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Strength and Orientation Tuning of the Thalamic Input to Simple Cells Revealed by Electrically Evoked Cortical Suppression

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Summary

Is thalamic input to the visual cortex strong and well tuned for orientation, as predicted by Hubel and Wiesel's (1962) model of orientation selectivity in simple cells? We directly measured the size of the thalamic input to single simple cells intracellularly by combining electrical stimulation of the cortex with a briefly flashed visual stimulus. In nearby cells, the electrical stimulation evoked a long-lasting inhibition that prevented them from firing in response to the visual stimulus. The visually evoked excitatory postsynaptic potentials (EPSPs) recorded during the period of cortical suppression, therefore, reflected largely the thalamic input. In 16 neurons that received monosynaptic input from the thalamus, cortical suppression left 46% of normal visual response on average (12%–86% in range). In those cells tested, this remaining visual response was as well tuned for orientation as the normal response to the visual stimulus alone. We conclude that the thalamic input to cortical simple cells with monosynaptic input from the thalamus is strong and well tuned in orientation, and that the intracortical input does not appear to sharpen orientation tuning in these cells.

Introduction

The primary visual cortex of mammals is located at a special position in the visual system, showing levels of processing that are not apparent at earlier stages of the visual pathway. The best known example is orientation selectivity: neurons in the visual cortex strongly prefer elongated visual stimuli with a specific orientation, whereas retinal and geniculate neurons do not. Hubel and Wiesel (1962) proposed that orientation selectivity originates from the excitatory convergence of several geniculate afferents, the receptive fields of which are aligned parallel to the preferred orientation of the postsynaptic cortical simple cell. A number of observations support this model. First, increases in stimulus length up to a certain point enhance the response of a cortical cell, and the optimal length of the stimulus is usually longer than the diameter of geniculate receptive fields at the same eccentricity (Gilbert, 1977; Rose, 1977). Second, the receptive fields of geniculate afferents encountered in a single cortical column are aligned parallel to the preferred orientation of cortical cells in the same column (Chapman et al., 1991). Third, strong correlations in firing that are indicative of monosynaptic connections are found between geniculate relay cells and cortical simple cells only when the receptive field of the geniculate cell is superimposed on a subregion of the simple receptive field of the same sign (Reid and Alonso, 1995). Together, these results give strong support to one aspect of Hubel and Wiesel's model, that is, that input from geniculate afferents gives rise to the elongated subregions of simple cell receptive fields. The second aspect of the model, that this spatial organization, in turn, gives rise to orientation selectivity, remains controversial.

Although the original model is appealing in its simplicity, it does not account for experimental evidence for the involvement of intracortical inhibition in determining the orientation selectivity of cortical neurons (Creutzfeldt et al., 1974; Morrone et al., 1982; Ramoa et al., 1986; Hata et al., 1988; Bonds, 1989; DeAngelis et al., 1992). These authors found that stimuli at nonoptimal orientations suppressed the background activity of cortical cells elevated by glutamate application or by the presentation of a conditioning stimulus at the preferred orientation. In addition, when $GABA_A$-mediated inhibition was blocked pharmacologically, the orientation selectivity of many cortical neurons was dramatically reduced (Sillito, 1975; Daniels and Pettigrew, 1975; Tsumoto et al., 1979; Sillito et al., 1980; Eysel et al., 1990). From these observations, it was suggested that intracortical inhibition tuned to the orthogonal orientation (cross-orientation inhibition) plays a major role in the generation of cortical orientation selectivity. In these models, it was also assumed that the contribution to orientation selectivity from the spatial organization of the geniculate input was relatively weak.

Recent intracellular recording from cortical neurons in vivo and in vitro have failed to reveal cross-orientation inhibition: intracortical inhibition was not significant at the orthogonal orientation but instead was strongest at the preferred orientation (Ferster, 1986; Weliky et al., 1995; but see Pei et al., 1994). Shunting inhibition at nonpreferred orientations was not apparent in intracellular records either (Douglas et al., 1988; Ferster and Jagadeesh, 1992). There is recent evidence, however, for large shunts occurring in response to stimuli of the optimal orientation (Borg-Graham et al., 1996; Carandini and Ferster, 1998, Invest. Ophthalmol. Vis. Sci., abstract; Hirsch, 1995, Soc. Neurosci., abstract), but these shunts do not have the properties appropriate to support the cross-orientation inhibition model. Lastly, intracellular blockade of inhibition did not change the orientation tuning of many cortical simple neurons (Nelson et al., 1994).

Neither Hubel and Wiesel's model nor cross-orientation inhibition models address one striking aspect of the behavior of cortical neurons, namely the contrast invariance of orientation selectivity. Because the responses of geniculate neurons grow with increasing stimulus contrast, a simple summation of thalamic inputs followed by a fixed threshold would predict that the orientation selectivity would decrease with increasing stimulus contrast in a way that is not observed experimentally (Sclar and Freeman, 1982; Skottun et al., 1987).

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A recent extension of Hubel and Wiesel's model that explicitly incorporates spatially opponent inhibition (Troyer et al., 1998) does account for the contrast invariance of orientation selectivity.

A third class of models, which also exhibit contrast invariance of orientation tuning, rely not on the suppression of the geniculate input by cross-orientation inhibition but on the amplification of geniculate input by recurrent excitation occurring within the cortical column (Douglas and Martin, 1991; Ben-Yishai et al., 1995; Douglas et al., 1995; Somers et al., 1995; Maex and Orban, 1997). This amplification is gated selectively by intracortical inhibition and thereby sharpens weak and poorly tuned geniculate input. To arrive at these results, however, the models make two key assumptions. First, the input from the lateral geniculate nucleus (LGN) is weak, constituting only about 5%–10% of the total excitatory synaptic input to a simple cell. Second, the geniculate input is at best only broadly tuned for orientation.

Support for the first assumption comes from anatomical observations suggesting that the geniculate synapses comprise 5%–10% of the total excitatory synapses present in layer 4 (Garey and Powell, 1971; Winfield and Powell, 1983; LeVay, 1986; Peters and Payne, 1993; Ahmed et al., 1994; but see LeVay and Gilbert, 1976). Perhaps more relevant to the feedback models of orientation selectivity, however, are physiological estimates of the relative strength of geniculate and cortical inputs to simple cells. Tanaka (1983) and Reid and Alonso (1995) found in their cross-correlation studies that each geniculate afferent could account for a significant fraction of the activity of a simple cell. Depending on the total number of geniculate afferents converging on a simple cell, the aggregate geniculate excitation could potentially dominate the cell's activity. An independent estimate of the size of geniculate input came from Ferster et al. (1996). They recorded intracellular visual responses from cortical simple cells while inactivating cortical interneurons by locally cooling the cortex. They estimated that the geniculate input contributed 37% of the total synaptic excitation of simple cells. This measurement, however, was necessarily indirect because the effect of cooling on the geniculate terminals could only be estimated. The current experiment, therefore, is designed to measure directly the size of geniculate input to a single neuron in layer 4 of the cat visual cortex.

The second assumption common to feedback models of orientation selectivity—that the geniculate input is broadly tuned in orientation—is also controversial. In the cooling study of Ferster et al. (1996), the visually evoked synaptic activity in simple cells during cooling was well tuned for orientation. One potential technical difficulty with this experiment was the gradient in temperature set up in the cortical layers by the cooling plate. As a result, ~15% of the visually evoked activity in layer 6 remained during cooling. Ferster et al. (1996), however, concluded that the synaptic input from layer 6 cells to layer 4 simple cells was negligible during cooling since the synaptic effect of layer 6 cells on layer 4 was reduced by >25-fold. Three factors contributed to this conclusion: (1) the 6-fold reduction in layer 6 cell activity itself, (2) the resulting reduction in facilitation of layer 6 cell synapses on layer 4 cells (Ferster and Lindström, 1985; Stratford et al., 1996), and (3) a 2-fold or greater reduction in synaptic efficacy caused by direct cooling of the synaptic terminals in layer 4. Nevertheless, we were interested in obtaining an independent test of the conclusions drawn by Ferster et al. (1996).

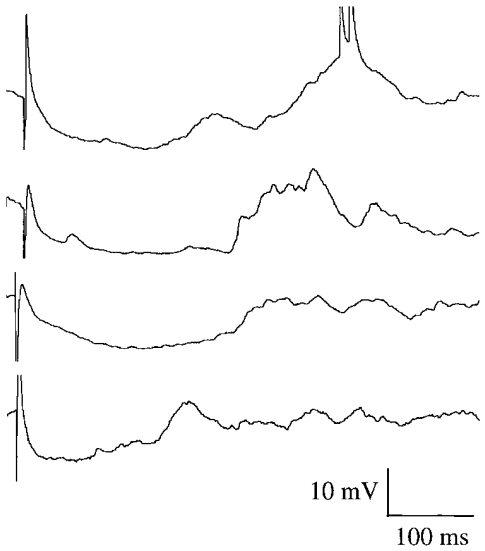

Figure 1. Intracellular Responses of Four Cortical Neurons to Electrical Stimulation of the Superficial Layers of Nearby Cortex

Electrical stimulation invariably evoked an early depolarization followed by a strong hyperpolarization, which lasted for 150–200 ms. The stimulus strengths were 400, 600, 600, and 400 μA from top to bottom. Stimulus artifacts and spikes are truncated.

In the current experiment, we suppressed the activity of cortical neurons not by cooling but by electrical stimulation of the nearby cortex. Electrical stimulation evokes a short-latency depolarization followed by a long-lasting hyperpolarization, during which the spikes normally evoked in cortical cells by a briefly flashed visual stimulus are almost entirely suppressed. At the same time, the visual activity in geniculate cells is largely unaffected. We recorded intracellularly from simple cells with monosynaptic input from the LGN and measured the amplitude and orientation preference of synaptic potentials evoked by brief visual stimuli during the electrically evoked suppression of cortical activity. The suppression of cortical activity, as in the cooling experiment, had little effect on the orientation tuning. It did, however, reduce the amplitude of the visual responses by 54% on average. We will present evidence that the remaining 46% of visually evoked synaptic potentials came largely from the geniculate afferents. The results of the current experiment indicate that the geniculate input is stronger than suggested by many anatomical studies and well oriented, as originally proposed by Hubel and Wiesel (1962).

Results

Electrical stimulation of the cortex as well as the afferent fibers invariably evokes strong and long-lasting inhibition in cortical cells (Li et al., 1960; Creutzfeldt et al., 1966; Watanabe et al., 1966; Berman et al., 1991). Records from four cells are shown in Figure 1. Electrical

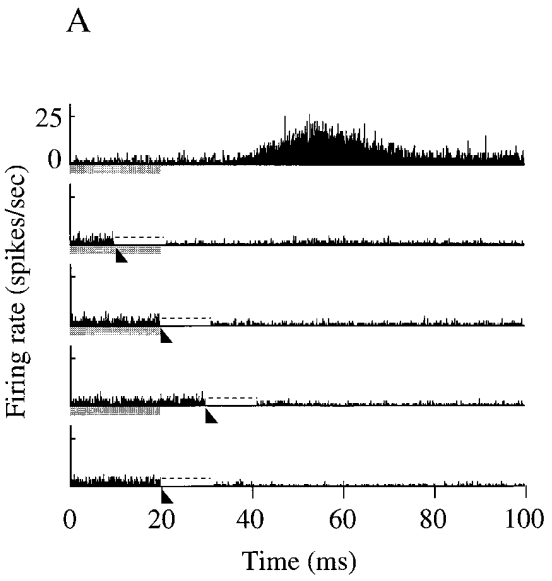

Figure 2. The Effect of Electrical Stimulation on the Visually Evoked Extracellular Activity of the Cortex

(A) Averaged firing rate evoked by a brief visual stimulation from 27 multiunit recording sites indicated in (B). Five conditions were tested: visual stimulation alone (top), electrical stimulation alone (bottom), and visual and electrical stimulation combined with three different relative delays (10, 20, and 30 ms). The visual stimulus, a stationary sinusoidal grating with optimal orientation and spatial frequency, appeared at time 0 and lasted for 20 ms (gray bar). The electrical stimulus was 200 μs in duration and 600 μA in strength (electrode negative). The timing of the electrical stimulus is indicated by an arrowhead. Of the three delays between the onset of the visual and electrical stimuli, 20 ms was most effective at suppressing the visual discharge. The shock artifact and electrically evoked action potentials were removed from the histograms (dashed lines following the electrical stimuli).

(B) Histological reconstruction of the recording track and the location of 29 multiunit recording sites. The electrolytic lesion marked the end of the track at 2 mm below the surface of the cortex. The arrows indicate two locations at which the geniculate afferents were encountered, as identified by their monocularity, lack of orientation tuning, nonzero spontaneous activity, and vigorous on or off response to a small spot of light. The spikes from these two locations are not included in the averaged firing rate in (A). The stimulating electrode (⊙) was located in layer 2/3.

stimulation of the upper layers of the cortex is followed by early depolarization, later hyperpolarization of 150–200 ms duration, and finally rebound excitation. Spontaneous action potentials were almost always suppressed during the hyperpolarization in the recorded cells. We speculated from this observation that the cortical discharges normally evoked by visual stimulation might also be suppressed by electrically evoked cortical inhibition. We tested this idea on extracellularly recorded activity in cortical neurons.

Visually Evoked Cortical Firing during Electrically Evoked Cortical Suppression

We recorded extracellular activity of cortical neurons evoked by a brief flash of an optimal sinusoidal grating in the absence and in the presence of cortical electrical stimulation. The records in Figure 2A show the average firing rate of 27 multiunit recordings obtained from the electrode penetration diagrammed in Figure 2B. All cortical layers were sampled in the penetration. The response to visual stimulation alone is shown in the top record. The visual stimulus came on at time 0 and lasted for 20 ms as indicated by the gray bar below each record. The brief visual stimulus evoked on average a short (50–60 ms) burst of action potentials. The response to the electrical stimulus alone is shown in the bottom record. The time of the electrical stimulation is indicated by an arrowhead. Immediately following the electrical stimulus, there is a period of ~10 ms during which the recording was disrupted by the shock artifact and short latency–evoked spikes. The record is blanked during this period (dashed lines). Following this period, however, it is clear that the spontaneous activity was reduced in frequency. Various combinations of visual and electrical stimulation with different relative latencies are shown in the middle three records. For all three conditions, the visually evoked action potentials were strongly suppressed, although the suppression was most complete with a 20 ms relative delay (third record from the top). Responses to visual stimuli longer than 20 ms were not completely suppressed. Thus, the maximum effect of the electrical stimulus in suppressing the cortical responses appears to be coincident with the peak of the $GABA_A$ component of the electrically evoked IPSP (Avoli, 1986; Connors et al., 1988; Douglas and Martin, 1991).

As shown in Figure 2B, the electrode penetration encountered neurons in all layers of the cortex. (The arrows indicate two locations at which geniculate afferents were encountered, as identified by their monocularity, lack of orientation tuning, nonzero spontaneous activity, and vigorous on or off response to a small spot of light. There, responses were not suppressed by the electrical stimulus and are not included in the histograms in Figure 2A). The degree of suppression was similar in the different layers, including layer 6. This result is in agreement with Krnjevic et al. (1966), who showed that the stimulation of the cortical surface evoked inhibition strong enough to suppress glutamate-induced neuronal activity throughout the cortical layers.

In all, 32 similar penetrations were made through the cortical layers (see below). In the same penetrations, different stimulus strengths for cortical shock were tried. Among the stimulus strengths tested (100 μA to 1 mA), 400 or 600 μA was chosen for further experiments as being strong enough to shut off most cortical activity but not too strong to affect visually evoked activity in the LGN (see below).

The Horizontal Extent of Electrically Evoked Cortical Inactivation

An additional control experiment was necessary to determine the effective radius of the electrically evoked cortical suppression. Given our choices for electrical stimulus timing and strength, we varied the horizontal

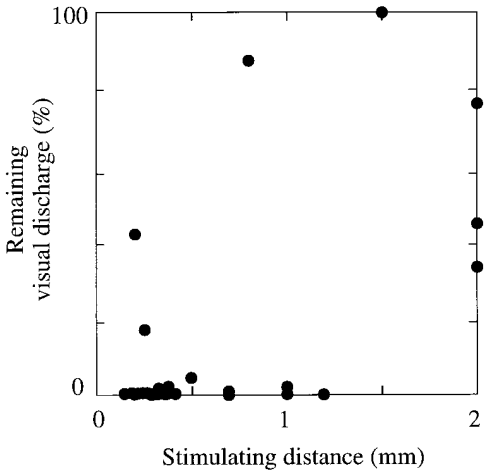

Figure 3. Effective Distance of Electrical Stimulation in Suppressing Visual Response in the Cortical Column

The percent visual discharge remaining in the cortical column during electrically evoked cortical suppression is plotted against the recording distance from the electrical stimulation for 32 tracks. In 22 of 24 tracks located <700 μm from the electrical stimulation, visual responses were suppressed by >95%.

distance (measured at the surface) between the stimulating and the recording electrodes. A total of 32 tracks of multiunit recordings were made in the visual cortex with electrode separations between 0.15 and 2.0 mm. Figure 3 shows, as a function of electrode separation, the percentage of the visually evoked cortical discharges (averaged from all of the recording sites in each track) remaining during shock inactivation. For 22 of the 24 tracks in which the stimulating and recording electrodes were located less than 700 μm distant from each other, the electrical stimulation almost completely suppressed the visual responses and most of the background activity. Even at 1 mm, the suppression, though less consistent, was nonetheless significant. We therefore kept the distance between the recording and the stimulating electrodes within 500 μm during the intracellular recording experiments.

Geniculate Activity during Electrically Evoked Cortical Suppression

As important as showing that the electrical stimulus suppressed cortical activity is a demonstration that the electrical stimulus did not affect the visual responses of geniculate afferents. For example, the electrical stimulus could antidromically activate geniculate relay cells from their axon terminals in layer 4 and subsequently activate perigeniculate inhibitory interneurons from relay cell collaterals. Alternatively, the electrical stimulus could activate layer 6 neurons, which project to geniculate relay cells, perigeniculate neurons, and intrageniculate inhibitory interneurons. Both possibilities could decrease the geniculate responses, and therefore the measured cortical responses to the visual stimulation, even in the absence of any effect of the electrical stimulus on cortical activity. We therefore recorded extracellular multiunit activity in the LGN to determine the cortical stimulus parameters that least affected geniculate activity. We again combined visual stimulation with electrical stimulation at different depths in the region of cortex corresponding topographically to the location of the LGN recording electrode. The visual stimulus consisted of a briefly flashed light or dark square. Four tracks of multiunit recordings were made in the A laminae of the LGN. In each track, keeping the electrical stimulus strength between 400 and 600 μA, there was a significant but incomplete suppression (30%–70%) of the geniculate visual discharge whenever the stimulating electrode was placed 500 μm or deeper from the surface of the cortex. Above this depth, the visual activity in the A laminae of the LGN was not detectably affected. Thus, for the intracellular recording experiments (and the control experiments described in the previous sections), the stimulating electrode was never placed deeper than 400 μm. Later histology confirmed the location of the stimulating electrode to be in the upper or middle part of layer 2/3 (e.g., see Figure 2B).

In summary, the extracellular multiunit recordings indicated the optimal parameters of the electrical stimulus: a relative delay between the visual and the electrical stimulation of 20 ms, a stimulus strength between 400 and 600 μA, a distance between the recording and stimulating electrodes of <500 μm, and a cortical depth of the stimulating electrode of <400 μm.

Cortical Neurons Lacking Monosynaptic Input from the LGN

The suppression of visually evoked spike activity in cortical cells, but not geniculate cells, makes strong predictions for the effects of the electrical stimulus on intracellularly recorded synaptic potentials: the effects should depend on the synaptic order of the connections between the cortical neuron and the LGN. Most neurons in layers 2 and 5, for example, do not receive monosynaptic input from the LGN but instead receive only polysynaptic input via other cortical neurons. If the suppression of activity in the cortical circuit is complete and includes the cortical interneurons mediating the geniculate input, then in these polysynaptic cells, the synaptic potentials evoked by visual stimulation should be completely suppressed by electrical stimulation. Because each polysynaptic cell receives convergent synaptic excitation from numerous other cortical cells, a demonstration of complete suppression of the visually evoked synaptic potentials in polysynaptic neurons would provide strong confirmation that electrical stimulation does indeed temporarily inactivate cortical neurons.

To identify polysynaptic neurons, we measured the latency of excitatory postsynaptic potentials (EPSPs) evoked by electrical stimulation of the LGN. If the latency was 2.3 ms or shorter, the cell was classified as receiving monosynaptic input from the LGN. If it was longer than 3 ms, the cell was classified as receiving polysynaptic input. Cells with a latency between 2.3 and 3 ms were discarded to avoid possible misclassification that could result from the small overlap in the latencies of the two populations (Ferster and Lindström, 1983).

The responses of a neuron lacking direct geniculate input are shown in Figure 4. The latency of the synaptic potentials evoked by the electrical stimulation of the

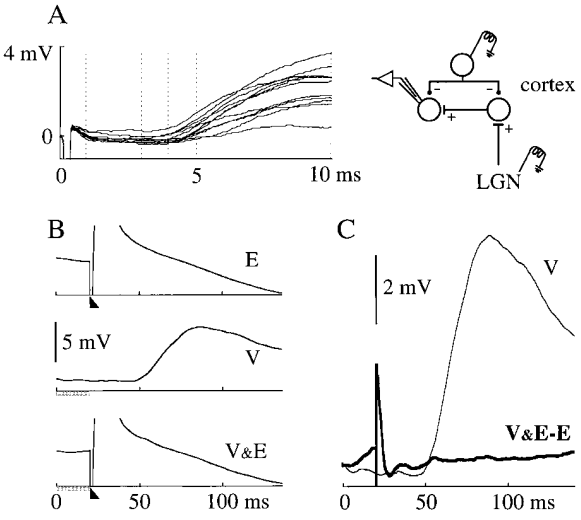

Figure 4. A Cell Lacking Monosynaptic Input from the LGN

(A) Electrical stimulation of the LGN evoked postsynaptic potentials in the cell with 3.8 ms latency.

(B) The averaged membrane potentials (n = 30 trials) to electrical stimulation of the cortex ("E"), visual stimulation ("V"), and visual and electrical stimulation combined ("V & E"). An arrowhead and a gray bar below each trace indicate the timing of the electrical and visual stimuli in turn.

(C) The response to electrical stimulation alone was subtracted from the response to combined visual and electrical stimulation to quantify the amount of visual input remaining during electrically evoked cortical suppression ("V & E − E"). The visual response was almost completely suppressed during electrically evoked cortical suppression in the cell.

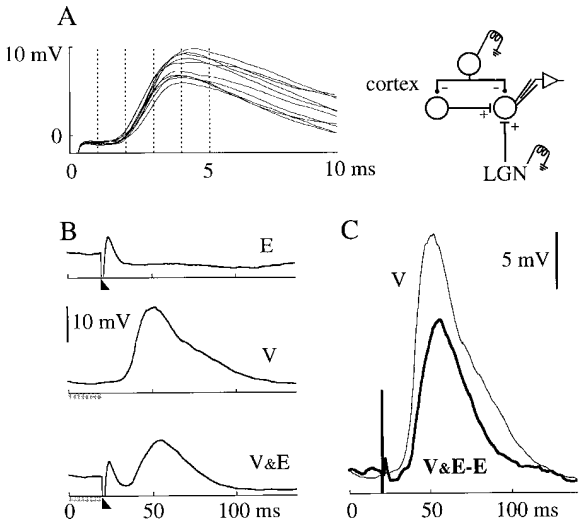

Figure 5. A Cell that Received Monosynaptic Input from the Thalamus

The layout of the figure is the same as in Figure 4.

(A) The latency of the EPSP evoked by the electrical stimulation of the LGN was 1.7 ms.

(B) The averaged intracellular responses (n = 20 trials) to visual stimulation ("V"), electrical stimulation ("E"), and visual and electrical stimulation combined ("V & E"). The electrical stimulus evoked a short-latency EPSP followed by an IPSP that hyperpolarized the membrane by 5 mV at the peak. The visual response was over 21 mV in amplitude, but was partially suppressed by the electrical stimulation.

(C) The subtraction of the electrical response from the response to combined visual and electrical stimulation ("V & E − E"), when compared to the response to visual stimulation alone ("V"), revealed the degree of the suppression to be 36%.

LGN was 3.8 ms (Figure 4A). This long latency indicates that the cell received only polysynaptic input from the LGN mediated through other cortical interneurons. Figure 4B shows the responses of the cell to electrical stimulation of the cortex (trace E), to visual stimulation (trace V), and to visual and electrical stimulation combined (traces V & E). The arrowhead and bar below each trace indicate the time of the electrical and visual stimuli. The electrical stimulation evoked early depolarization followed by long-lasting hyperpolarization, only a portion of which is contained in the trace. A 20 ms flashing sinusoidal grating with optimal orientation, spatial frequency, and spatial phase evoked a 7 mV response with 47 ms latency. But the visual response was clearly suppressed when the cortex was stimulated electrically 20 ms after the onset of the visual stimulus: traces E and V & E are almost identical.

To quantify the degree of suppression, we subtracted the response to electrical stimulation (E) from the response to combined visual and electrical stimulation (V & E). The result of the subtraction (V & E − E) should give an estimate of the visual component of the combined visual and electrical response (see Discussion). If, for example, the electrical stimulus completely suppressed the visual response of all of the cortical cells presynaptic to the recorded cell, then the response to combined electrical and visual stimulation would be no different from the response to electrical stimulation alone and the subtraction would yield a flat trace. Figure 4C shows the result of the subtraction (trace V & E − E) along with the visual response (trace V) for comparison. It appears that the electrical stimulation completely suppressed the visual response in this cell, as was the case for most of the cortical cells lacking monosynaptic geniculate input in our sample.

Cortical Neurons with Monosynaptic Excitation from the LGN

Having confirmed that the electrical stimulus suppresses a large fraction of the visually evoked cortical activity, we can now examine the effects of the electrical stimulus on those neurons that receive direct input from the LGN, i.e., monosynaptic neurons. Cortical neurons were classified as monosynaptic when the latency of EPSPs evoked by the geniculate stimulation was shorter than 2.3 ms. The cell in Figure 5, for example, had a latency of 1.7 ms (Figure 5A). Most monosynaptic cells had simple receptive fields, as did the cell in Figure 5. As a result, its response to the flashed grating was strongly dependent on spatial phase (thin traces in Figure 6). For subsequent analysis of the suppressive effects of cortical stimulation, only the response to the optimal phase was considered. The response of the cell to the briefly flashed grating at the optimal spatial phase started 30 ms after the onset of visual stimulus and was over 21 mV in amplitude (trace V in Figure 5B and 0° spatial phase trace in Figure 6). The electrical stimulus

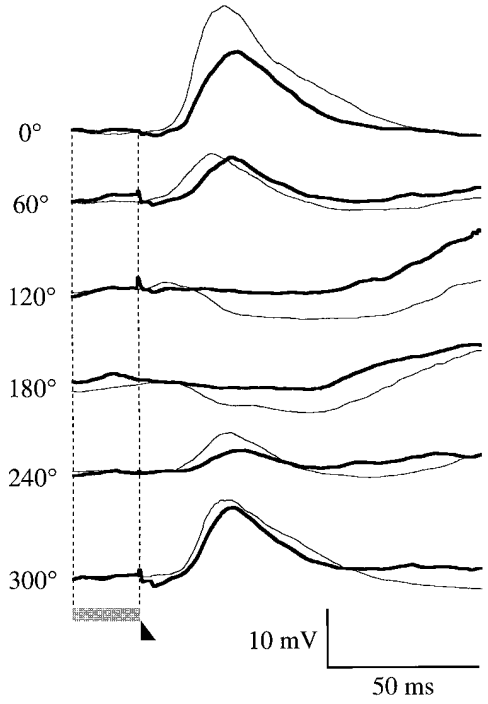

Figure 6. Averaged Responses (n = 20 Trials) of the Same Simple Cell as in Figure 5 to a Flashed Sinusoidal Grating of Optimal Orientation but Different Spatial Phases

The gray bar and arrowhead in the bottom of the figure indicate the timing of visual and electrical stimulation in turn. Spatial phase was optimal at 0°. At 180° spatial phase, the grating evoked a significant hyperpolarization (thin traces) in accordance with the push-pull model of inhibition in simple cells (Ferster, 1988). The same subtraction described earlier showed that the electrical stimulation reduced the amount of depolarization evoked by on-spatial phases and almost completely suppressed the hyperpolarization evoked by off-spatial phases (thick traces).

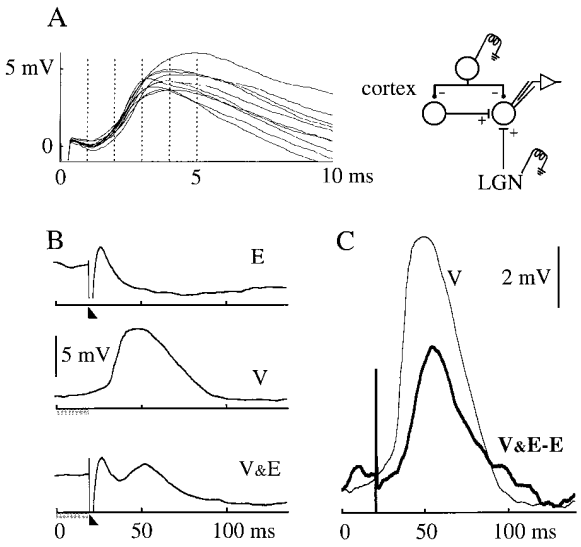

Figure 7. A Second Cell with Monosynaptic Input from the LGN

The layout of the figure is the same as in Figures 4 and 5.

(A) The synaptic latency from the LGN was 1.2 ms.

(B) The averaged intracellular responses (n = 20 trials) to visual stimulation ("V"), electrical stimulation ("E"), and visual and electrical stimulation combined ("V & E"). Electrical stimulation hyperpolarized the membrane by 3 mV at the peak. The visual response was 29 ms in latency and 8 mV in amplitude. The electrical stimulation partially suppressed the visual response.

(C) The visual response remaining during cortical inactivation induced by electrical stimulation ("V & E − E") was 50% of the normal visual response ("V").

reduced but did not completely suppress the visual response (traces V & E in Figure 5B). The same subtraction as in Figure 4 revealed that the electrical stimulation reduced the amplitude of the visual response by 36% (Figure 5C). The remaining 64% presumably originated from the geniculate activity.

A second cell with monosynaptic input from the LGN is shown in Figure 7. The latency of the response to the electrical stimulation of the LGN was 1.2 ms (Figure 7A). The visually evoked response of the cell was 8 mV in amplitude and 29 ms in latency (trace V in Figure 7B). Electrical stimulation reduced the visual response of the cell to 50% of normal (Figure 7C).

Effects of Cortical Suppression on Response Amplitude in the Sampled Population

Altogether, we recorded intracellularly from 39 cortical neurons (Figure 8). Synaptic order from the LGN was determined in each cell by the latency of EPSPs evoked by the geniculate electrical stimulation, as described earlier. Sixteen neurons were classified as receiving monosynaptic input from the LGN (closed circles) and 19 neurons as receiving only polysynaptic thalamic input via other cortical neurons (open circles). Four neurons with intermediate latency (open triangles in Figure 8A) were omitted from further consideration. The fraction of the visual response remaining during shock inactivation was calculated from the ratio of the amplitude of the subtracted response to the amplitude of the normal visual response (Figures 4, 5, and 7C). The percent remaining response is plotted against the latency of the synaptic potentials evoked by the geniculate stimulation in Figure 8A. In 16 of the 19 polysynaptic neurons (open circles), the visual response was completely suppressed by the electrical stimulation. Most small nonzero values (positive and negative) result from gradual changes over time in the response to electrical stimulation, which made minor distortions of the result of the subtraction procedure. A significant visually evoked synaptic potential was recorded during cortical suppression in only three cells. On average, the electrical stimulation reduced the visual response to 2%. This result, together with the multiunit extracellular recordings (Figure 2), clearly shows that the electrical stimulation of the cortex strongly suppresses the visually evoked responses of cortical cells.

In 16 neurons with monosynaptic input from the LGN (closed circles), however, cortical stimulation on average suppressed only 54% of the normal visual response. The visual response remaining after cortical stimulation, which we interpret as originating almost exclusively from the LGN, ranged from 12%–86%. One question that arises is the source of the large variability in the fraction of the visual response that remained during cortical inactivation. For example, is the geniculate input fixed in

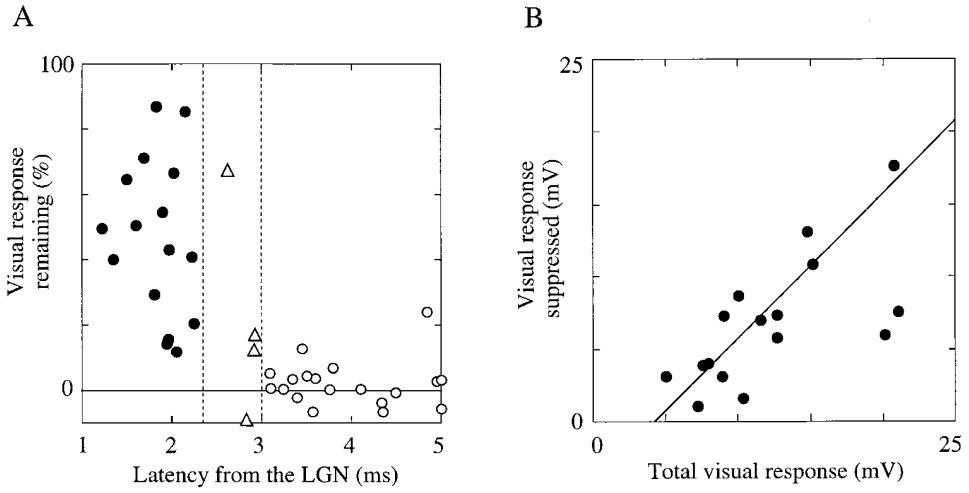

Figure 8. The Fraction of the Visually Evoked Response Remaining during Electrical Stimulation as a Function of the Geniculate-Evoked EPSP Latency, and the Amplitude of the Suppressed Component of the Visual Response as a Function of the Amplitude of the Total Visual Response

(A) The percentage of visual response remaining during cortical inactivation is plotted against the synaptic latency from the LGN for 39 cells in our sample. The latency of postsynaptic potentials evoked by the electrical stimulation of the LGN ranged from 1.2–5 ms. Sixteen cells with latency of 2.3 ms or less (closed circles) were classified as receiving monosynaptic input from the LGN. Nineteen cells with latency of 3 ms or more (open circles) were classified as receiving only polysynaptic input from the LGN through other cortical interneurons. Four cells with intermediate latency (open triangles) were discarded from the analysis. Visual responses of 19 neurons lacking direct geniculate input were much more strongly suppressed than those of 16 neurons with monosynaptic input from the LGN (2% and 46% remained on average). Most nonzero values for the neurons lacking direct geniculate input (positive and negative) result from gradual changes in the responses to electrical stimulation over time. In only three cells was a detectable synaptic potential evoked by the visual stimulus recorded during cortical suppression.

(B) The amplitude of the response component suppressed during cortical inactivation is plotted against the amplitude of the total visual response for neurons with monosynaptic input from the LGN. The slope of the regression line is 1.01 with an x intercept of 4.5 mV (omitting the two outliers with 20 mV total response).

size while the cortical contribution varies? The graph in Figure 8B suggests a tendency in this direction: when the size of the suppressed component of the response is plotted against the size of the total visual response, except for the two outliers at 20 mV total response, the monosynaptic cells fall approximately along a line of slope 1, which intercepts the x-axis at about 4.5 mV. In other words, there is a geniculate input that ranges from 2–8 mV in each cell, with a more variable component of between 1 and 18 mV originating from within the cortex.

In four neurons with direct geniculate input, the visual stimulus evoked spikes during the electrically evoked cortical suppression. The cell in Figure 5, for example, fired in response to the flashing grating after the electrical stimulation (spikes were removed prior to averaging using a median filter; see Experimental Procedures). We do not think that these spikes indicate that the shock inactivation was incomplete. Since little visually evoked activity was observed after the electrical stimulation in extracellular control experiments, and since very few visually evoked EPSPs were observed in polysynaptic neurons after the cortical shock, these spikes observed during cortical inactivation may have occurred as a result of changes in the electrical properties of the recorded cells caused by the patch recording.

Orientation of the Geniculate Component of the Visual Response

The orientation tuning of the geniculate input was determined using flashing gratings in nine simple neurons that received monosynaptic input from the LGN. The thin traces of Figure 9 show the responses of two cells to flashing gratings of three or four different orientations. Only the response to the optimal spatial phase at each orientation is presented. The stimulus orientation is indicated by the grating below each trace, with the optimal orientation at the far left. As before, the response to electrical stimulation was subtracted from the response to visual and electrical stimulation combined (thick traces). For the cell in Figure 9A, the visual response remaining during cortical inhibition was 20%, 29%, and 27% of the total visual response. For the cell in Figure 9B, it was 64%, 68%, 60%, and 65%. If cortical amplification were to sharpen the orientation tuning of the geniculate input, this percentage would be significantly smaller at the optimal orientation, reflecting the relatively larger contribution of cortical amplification at optimal orientation. In both cases, however, the suppression was similar at each orientation tested.

Orientation tuning curves were constructed from each set of thick and thin traces for all nine simple cells tested, along with a tuning curve obtained from the F1 component of the responses to drifting gratings of 12 different orientations (Figure 10). The peaks of each of the three orientation tuning curves were normalized to 1. In some cases, the orientation tuning measured with flashing gratings (open circles) was a little broader than the tuning curve measured with drifting gratings (thin line), in agreement with previous comparisons of orientation tuning made with flashing and drifting bars (Henry and

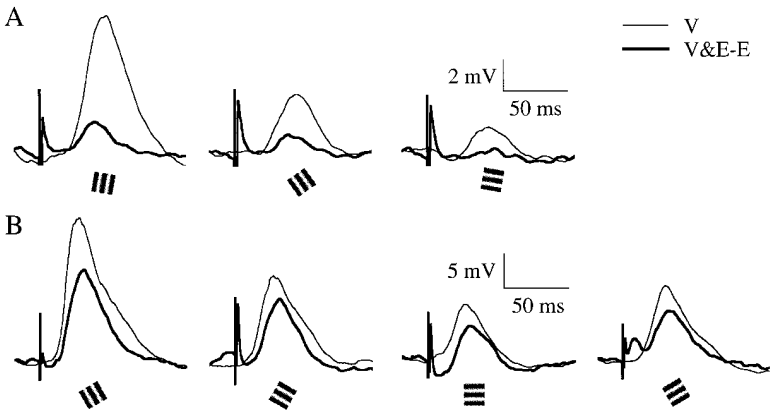

Figure 9. Orientation Tuning of the Remaining Visual Response during Cortical Suppression

(A) Averaged normal (thin traces) and cortically suppressed (thick traces) responses (n = 30 trials) evoked in a single cell by stimuli of three different orientations. The test orientations are indicated by the small grating below each trace. The optimal orientation is to the left and the orthogonal orientation is to the right. Only the response to the optimal spatial phase is shown for each orientation. The percent of the visual response remaining during cortical suppression was 20%, 29%, and 27% from left to right.

(B) Averaged responses (n = 20 trials) at four different orientations for a second simple cell. The proportion of the visual response remaining during cortical suppression was 64%, 68%, 60%, and 65% from left to right.

Dreher, 1974; Wörgötter et al., 1990). The orientation tuning of the visual response measured during cortical inactivation (closed circles) is broadened somewhat compared with that of the total visual response (open circles) in the second and the ninth neurons, and sharpened slightly in the sixth and the eigth neurons, but overall no consistent trend is apparent.

To compare quantitatively the orientation selectivity of the visual input remaining during cortical inactivation with the orientation selectivity of the total visual input, the data points from Figure 10 were fitted to a Gaussian curve. The tuning width was then measured as half-width at half-height of the fitted curve. The orientation tuning width of the remaining visual input is plotted against that of the total visual input for each simple cell in Figure 11A. The average tuning width was 31° ± 8° for the total visual input and 30° ± 8° for the visual input remaining during cortical inactivation.

The above results would indicate that the cortical circuitry does not significantly sharpen orientation tuning. If this is the case, then one might expect that the sharpness of orientation tuning would not be determined by the percentage of the visual response contributed by cortical inputs. In Figure 11B, therefore, we have plotted the widths of the orientation tuning curves against the percent of the visual response suppressed by cortical inactivation. The figure shows little correlation between these two parameters.

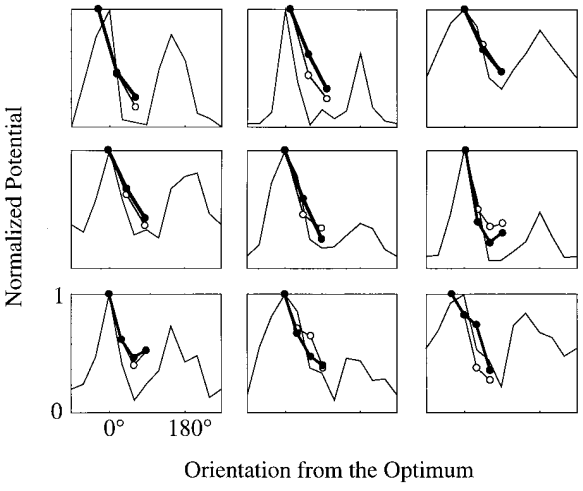

Figure 10. Orientation Tuning Curves for Nine Simple Cells with Monosynaptic Input from the LGN

The orientation tuning measured from the F1 component of the response to optimal drifting gratings of 12 different orientations is drawn in the background. The orientation tuning curves measured with flashing gratings of three or four different orientations are indicated by open circles. Orientation tuning curves measured with flashing gratings during electrically evoked cortical suppression are indicated by closed circles. The three orientation tuning curves for each neuron are normalized to 1. The second and the seventh cells from top left to bottom right are the same cells in Figures 9A and 9B.

Discussion

Two independent methods of cortical inactivation, cooling (Ferster et al., 1996) and now electrical stimulation, indicate that the thalamic input to cortical simple cells is well tuned for orientation. The current experiment shows, in addition, that the thalamic input comprises a significant fraction of the total, 46% on average, with the remaining presumably originating from other cortical neurons. One of the immediate questions that our experiment raises is how effective the electrical stimulus was in suppressing all synaptic inputs to simple cells that arise from sources other than the LGN. The most prominent source of synaptic input is other cortical cells within the same column as the recorded cell. Control experiments showed that the electrical stimulus almost completely suppressed the visual discharges of cortical neurons in all layers within a radius of ~700 μm. Another source of nongeniculate input is cortical neurons outside of the inactivated region. Neurons in the upper layers, for example, receive long range axonal connections from nearby columns with similar orientation tuning (Ts'o et al., 1986; Gilbert and Wiesel, 1989; Weliky et al., 1995). Axons from the neurons in layers 5 and 6 project as far as 5–6 mm within area 17 (Gilbert and Wiesel, 1979, 1983). We attempted to confine our visual stimuli to the classical receptive field of the recorded

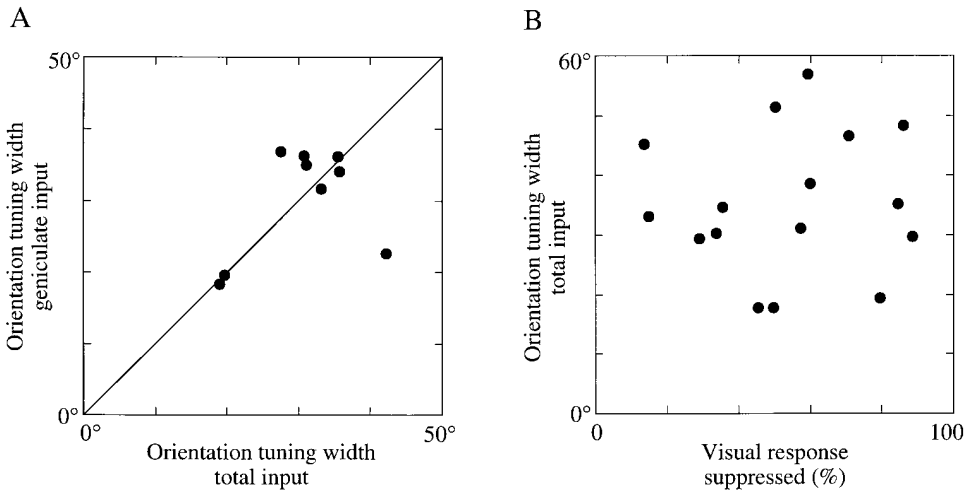

Figure 11. Changes in Orientation Tuning Width Caused by Cortical Stimulation, and the Relation between Tuning Width and the Size of the Cortical Component of the Visual Response

(A) Orientation tuning width of the visual input remaining during cortical suppression plotted against the orientation tuning width of the total visual input. The data points from total visual response and the remaining visual response in Figure 10 were fit to a Gaussian curve, and the tuning width is measured as half-width at half-height of the Gaussian.

(B) The orientation tuning width plotted against the percent of the visual response suppressed by cortical inactivation in 16 cells with monosynaptic input from the LGN. The orientation tuning width was measured as the half-width at half-height of a Gaussian curve fit to the orientation tuning curve obtained from the responses to drifting optimal sinusoidal gratings.

cells in order to minimize visual activation of neurons beyond the electrically suppressed region.

Retinotopically organized projections from other cortical areas, for example area 18 or area 17 of the opposite hemisphere, might have contributed to the visual response remaining during shock inactivation. The best evidence against this possibility, however, is the control provided by the cells in our sample that received input only from other cortical neurons. If there were substantial nongeniculate inputs, either from other cortical areas or from within area 17, that were activated by the visual stimulus but were not inactivated by the electrical stimulus, then the visually evoked responses of these polysynaptic cells should remain after electrical stimulation. This was not the case in most of the polysynaptic cells in our sample. Either these inputs were not strongly activated by the brief visual stimulus or the suppressive effects of the electrical stimulus spread to these regions through ortho- or antidromic connections.

Overall, we can estimate the size of the remaining nongeniculate inputs from the extracellular and intracellular control experiments. In Figure 3, the average remaining visual activity during shock inactivation in the 24 extracellular penetrations with electrode separations of less than 700 μm is 2%–3% of the normal. The average remaining synaptic activity during shock inactivation in 19 cells with only polysynaptic input from the LGN was also 2%–3%. It is clear from these controls that activity of the cortical circuit is severely disrupted by electrical stimulation of the cortex.

Even assuming that the entire visually evoked response recorded in combination with electrical stimulation did actually originate from the LGN, there are still several factors that might have influenced our estimates of the proportion of the total visual response arising from the LGN: changes in input resistance, changes in driving force, anesthesia-induced cortical depression, and inhibition in the total visual input.

First, the electrical stimulus evokes an abnormally strong inhibition that is peaking simultaneously with the visual response. If this inhibition generates a large reduction in the input resistance, the assumption of linear summation between visual and electrical responses implicit in our subtraction procedure would be invalid, and an underestimation of the size of the geniculate input would result. Alternatively, the electrical stimulus could suppress the spontaneous activity of neighboring cortical cells. The resulting withdrawal of spontaneous synaptic activity would increase the input resistance of the cell and lead us to overestimate the proportion of the thalamic input contributing to the total visual response. Experimental evidence favors the first possibility: in vivo estimates of the drop in input resistance during the peak of electrically evoked inhibition in cortical neurons range from 16% (Douglas and Martin, 1991) to 30% (Dreifuss et al., 1969). Electrically evoked shunting inhibition, however, is unlikely to generate the relationship between the size of the visual response and the size of the cortical component of the visual response that is seen in Figure 8B.

Second, the driving force for visually evoked EPSPs is increased by the hyperpolarization induced by the electrical stimulation. This increase in driving force for EPSPs would result in an overestimation of the size of the geniculate input. The membrane potential of 16 monosynaptic cells was hyperpolarized by an average of 5 mV at the peak of electrically evoked IPSPs, which would lead to a 10% increase in driving force on EPSCs and therefore a 10% increase in the amplitude of EPSPs.

Third, the responses of cortical neurons to the visual

stimulus might already have been weaker than normal prior to the application of the electrical stimulus—for example, from anesthesia. This would result in an overestimation of the proportion of the geniculate input in the normal visual responses.

Fourth, the total visual response might contain superimposed EPSPs and IPSPs, though clearly the former are dominant. If this is true, then the amplitude of the total visual response is less than the visually evoked excitatory input. This would lead us to overestimate the proportion of the total excitatory input that arises from the LGN. At least one significant inhibitory input, push-pull inhibition (Ferster, 1986), is unlikely to have been activated by the flashing grating: on inhibition in the off subregion and off inhibition in the on subregion is kept to a minimum, since the grating is flashed at the optimal phase. There could, however, be other inhibitory inputs with different receptive field properties that could have been activated by the visual stimulus. We have no way of estimating their strength from the current experiments.

Because of these four factors (and perhaps others), there is some uncertainty in the exact proportion of the visual response that arises from the LGN. Even so, we speculate that these factors do not change our estimate by a large proportion. There have been two measurements of physiological strength of geniculate input to the cortex based on extracellular recording. Tanaka (1983) and Reid and Alonso (1995) studied the connection strength between a geniculate afferent and a cortical simple neuron using cross-correlation analysis. In these studies, the spike activity of a single geniculate afferent appeared to account for up to 10% (Reid and Alonso, 1995) or more (Tanaka, 1983) of the spike activity of a postsynaptic simple cell. Given that a number of geniculate neurons converge on a single simple cell, the total amount of activity accounted for by all presynaptic geniculate afferents combined—the number that we have measured in the current experiment—is likely to be much higher than 10%.

In addition to the above cross-correlation studies, Ferster et al. (1996) estimated the geniculate contribution based on an experiment in which the cortical circuit was inactivated by cooling, rather than by electrical stimulation. Because of the direct effect of cooling on the geniculocortical synapses, however, the estimate was necessarily indirect. These authors assumed that cooling reduced the size of the geniculate component of visual response by the same factor as the cooling reduced the size of the geniculate component of electrical response. Under this assumption, they concluded that the input from the LGN to simple cells comprises 37% of the total visual input on average.

Our measurements of the percentage of the geniculate input from the current experiment (46%) and the previous estimate from cortical cooling (37%) are much larger than what was expected from many anatomical studies (Peters and Payne, 1993; Ahmed et al., 1994). Either these anatomical studies have underestimated the size of the geniculate projection (see LeVay and Gilbert, 1976) or the physiological strength of a synaptic input does not necessarily reflect its strength defined anatomically. Different types of excitatory synapses can give rise to differing excitatory inputs for a number of reasons. Geniculate terminals are larger than cortical terminals (Ahmed et al., 1994) and may have more active transmitter release sites. Geniculate neurons might also fire at higher frequencies than cortical neurons. Synapses of cortical origin are distributed differently within the dendritic tree than synapses of geniculate origin (Ahmed et al., 1994). Lastly, synchronization of activity in the presynaptic geniculate population could boost the efficacy with which they elicit action potentials in the postsynaptic cortical neuron (Alonso et al., 1996). If, on average, the LGN provides simple cells with one-third to one-half of their visually evoked excitatory input, then the cortical circuit appears to amplify the geniculate input by 2- to 3-fold. This amplification, however, is smaller than the 10-fold or more originally suggested by Douglas and Martin (1991) or by Somers et al. (1995). More importantly, this amplification appears not to sharpen the orientation selectivity of simple cells, since the amplification factor does not vary systematically with orientation in a cell (Figure 10). Nor does the amount of visual input generated in the cortical circuit correlate with the sharpness of the orientation tuning (Figure 11B). The cortical input, therefore, seems to have nearly the same orientation tuning as the geniculate input.

One mechanism that does appear to sharpen orientation tuning is the spike threshold. The orientation tuning width of the F1 component of the synaptic potentials measured by drifting gratings was $35° \pm 10°$ on average for 14 simple cells in our sample. Twelve of them spiked during the recording period. The average tuning width calculated from firing rates of 12 simple cells was $20° \pm 3°$, well within the range previously observed (Campbell et al., 1968; Rose and Blakemore, 1974; Albus, 1975; Hammond and Andrews, 1978; Heggelund and Albus, 1978; Gizzi et al., 1990). This tuning width from firing rate was substantially sharper than that calculated from synaptic potentials of the same cells ($34° \pm 10°$) (see also Carandini and Ferster, 1998, Invest. Ophthalmol. Vis. Sci., abstract). It appears, then, that the spike threshold serves to sharpen orientation selectivity in the same way that it sharpens direction selectivity (Jagadeesh et al., 1993, 1997). The spatial organization of the thalamic input to simple cells into rows (Chapman et al., 1991; Reid and Alonso, 1995) may be the first step in establishing orientation selectivity in simple cells. Thalamic input may also provide a large portion of the excitatory input into simple cells. But several properties of cortical simple cells remain unaccounted for. Foremost is the contrast invariance of orientation selectivity (Sclar and Freeman, 1982; Skottun et al., 1987). If the thalamic input followed by a threshold were the only mechanisms of orientation selectivity, then an increase in contrast of the visual stimulus, which increases the responses of thalamic relay cells, should increase the width of orientation tuning. For example, at low contrasts a stimulus oriented a few degrees from optimal might evoke a subthreshold synaptic potential, while at high contrasts it would evoke a suprathreshold synaptic potential. This does not occur in cortical cells. Orientation selectivity, at least measured with drifting gratings, is more or less invariant with contrast. (Contrast dependence of orientation tuning has not been reported for flashing gratings.) Perhaps the cortical portion of the synaptic inputs,

either excitatory or inhibitory, accounts for this invariance, as proposed in several models of cortical function (Carandini and Heeger, 1994; Somers et al., 1995; Troyer et al., 1998). Our results pertain only to simple cells with monosynaptic input from the LGN. It is possible that cortical amplification contributes significantly to the orientation tuning of other neurons in the cortex, such as complex cells that receive input only from other cortical neurons. Ringach et al. (1997), for example, have found that orientation selectivity in complex cells of the macaque evolve over time in a way that suggests the contribution of intracortical connections.

Experiments on the thalamic input to cortical cells by Chapman et al. (1991) and by Reid and Alonso (1995) give strong support for one element of Hubel and Wiesel's original model, namely that the elongated receptive fields of simple cells are shaped by the spatial arrangement of receptive fields of on- and off-centered thalamic afferents. The evidence presented here, together with previous experiments using cooling to suppress cortical activity (Ferster et al., 1996), supports a second critical feature of Hubel and Wiesel's model, that this spatial arrangement of thalamic input alone is strong and well tuned for orientation.

Experimental Procedures

Animal Preparation

Adult cats weighing 2–3 kg were used for acute experiments. The cats were initially anesthetized by intramuscular injection of ketamine hydrochloride (30 mg/kg) and acepromazine maleate (0.3 mg/kg). A cannula was inserted into a femoral vein, and sodium thiopental was infused to maintain the anesthesia for the rest of the experiment (1–2 mg/kg/hr). A cannula was inserted into the second femoral vein for later infusion of the muscle relaxant pancronium bromide to minimize motion of the eyes (0.2 mg/kg initial dose, 0.2 mg/kg/hr maintenance dose). A tracheal cannula was inserted for artificial respiration after the infusion of muscle relaxant. The cat was then mounted in a stereotaxic head holder and its cervical vertebrae suspended from a clamp. The nictitating membranes of the eyes were retracted by phenylephrine hydrochloride (10%). The pupils were dilated by the application of atropine sulfate (1%). A pair of contact lenses with 4 mm artificial pupils, together with convex auxiliary lenses, focused the eyes onto an oscilloscope screen 40 cm in front of the cat. After paralysis, respiration rate was adjusted to maintain expired CO_2 at 3.5%–4%. To minimize movement of the brain caused by respiration, a bilateral pneumothorax was performed. Body temperature was maintained at 38.3°C. To ensure that the cat was properly anesthetized, muscle relaxant was not infused until the major surgery was finished. After paralysis, depth of anesthesia was assessed by examining the heart rate and electroencephalogram (EEG), which was recorded from two cranial screws. At the end of the experiment, the cat was killed with an intravenously applied overdose of pentothal.

Visual Stimulation

An optimal sinusoidal grating (64% contrast, 20 cd/m^2 mean luminance) was flashed for 20 ms on an oscilloscope screen (Tektronics 608). For extracellular experiments, optimal orientation and spatial frequency were determined by listening to the responses on an audio monitor. For intracellular experiments, optimal orientation and spatial frequency were quantitatively determined from computer-controlled visual stimuli. Responses of simple cells are dependent on the spatial phase of the grating (Movshon et al., 1978), so flashing gratings were presented at four or six different spatial phases. Only the responses to the optimal phase were chosen for analysis. The visual stimuli barely covered the classical receptive field to avoid stimulating cortical areas far from the recorded cell. All visual stimuli were presented monocularly to the dominant eye at a frequency of 1 Hz or less.

Electrical Stimulation

Cortical and geniculate stimulating electrodes were fashioned from lacquer-coated tungsten wire etched to a point with 100–150 μm (cortex) or 250 μm (LGN) of the tip left exposed. Stimuli were 200 μs in duration, and were electrode negative. The stimulating electrode in the LGN was placed at an area representing the region of the visual field in which the receptive fields of the recorded cortical neurons were located (usually 2°–3° below and lateral to the area centralis). Geniculate stimuli were 1 mA in amplitude. Cortical stimuli varied in strength (see Results) and were delivered at a frequency of 1 Hz or less.

Recording

Multiunit recordings were made with etched tungsten microelectrodes (Hubel, 1957). To identify the laminar location of recording sites in the track, an electrolytic lesion was made by current injection (about 4 μA for 5–10 s) at the end of each track. After the perfusion, the brain tissue was sectioned and processed with a Nissl stain. Intracellular membrane potential was recorded with the whole-cell patch method in current-clamp mode (Ferster and Jagadeesh, 1992). The pipettes were filled with internal solution containing (in mM): 130 K^+-gluconate, 2 $MgCl_2$, 5 HEPES, 1.1 EGTA, 0.1 $CaCl_2$, and 4 Na_2ATP that was buffered to pH 7.3 and adjusted to 285 mOsm. Electrode resistance ranged from 8–18 MΩ. Seal resistances were >1 GΩ. Resting potentials averaged -55 ± 8 mV. No systematic difference in the resting membrane potentials was observed among the different experimental conditions. Intracellular recordings were made in area 17/18 (lateral 1 to lateral 3 and AP-0 to AP-9 in Horsely-Clark coordinates). Once the recording and stimulating electrodes were in place, warm agar (3% in normal saline) was placed in the craniotomy to prevent drying of the cortex and to reduce respiratory and cardiovascular pulsations.

Intracellular potentials were low pass filtered and digitized at 15 kHz for storage and analysis by computer. Prior to averaging and measuring the amplitudes of visually and electrically evoked potentials, each record was median filtered to remove action potentials (Jagadeesh et al., 1997).

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