stimulation. When the GABA blockade is administered, the response is elevated but does not reach the 95% CI of the control curve. In C, the response is suppressed during peripheral stimulation. The response during the GABA blockade does not recover to control values and remains at the peripherally influenced response suggesting that the peripheral influence is not originating within area 17. The dashed horizontal line is baseline activity.

that neural activity at the site of the peripheral electrode may contribute to the suppression of the recorded cell, but not as strongly as the case described in Fig. 5A.

Fig. 5C displays a more salient observation. The control curve peaked at -20.5 deg with a response rate of 33 spikes/s. Adding the peripheral stimulus yielded an orientation tuning curve with a

suppressed response and a slight leftward shift in CoM. However, when the GABA blockade was administered, the response did not return toward the control values. Rather, the curve measured during iontophoresis of GABA was nearly identical to the curve measured during peripheral stimulation without the GABA. The efficacy of the application of GABA for inactivating neural activity at the peripheral site was validated, and subsequent recovery measurements were at the appropriate levels. This result suggests that, in some cases at least, neural activity at the site of the peripheral electrode has no influence on the recorded cell.

Of the 22 cells that showed an influence from the peripheral stimulation, recordings from 19 remained stable for the duration required to complete the GABA iontophoresis and recovery phases. The responses of all 19 cells returned to reduced levels (with PRF stimulation) after dissipation of the GABA and returned to control values when the peripheral stimulus was removed. The responses of only 7/19 cells (37%) returned to control levels during GABA injection with the two-grating stimulus, implying that for these cells the inhibitory influence arose from the blocked site in area 17. The responses of nine cells (47%) remained at reduced levels during inactivation of the peripheral site, showing no statistically significant recovery. The remaining three cells (16%) showed responses during iontophoresis that fell between the control response and peripherally suppressed response. These results are important in that only one-third of the cells confirmed that the suppression was originating from the peripheral site in area 17. The implication is that neural activity from regions other than area 17 plays some role in modulating the response of the recorded cell during stimulation of the PRF.

Validation of GABA iontophoresis

To ensure the results described above were unambiguous, we verified the effectiveness of GABA iontophoresis for cases in which disinhibition did not occur during the GABA microinjection. Several possibilities exist that would cause the curve to remain at levels consistent with the peripherally altered response in the presence of GABA. GABA may not have been adequately distributed to the cell cluster if the electrode was blocked or the current was not sufficient. Additionally, the peripheral cell cluster may not have been silenced despite the delivery of GABA to the region if the solution was not at the appropriate concentration or pH level. Either of these situations would effectively result in our simply remeasuring the influence of activation of the PRF on the recorded cell. In cases where the GABA did not cause the recorded cell measurement to return to control values, two supplementary trials were performed to eliminate possible misinterpretations of the results.

To verify that the GABA was adequately silencing the peripheral region, recordings were made directly from the peripheral electrode during GABA application. The peripheral site was stimulated at its optimal parameters to induce a response that we monitored by ear. In all cases, GABA injection completely eliminated the peripheral response or reduced it to the point that it was barely audible. We could not determine whether the GABA administration blocked the activity of *all* cells responding to the stimulation of the peripheral receptive field because some cells might have been outside the range of the electrode's recording capability. In the orientation domain, a single hypercolumn spans approximately 0.8 mm and extends the entire depth of the cortex (Hubel & Wiesel, 1962). The extent of GABA diffusion is variable depending on specific solutions used, physical properties of mi-

cro-pipette and injection current, and consequently is difficult to estimate. Martinez-Conde et al. (1999) performed control experiments that showed the sphere of inactivation silenced a field of cells with a 300- μm radius (Herz et al., 1969; Martinez-Conde et al., 1999). Additionally, iontophoretic application of GABA has been proven to extend through all layers of the cortex (Kisvarday et al., 1986), since there is a tendency for the injected GABA to migrate up the pipette body. A stimulus of a given orientation will only activate a fraction of the columns within the corresponding hypercolumn. A 300- μm radius of inactivation would likely encompass the range of columns within a given hypercolumn that would selectively respond to the peripheral stimulus. Furthermore, the diameter of the peripheral stimulus was reduced to the smallest size that resulted in a change in the response at the peripheral site in order to minimize the population of neurons activated during peripheral stimulation. This combined evidence suggests that the GABA should have inactivated a significant portion of the cells responding to the peripheral stimulus. However, without a workable verification procedure, we cannot be certain that GABA silenced the entire population of cells activated by the peripheral stimulus. Incomplete inactivation is certainly a possibility in cases of partial recovery with GABA. The partial recovery toward the control values suggests the likelihood that the GABA was silencing many of the cells causing the peripheral modulation of the recorded cell, while a select group remained active and continued to send modulatory signals to the recorded cell.

Incomplete inactivation of the peripheral site may provide a reasonable explanation for the partial recovery seen in three cells, but it does not explain those cells where GABA administration resulted in no noticeable release of inhibition. For the above argument to apply to these nine cells, a select population lying outside the sphere of GABA inactivation would have to be responsible for the entire suppressive influence on the recorded cell. We do not believe this to be the case. The peripheral stimulus was optimized in terms of both location and spatial configuration for the neurons closest to the recording/injection electrode pair, and we confirmed that GABA injection silenced this population. While in all cases there were doubtless cells near to the sphere of GABA inactivation that continued to respond, these would respond less vigorously because due to their displacement, the stimulus was not optimized for them. To conclude that the cells showed no recovery because of incomplete inactivation, one must assume that this subpopulation, responding weakly to a nonoptimal stimulus, was responsible for the entire suppressive influence on the recorded cell. We cannot rule that possibility out, but since we found no recovery in nearly half of our cases, we consider this scenario unlikely.

The second supplementary investigation confirmed that the iontophoretic application of GABA did not directly inhibit the recorded cell activity. We presented the CRF stimulus alone during GABA injection. The orientation tuning curve of the recorded cell would not match control values if the GABA were directly affecting its state. In all cases, the GABA micropipette was located sufficiently far from the recording electrode that there was no change in the recorded cell response.

Discussion

Defining the peripheral influence

Most previous experiments have examined the influence of stimulating the ERF on the CRF response characteristics by presenting

an annular stimulus outside the CRF, thereby stimulating the entire surround region. This can result in both suppression and facilitation (e.g. Li & Li, 1994; Sengpiel et al., 1997). Levitt and Lund (1997) determined that the qualitative impact of the surround depended on the relative contrast level between the CRF and ERF stimuli. Our stimulus configuration reduced the population of peripheral cells that were stimulated so that we could better isolate contributions of discrete regions of the ERF. In this condition, only suppression occurred from stimulation of the discrete PRF. Why we observed only suppression remains unresolved, but its dominance may arise from architectural principles. Previously described facilitation may have resulted from inexact definition of the CRF. Subthreshold excitatory regions are found in the fringes of the CRF. An annular stimulus placed directly outside the center stimulus would integrate throughout this subthreshold region, increasing the excitatory response. This could be interpreted as facilitation from the periphery that is actually central in origin. Crook et al. (2002) reported co-linear facilitation from bars placed along the flanks of a stimulating bar within the CRF. Again, the increase in response may have been from activation of subthreshold regions in the CRF, although their results are not necessarily comparable to ours because they are using discrete elements (i.e. bars) rather than gratings. Another possible explanation of why we consistently reported suppressive influences from outside the CRF is synaptic summation. A postsynaptic neuron receiving both excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) may be affected more by the inhibitory connections which frequently synapse closer to the cell body, and therefore yield a more powerful influence on the cell potential (LeVay, 1973; Fairen & Valverde, 1980). Additionally, smooth stellate cells may intensify their influence by contacting multiple locations on the same recorded cell (Fairen & Valverde, 1980; Somogyi et al., 1983). Therefore, for a recorded neuron receiving EPSPs and IPSPs from a small population of cells stimulated by the peripheral stimulus, the inhibitory signal might dominate the modulatory effect due to the strategic location of inhibitory synapses. Synaptic summation may also explain the ability of a small, localized peripheral stimulus to suppress the CRF response at levels comparable to the entire ERF stimulation (i.e. with an annular stimulus). With an annular stimulus, the population of activated cells is much larger. However, peripheral communications within this population of cells will likely have modulatory interactions amongst themselves that would affect their influence on the CRF response.

Characterization of localized peripheral suppression

We oriented the peripheral stimulus so as to elicit a maximum response at the peripheral site independent of the orientation preference of the individual cell being studied. We then examined the relationship of the peripheral stimulus orientation to the characteristics of the observed modulation. Two observations are salient. First, the peripheral stimulus that most often modulated the response was oriented 10–30 deg from the preferred orientation of the recorded cell (Fig. 4). We further found that although the peak response did not shift in a predictable direction relative to the peripheral stimulus orientation, the CoM consistently shifted away from the peripheral stimulus orientation (i.e. a repulsive effect) (Table 1). Because the CoM shifted more consistently than the peak orientation, the peripheral stimulus does not simply suppress the recorded cell response, but selectively modulates the response to specific orientations so that the recorded cell becomes more

responsive to a skewed group of orientations. Considering that peripheral stimuli oriented 10–30 deg from the tuning peak generally causes a repulsive activity shift suggests that the peripheral stimulation causes the most substantial suppression at orientations similar to its own.

Earlier work (e.g. Knierim & van Essen, 1992; Levitt & Lund, 1997; Sengpiel et al., 1997) characterized the relationship between the surround and center regions of the receptive field as iso-orientation suppression by annular surrounds. We found that discrete stimuli placed outside the CRF can exert varied influences on the response of the recorded cell. For example, one PRF stimulus may cause uniform suppression, while a separate PRF stimulus in a different region of the ERF may cause a shift in tuning. We speculate that simultaneous stimulation of two PRF sites may yield yet another unique influence on the recorded cell. While the CRF response alone has a static, repeatable response, the ERF influence is overall less predictable and will depend on the population of cells activated by the combination of stimuli placed outside the CRF.

Origins of the peripheral suppression

Stimulation from outside the CRF generally suppresses the excitatory response of cortical cells in area 17. Anatomical evidence provides a feasible path for peripheral interactions in area 17. Long-range horizontal connections typically synapse at like-oriented pyramidal cells in other hypercolumns (T'so et al., 1986; Gilbert & Wiesel, 1989). The cells located within the vicinity of the recorded cell may then elicit responses from neighboring inhibitory interneurons that suppress the recorded cell's response to that specific orientation. Although these horizontal collaterals usually connect to other pyramidal cells *via* excitatory synapses, an estimated 20% of their postsynaptic targets are GABAergic smooth stellate cells (Kisvarday et al., 1986; McGuire et al., 1991) that in turn have synapses that are most likely inhibitory (LeVay, 1973). Another course for inhibitory influences in the striate cortex are large basket cells with axonal projections reaching as far as 1.5 mm in area 17 (Somogyi et al., 1983) which provide a direct means for peripheral cells in neighboring hypercolumns to inhibit the response of recorded cells.

While intracortical communication within area 17 is a potential source for peripheral interactions, feedback from other cortical areas has also been explored as a source of modulation (Alonso et al., 1993; Hupe et al., 1998; Martinez-Conde et al., 1999). By constructing diameter tuning curves and defining the CRF diameter at the maximum response level, Cavanaugh et al. (2002) postulate that the long-range horizontal connections within area 17 provide the cytoarchitecture for the subthreshold fringes of the CRF. They further suggest that based on the relative size differences between RF diameters in area 17 and higher cortical areas (i.e. area 18) the influences from stimulation outside the CRF result from top-down processes. Angelucci et al. (2002) further provides the anatomical evidence to support this argument. Our results provide support for the notion that both interconnectivity between cells within area 17 and from cells outside area 17 act in unison, and in some cases separately, to provide peripherally induced suppression.

Our iontophoretic studies, for example, suggest that the horizontal connections within area 17 are involved in peripherally induced suppression, but are often not the exclusive source of peripheral modulation. Fig. 6 illustrates the connections that could explain the effects we observed. In the top panel, the response amplitude of a recorded cell is suppressed when a cell cluster that

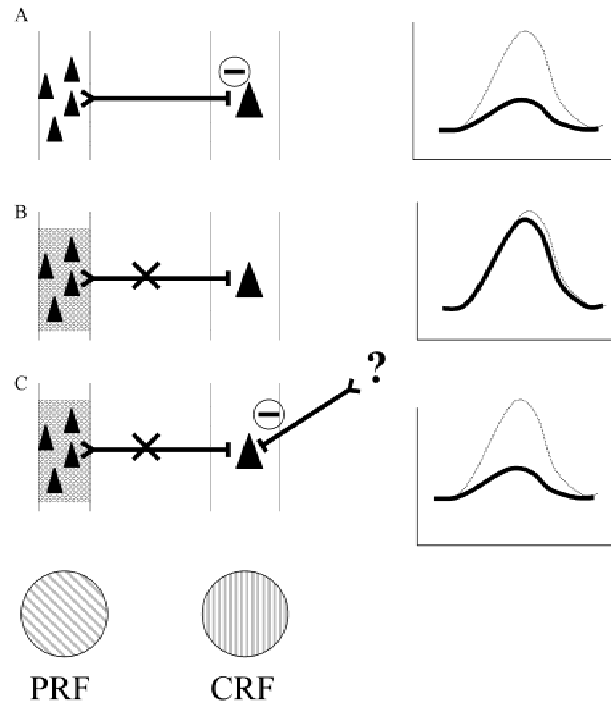


Fig. 6. Models of area 17 circuitry. The top left diagram shows a peripheral set of cells within area 17 that have an inhibitory influence over a recording cell with a discrete receptive field. The responses on the right show a control curve when the CRF is stimulated alone (dotted line) and suppressed response when the peripheral site is stimulated simultaneously. When the peripheral set of cells is blocked with GABA (shaded region, middle panel), the peripheral influence is eliminated. The response returns to values similar to the control. In the bottom panel, the response remains at suppressed levels despite the GABA blockade in area 17 indicating that the peripheral influence may originate outside area 17.

drives inhibitory interneurons is activated by the peripheral stimulus. When GABA is applied at the remote site to block the peripheral activity (middle panel), the excitatory drive to these interneurons is no longer present, reducing peripherally induced suppression. We were able to effectively manipulate the peripheral site, reversibly turning its influence “ON” with a specific stimulus and “OFF” with iontophoretic application of GABA to demonstrate its influence on the recorded cell. If the origin of the peripherally induced suppression were restricted to area 17, inactivation of the peripheral cell cluster by GABA application should have caused the neuronal response to return to control values more consistently. Another possible explanation for a more indirect peripheral influence would be that the peripheral influence arises primarily in extrastriate area (e.g. area 18) and we were blocking the feedforward projections of the peripheral activity from area 17 to area 18. Regardless of which explanation is appropriate, only one-third of the cells tested during application of GABA displayed a complete return to control levels.

We observed two other results. In three cells the response partially recovered during the peripheral blockade, and in nearly half of the cells (9/19) the recorded cell response remained at the modulated level. This evidence raises the possibility of a nonlocal origin of response suppression (Fig. 6, lower panel). Because the recorded cell in most cases showed no recovery during inactivation of the region of area 17 corresponding to the peripheral stimulus, the origin of the suppression is most likely elsewhere. Retinotopic

mapping constrains the region of the brain from which the peripheral modulation could originate to the sites in register with the PRF. Of the areas directly connected to area 17, the lateral geniculate nucleus (LGN) is immediately ruled out for several reasons. Projections from the LGN make undeviating monosynaptic connections (Garey & Powell, 1971; Bullier et al., 1984), and it has limited lateral interactions (Orban, 1984). Furthermore, anatomical (Garey & Powell, 1971) and physiological (Tanaka, 1985) studies show that LGN afferents are purely excitatory. Therefore, the LGN is not a structurally viable candidate to support complex peripheral interactions.

The evidence for peripheral suppression from area 18 poses a more feasible origin for response suppression from stimuli outside the CRF. A laminar distribution of GABA-immunoreactive processes exists both within and between orientations columns in area 18 (Matsubara et al., 1987). Cortico-cortical projections from area 18 to area 17 (Bullier et al., 1984) generally preserve spatial locality of receptive fields (Salin et al., 1992). Furthermore, these projections from area 18 modulate the activity of cells in area 17 with overlapping receptive fields. Modulation between retinotopically matched sites in areas 18 and 17 have been interrupted with focal blockades of layer 5 (Alonso et al., 1993) and layers 2/3 (Martinez-Conde et al., 1999) of area 18.

Perhaps the most conspicuous evidence suggesting that area 18 feedback from peripheral receptive fields influences area 17 is the direct thalamic projection to area 18 of cats (Orban, 1984) which transforms the originally hypothesized serial organization of areas 17 and 18 to that of a parallel pathway with reciprocal interactions (Tretter et al., 1974). With independent thalamocortical projections to both areas 17 and 18, retinotopically matched activity may be preserved despite a focal blockade in one of the areas. With the two-stimulus paradigm, area 18 receives a discrete excitatory thalamic projection of the peripheral input, and blocking the peripheral activity in area 17 does not interrupt the modulatory signal. Independent peripheral modulation arising from both areas 17 and 18 is also a reasonable explanation for the three cases of partial recovery found during GABA application in area 17.

The receptive field as a process (not an architecture)

The concept of a receptive field has evolved since the initial reports of Hubel and Wiesel (1962). Far more complex than a discrete window of the visual field signaling a static range of stimulus conditions, the response properties of the CRF are recurrently altered according to the context of the surrounding region. The discovery of surround modulation has forced the redefinition of the receptive field to encompass these influences. The exact nature of the interactions eludes a definitive explanation but has demonstrated nonlinear interactions increase with the complexity of stimuli used, resulting in seemingly conflicting results. Thus, stimulation outside the CRF yields facilitation (Maffei & Fiorentini, 1976; Toth et al., 1996) and suppression both iso-orientation selective (Nelson & Frost, 1985; Li & Li, 1994) and nonselective (Bishop et al., 1973; Sillito et al., 1995). Although a nonspecific gain control system (e.g. Heeger, 1992) accounts for contrast dependency of surround interactions (Toth et al., 1996; Levitt & Lund, 1997), it does not explain the shifts in tuning properties of the recorded cell from secondary stimuli placed both inside (Kabara & Bonds, 2001) and outside (Gilbert & Wiesel, 1990; Sengpiel et al., 1997) the CRF. The collective results suggest that neural populations, rather than the individual cell, determine the spatial properties of its receptive field.

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