Striate cortex increases contrast gain of macaque LGN neurons

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Abstract
Recurrent projections comprise a universal feature of cerebral organization. Here, we show that the corticofugal projections from the striate cortex (V1) to the lateral geniculate nucleus (LGN) robustly and multiplicatively enhance the responses of parvocellular neurons, stimulated by gratings restricted to the classical receptive field and modulated in luminance, by over two-fold in a contrast-independent manner at all but the lowest contrasts. In the equiluminant plane, wherein stimuli are modulated in chromaticity with luminance held constant, such enhancement is strongly contrast dependent. These projections also robustly enhance the responses of magnocellular neurons but contrast independently only at high contrasts. Thus, these results have broad functional significance at both network and neuronal levels by providing the experimental basis and quantitative constraints for a wide range of models on recurrent projections and the control of contrast gain.

Keywords: Striate cortex, Contrast gain, LGN, Macaque monkey, Vision

Introduction
Recurrent projections comprise a universal and anatomically prominent feature of cerebral organization in all sensory and motor systems (Rockland & Pandya, 1978; Pandya & Yeterian, 1985; Fellem & Van Essen, 1991; Salin & Bullier, 1995). Even so, and despite strong evidence for specialized functions of corticofugal pathways in the feline visual system for selectively facilitating the transmission of signals from binocularly viewed objects that are near the fixation plane (Schmelz & Singer, 1977; Tsumoto et al., 1978), for enhancing length tuning of lateral geniculate nucleus (LGN) neurons (Murphy & Sillito, 1987), and for improving the detection of focal orientation discontinuities (Sillito et al., 1995), an understanding of their general function and significance has remained controversial and a matter of broad current interest. Indeed, the effects of reversible inactivation of V1 on LGN function have been so variable with respect to the resultant strength and consistency of residual evoked responses in the LGN (Kalil & Chase, 1970; Baker & Malpeli, 1977) that Crick and Koch (1998) upon reviewing the literature concluded that the visual cortex has only weak excitatory and modulatory effects on the receptive-field properties of geniculate cells.

Others, applying principles of predictive coding, have suggested that some feedback projections may suppress predictable features of the input so that only the unexpected residua are projected forward (Mumford, 1992; Rao & Ballard, 1999). In discussing the latter predictive model with applicability to both corticofugal and corticocortical recurrent projections. Koch and Poggio (1999) note that “it will be critical to unravel the precise function of corticocortical feedback projections and their biophysical model of operation, whether linearly subtractive as in Rao and Ballard’s model or modulatory multiplicative (or divisive).” Thus, even some of the most basic issues concerning the functional role of the corticofugal visual system in the primate remain unresolved.

In our attempt to determine the most general function of the corticofugal pathways from the striate cortex, V1, to the LGN, we first determined the contrast–response functions for parvocellular and magnocellular neurons and then reversibly inactivated V1 by cooling. The corticofugal pathways originate in layer 6 of V1 (Fitzpatrick et al., 1994). Based upon the similar results by others studying corticocortical feedback under sufentanil anesthesia (Nothdurft et al., 1999) and in awake animals (Knierim & Van Essen, 1992; see also Discussion), we assume that the corticofugal pathways are also largely normally active during both the pre- and post-cooling control periods and are largely inactivated during cooling of V1. Thus, we infer that the corticofugal pathways normally produce changes in activity that are the converse to those observed during cooling of V1.

We have attempted to circumvent some of the possibly confounding effects of stimulus design in previous studies. First, we predetermine the optimal stimulus parameters for stimuli modulated in luminance or chromaticity. We then explore the full range of Michaelson contrasts to calculate contrast–response functions—a fundamental neuronal response characteristic—using interleaved
stims to minimize the distorting effects of random changes in cortical excitability. In contradistinction to previous studies in the macaque (Hull, 1968; Marrocco & McClurkin, 1985), we then limit these stimuli to the classical receptive field (center and surround) to avoid effects induced by stimulation of the extended surround. This distinction may be important because the effects of stimulation of the extended or nonclassical surround of LGN neurons on their activity are largely suppressive and are mediated at least in part by corticofugal activation (Marrocco et al., 1982; Marrocco & McClurkin, 1985). This is not to minimize the role of the suppressive surround and its partial control by cortical feedback in the overall function of corticofugal pathways; rather, we believe that our present studies of the corticofugal projections subserving the classical center and surround comprise an essential first step before the subsequent issue of the extended surround can be addressed.

Methods

Anesthesia and analgesia

Six macaque monkeys (Macaca fascicularis) were maintained under sufentanil anesthesia with arterial pulse and blood pressure continuously monitored. Animal care was in accordance with institutional guidelines. The dose of sufenta was adjusted, generally within the 2–8 μg/kg/h range, to eliminate pain as judged by precluding abnormal increases in pulse or blood pressure either spontaneously or in response to tail pinch. The animals were paralyzed with Pavulon 0.2 mg/kg/h so as to maintain retinal fixation and ventilated so as to keep the exhaled CO₂ close to 4%.

Optics

After inducing cycloplegia of each eye by topical application of drops of ophthalmic atropine, we utilized slit retinoscopy to select contact lenses that would focus each eye on the monitor set at a distance of 1 m. Additional trial lenses were used when necessary to adjust the refraction to within 0.25 diopters. When we compared refractive corrections based on retinoscopy with those obtained by optimizing the contrast–response function of individual LGN neurons to sine-wave gratings of high spatial frequency, we obtained comparable results. The positions of the optic discs and foveae were back-projected using a reversible ophthalmoscope and mapped.

Monitor characteristics

Stimuli were displayed on a 17-inch color monitor (EZIO XT-C7S) with D65 white point (CIE standard) and with a spatial resolution of 640 by 480 pixels and a refresh rate of 160 Hz. A Minolta CL-100 chroma meter was used to measure the tristimulus values and intensity response of the R, G, and B phosphors. Monitor gamma was corrected using lookup tables.

The unit vectors along each dimension in color space were made similar to those used by Lennie et al. (1990). Unit modulation along the luminance axis produced a Michaelson contrast of 1.0. Along the constant RG axis unit modulation produced a contrast of 0.84 to the B cones with no contrast to other cones. Along the constant B axis unit modulation produced a contrast of 0.023 to the R cones, a contrast of 0.045 to the G cones and no modulation to the B cones.

Reversible inactivation of V1 by cooling

We used a silver cooling plate of 17 × 18 mm attached to a Peltier device to transdurally cool and subsequently rewarm the dorsal surface of the macaque striate cortex. A 2-mm-diameter hole in the center of the plate permitted us to insert a microelectrode through the dura and advance it to reach the layer 6–white matter interface which was recognized by the depth below which we ceased recording from cortical neurons. We then withdrew the electrode until we once again recorded from cortical cells in the functionally identified deepest cortical layer. Using a thermostor at the surface of the plate, we could monitor temperatures necessary to inactivate activity in layer 6 in response to a drifting bar or grating. Effective surface temperatures to inactivate the deep layers ranged from 9°C to 12°C. The region of V1 cooled by our probe included a sector of the inferior visual field out to about 5 deg along both vertical and horizontal meridia exclusive of the more laterally located central 1–2 deg. Consequently, we searched for retinotopically corresponding recording sites within the LGN.

Confirming previous results (Hull, 1968; Kalil & Chase, 1970; Baker & Malpeli, 1977; Marrocco & McClurkin, 1985), we found no effects on the activity of LGN neurons unless such neurons were retinotopically related to the region of V1 that was cooled. Moreover, Hull (1968) and Kalil and Chase (1970) have already confirmed that cooling of V1 does not alter LGN temperature. The latter group also confirmed that cortical cooling did not produce either local vascular changes within the LGN or changes in systemic blood pressures. Thus, they conclude that local cooling of V1 does not produce any significant nonspecific effects in the LGN.

Moreover, we carried out controls on the viability of activity in the superficial layers of V1 in order to see if such activity returned to baseline after a single cooling cycle. We selected superficial cells for this test because these neurons are physically closest to the cooling probe and thus likely to be subjected to the most extreme effects of cooling. Responses of superficial cells in V1, tested for spatial-frequency selectivity, ceased during cooling and spatial-frequency selectivity curves subsequently returned to baseline during recovery. These studies also showed that although the action potentials and the hyperpolarizing afterpotentials slowed progressively during cooling, they returned to control levels during recovery. This suggests that cooling of V1 to temperatures such as we have employed for relatively short periods of 3–6 min does not necessarily produce irreversible damage to the striate cortex—at least as long as enough time is allowed between successive coolings for recovery. Even so, we typically carried out only four to five cooling cycles in a given hemisphere before switching to the other side.

Identification of LGN neurons

We initially searched for the parafoveal representation (i.e. central 2–5 deg) of the contralateral inferior visual field of the LGN studied so that we could selectively inactivate the retinotopically corresponding exposed surface of V1. We directed a tungsten microelectrode vertically through the cortex towards the LGN at coordinates 11 mm lateral to the midline and 3 mm posterior to the central sulcus (R. Shapley, personal communication). Along the way to the LGN, we encountered neurons with very large binocularly driven receptive fields and with response properties typical of those of cells of the perigeniculate nucleus (Funke & Eysel, 1998) at depths of 18–20 mm below the cortical surface.
before the microelectrode entered the upper layers of the LGN wherein response characteristics changed abruptly.

The first such neurons that we encountered had ON-Center well-localized receptive fields, exhibited pronounced chromatic opponency in three-dimensional (3D) color space (Derrington et al., 1984) and were selectively driven by the contralateral eye. With further advance of the microelectrode, we encountered ON-Center chromatically opponent cells driven by the ipsilateral eye. With still deeper penetration of the microelectrode, we recorded in the anticipated sequence from the two predominantly OFF-center parvocellular layers before the microelectrode reached the two magnocellular layers. When we did not reach populations of LGN cells in retinotopic correspondence to cells on the exposed surface of V1, we re-positioned the microelectrode in accordance with the topographic mapping of the macaque LGN by Malpeli and Baker (1975). In all studies, the ineffective eye was covered during stimulation of the effective eye.

In some experiments, we initially studied parvocellular neurons. In others, we first sought out and studied magnocellular neurons so as to even up the numbers of such cells studied and to eliminate any bias that magnocellular neurons might otherwise be selective studied late in the course of the experiments and only after several cooling cycles of the striate cortex. Thus, differences in corticofugal effects on these cell types reflect genuine functional differences which are not related to the order in which cells were studied.

At the end of each experiment, the animal was euthanized by intravenous injection of sodium pentobarbital 100 mg/kg and the brain was fixed in 10% formalin. Tracts through the LGN were confirmed histologically in the first three experiments. Thereafter, we relied on functional identification. We chose not to make electrolytic lesions within the main body of the LGN because such lesions might destroy corticofugal fibers projecting to deeper LGN cells that we might wish to study.

**Determination of chromatic opponency**

Responses of LGN cells to a set of gratings spaced 45 deg apart in the three principal planes in the color space were fit to a model that assumes linear summation of cone signals by LGN cells. The direction of the vector yielding maximum response was used to characterize the chromatic sensitivity of the cell. Following Lennie et al. (1990), we use $\theta$ to denote the elevation above the equiluminant plane and $\phi$ to denote the azimuth in the equiluminant plane with $\phi = \theta$ along the constant B axis.

**Functional identification of LGN neurons**

Magnocellular neurons can be distinguished from parvocellular neurons by their poor sensitivity to modulation in the equiluminant plane. In this study, a cell was classified as color sensitive if the elevation of its maximum response was less than 60 deg. Examination of the LGN data presented by Derrington et al. (1984) shows that no magnocellular cells in their sample would be classified as color sensitive using this criterion. Color-sensitive cells were tentatively identified as parvocellular neurons. Noncolor-selective neurons with low contrast sensitivity (i.e. with thresholds at contrasts of close to 0.03) were tentatively identified as magnocellular neurons (Derrington & Lennie, 1984; Kaplan & Shapley, 1986). These tentative identifications of cell types were accepted only when they correlated well with the laminar localization of cell types predicted from the expected alternation of eye preferences as the microelectrode vertically traversed the LGN.

**Selection of stimulus parameters**

The approximate extent of the diameter of the classical center and surround of each receptive field was calculated using a difference-of-Gaussian model to best fit the spatial-frequency selectivity curve. The contrast–response functions for both magnocellular and parvocellular neurons were then tested with drifting sine-wave gratings modulated in luminance over a range of contrasts at a temporal frequency of generally 8 Hz (range 4–12 Hz) over the predetermined classical center and surround at a spatial frequency close to the highest spatial frequency before responses began to fall off on the high spatial frequency side. Magnocellular neurons were studied at spatial frequencies from 0.5–2 cycles/deg with a median value of 0.5 cycle/deg and parvocellular neurons were studied at spatial frequencies of 0.25–8 cycles/deg with a median value of 0.5 cycle/deg. Aperture widths for magnocellular neurons ranged from 1–4 deg with a median value of 2 deg; aperture widths for parvocellular neurons also ranged from 1–4 deg but with a median value of 1.5 deg.

**Results**

Contrast–response functions for 25 LGN neurons on which we were able to complete the full cycle of tests were determined for drifting sine-wave gratings modulated in luminance before, during, and after reversible cooling of the ipsilateral striate cortex. In addition, we were also able to hold a subset of five parvocellular neurons long enough after the luminance studies were completed to carry out a second cooling cycle while testing contrast–response functions using chromatically opponent gratings of very low spatial frequency modulated along the neuron’s preferred azimuth in the equiluminant plane (Derrington et al., 1984; Lennie et al., 1990). In almost all cases, the contrast gain, which we define as the amplitude of the first harmonic of a cell’s response to drifting gratings, divided by contrast, was substantially reduced for both magnocellular and parvocellular neurons usually within 2–5 min after cooling had begun. Recovery to baseline values after cooling generally took 10–15 min but sometimes longer. On average, pre-cooling and recovery control values were similar (Fig. 1a) and responses observed during cooling were substantially lower (Fig. 1b).

The amplitudes $R$ of the first harmonic of each cell’s responses to drifting sine-wave gratings as a function of the Michelson contrast $c$ were fitted to both the Michaelis–Menten equation as applied to visual physiology by Naka and Rushton (1966) and power functions; see also Hering (1874). In the former equation, $R = R_{\text{max}} c/(c^2 + b^2)$, where $R_{\text{max}}$ represents the derived maximum value and $b$ the semisaturation contrast, that is, the contrast required to evoke a response equal to one-half the derived maximum value. In the latter case, the power function $R = f(a, b, c)$ is represented as a straight line in the log–log plot $\log(R) = a + b \log(c)$. We have chosen those functions that fit the data by minimizing the RMS (root mean square) error and which were then plotted on both log–log and linear–linear scales with $b$ in the former instance representing the slope on the log–log plot.

We have chosen to fit the contrast–response functions of parvocellular neurons by power functions rather than by the Michaelis–Menten equation. The responses of such cells do not show saturation at high contrasts and their responses in log–log coordinates look
linear (Fig. 2a) confirming Derrington and Lennie (1984). Such fits by power functions requires only two free variables compared to the three required by the Michaelis–Menten equation and avoids the implausible generation of semisaturation contrasts (b) substantially greater than 1.0 that invariably follows when we try to fit the data to the Michaelis–Menten equation.

When response versus contrast was plotted on a log–log scale for gratings modulated in luminance before, during, and after cooling, parvocellular neurons, on average, underwent a largely uniform decline in responsivity of just over an octave spanning most of the contrast range as shown for the combined responses of ten such neurons (Fig. 2a). Because responses before and after cooling were so similar (Fig. 1), we could have combined these responses and obtained even smaller standard errors of the means than are shown in Fig. 2. However, because the differences in the curves for the population before and during cooling are statistically significant anyway (see below) and because we would prefer to display data for comparable members of trials, we chose not to average the pre- and post-cooling control results.

The shift of the contrast–response functions of ten parvocellular neurons (seven ON-center and three OFF-center) cells to the right (or down) following inactivation of V1 is statistically significant and occurs without a statistically significant change in slope (Table 1). The near-uniform response suppression in the log–log plot over most of the contrast range suggests that inactivation of V1 

\[ V1 \text{ divisive} \] decreases the activity of LGN neurons. Conversely, in the absence of such inactivation, that is, with V1 normally active, the effect of V1 on parvocellular neurons is to 

\[ V1 \text{ multiplicatively} \] enhance the contrast gain of these cells on average by just over two-fold or equivalently by just over an octave (Fig. 2a). This suggests that feedback from V1 becomes independent of stimulus contrast. This independence could be related to selective neurons in V1 that saturate at low contrasts (0.1) (Sclar et al., 1990; Albrecht & Hamilton, 1992). These effects hold over the entire range of observed preferred spatial frequencies from 1–8 cycles/deg.

The suppressive effects of cooling on ten magnocellular neurons (six ON-center and four OFF-center cells) (Fig. 2b) were on average similar to those observed in parvocellular neurons (Fig. 2a) at high contrast but had different characteristics at lower contrast. At higher contrasts there is an almost parallel downward shift in magnocellular responses as a consequence of inactivation of V1. At these higher contrasts, the effect of cooling V1 on magnocellular neurons looks similar to those of parvocellular cells (Fig. 2a), that is, a multiplicative contrast–independent shift. This effect could be related to V1 cells that saturate at contrasts above 0.2 (Sclar et al., 1990; Albrecht & Hamilton, 1992). At these contrasts or higher, the responses of magnocellular neurons are more than two-fold greater when the corticofugal pathways are open. At lower contrasts, however, the effect of cooling of V1 on magnocellular neurons is strongly contrast dependent (Fig. 2b). This effect could be related to the frequency-dependent increase in the amplitude of excitatory postsynaptic potentials (EPSPs) of LGN cells by corticofugal excitation (Lindstrom & Wrobel, 1990). The shift of the contrast–response function to the right (or down) after inactivation of V1 (Fig. 2b) is statistically significant as is the decrease in the slope of the response function (Table 1).

The differential effects of cooling on magnocellular and parvocellular neurons at low contrasts is not likely due to a difference in stimulus parameters used to test these two populations. These parameters were rather similar (see Methods).

Cooling also depressed the contrast–response function measured using chromatically opponent equiluminant stimuli for parvocellular neurons that were strongly tuned along either the red–green (four cells) or blue–yellow axes (one cell). Stimuli were also limited to the classical receptive field and presented at very low spatial frequencies because such frequencies optimize responses of parvocellular LGN cells for equiluminant stimuli (Derrington et al., 1984). A subset of five such neurons were held long enough to be tested over the contrast range to both gratings modulated in luminance (Fig. 2c) and gratings of very low spatial-frequency selectivity modulated in chromaticity in the equiluminant plane (Fig. 2d). Cooling suppressed the responses to chromatically opponent stimuli even more strongly than those to gratings modulated in luminance especially at high contrasts. The extent of the
suppression decreased logarithmically with lower contrast which can be approximated as the change of the line slope in the log–log plot (Fig. 2d) resembling that of magnocellular neurons at lower contrasts (Fig. 2b).

Because inactivation of V1 has a stronger effect on the responses of parvocellular neurons to changes in chromatic contrast than to changes in luminance contrast, we could show that the changes in the intercept and slope of response functions to changes in chromatic contrast by inactivation of V1 (Fig. 2d) are statistically significant even for a population of five cells (Table 1). The mean slope calculated from slopes of individual cells for the chromatic contrast–response function was 0.835 in the control and 0.404 during cooling; this difference was highly significant in a t-pair Student test (t = 5.62, P < 0.0025). Conversely, the mean slope for the luminance contrast–response function for the same cells (Table 1) was 0.609 in the control and 0.649 during inactivation of V1; this difference is not significant in a t-pair test (P > 0.5).

We have confirmed the above differences by also applying a nonparametric test. We have evaluated the responses of these same cells to contrast changes in luminance and in the equiluminant plane using the sign test. We have first tested the null hypothesis that intercept values (parameter a in the power function \( R = 10^a c^b \)) during control and cooling are from the same populations for luminance and for color stimuli. We have rejected this null hypothesis and showed
Table 1. Summary of the statistical analysis for either cell populations or means of individual cell values—the latter indicated by “mean ind”.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>ec</th>
<th>N</th>
<th>par</th>
<th>mean</th>
<th>95% conf int</th>
<th>sig</th>
<th>Statistical test</th>
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<tr>
<td>Control</td>
<td>10</td>
<td>a</td>
<td>1.449</td>
<td>(1.394, 1.504)</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cool</td>
<td>10</td>
<td>a</td>
<td>1.062</td>
<td>(0.896, 1.227)</td>
<td>*P &lt; 0.05</td>
<td></td>
<td>*t-test population</td>
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<tr>
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<td>0.610</td>
<td>(0.431, 0.788)</td>
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<td>*t-test population</td>
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<td>*Sign test population</td>
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<td>(0.297, 0.376)</td>
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<tr>
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<td>(0.955, 1.625)</td>
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<td></td>
<td>*Sign test population</td>
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<tr>
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<td>a</td>
<td>0.628</td>
<td>(0.449, 0.807)</td>
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<tr>
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<td>(0.474, 1.115)</td>
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<tr>
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<td>0.404</td>
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<tr>
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<td>b</td>
<td>0.403</td>
<td>(0.307, 0.504)</td>
<td>*</td>
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<td>*Sign test population</td>
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In left column, cell types are specified as magnocellular by “Magn” or parvocellular by “Parvo.” Studies in which contrast is modulated in lumiance indicated by “lum” and in equilumiance indicated by “equilum.” Experimental condition “ec” specific for either “control” or during cooling of V1 by “cool.” Number of cells signified by “N.” The parameter analyzed signified by “par” for either (a)—intercept or (b)—the slope. The 95% confidence interval for parameters of the linear regression after logarithmic data transformation signified by “95% conf int.” Part of the data was also analyzed using the t-pair Student test and sign test for intercept or slope differences related to the individual cells. The probability of the statistical significance “sig” of the changes in the (a) or (b) parameter as an effect of V1 cooling is indicated by the (* P values: “n.s.” indicates not statistically significant. In statistical tests for cell populations, the responses of the individual cells to each contrast were averaged and logarithmically transformed. The confidence intervals of the linear regression parameters were then compared before and after cooling. In the tests for the means of individual values (mean ind), the contrast responses of each individual cell were also logarithmically transformed and the coefficients of the linear regression were compared before and during cooling. The t-pair Student test was performed on the population of these parameters before and during cooling.

with the probability (*P < 0.05) that b is from different populations before and during cooling for color but not for lumiance. Thus, in the absence of cortical inactivation, corticofugal activity produces a contrast-dependent change of the contrast gain of parvocellular neurons responding to full-field chromatic stimuli.

Recurrent projections enhance different parvocellular neurons to different extents inasmuch as some cells produced responses scarcely greater than zero to low contrast stimuli modulated in lumiance (Fig. 3a) or chromaticity (Fig. 3c). This result suggests that the output of some LGN cells—at least in anesthetized animals—may be substantially dependent on corticofugal activity as well as upon retinal input and that the corticofugal projections are nonuniform with respect to the strength of their input on target cells.

Averaged responses of magnocellular and parvocellular individual neurons were also analyzed by comparing averaged coefficients of Michaelis-Menten or power functions before and during cooling of V1. We did not find statistically significant differences in these results for magnocellular and parvocellular ON- or OFF-center cells. Our control contrast-response functions were generally consistent with those of others (Sclar et al., 1989).

Averaged responses of individual magnocellular neurons were fitted with the Michaelis-Menten equation yielding a mean R_{max} of 43.1 ± 8.1 (SEM—standard error of the mean) spikes/s in control conditions and 24.5 ± 4.9 spikes/s during cooling. The difference of 18.2 ± 4.3 spikes/s is statistically significant (*P < 0.01, r-pair Student test). The semisaturation contrast b and exponent n coefficients did not change significantly during cooling. Responses of individual parvocellular neurons were fitted before and during cooling using the Michaelis-Menten equation and a power function. In the control conditions, R_{max} was 70.8 ± 14.4 spikes/s, during cooling R_{max} was 27.7 ± 3.9 spikes/s which means that V1 inactivation decreased R_{max} in a statistical significance way (*P < 0.04), whereas the semisaturation contrast n did not differ before and during cooling. Using the power function, we obtained the mean intercept a which is related to log R_{max}/b^n and was 1.34 ± 0.08 spikes/s in controls and 0.93 ± 0.10 spikes/s during cooling. The difference 0.42 ± 0.08 spikes/s was statistically significant (*P < 0.002, r-pair Student test). Cooling did not significantly change the mean slope which was 0.73 ± 0.07 in the control and 0.74 ± 0.007 during cooling. This slope equals the exponent n of the Michaelis-Menten equation for contrasts much less than the semisaturation contrast.

Inactivation of V1 did not significantly modify the spontaneous mean level of LGN activity. For example, for the ten parvocellular neurons of Fig. 2a, the mean value of spontaneous activity dropped from 42.3 ± 11.58 to 37.2 ± 10.31 spikes/s after cooling of V1. The difference of 5.1 ± 6.75 did not attain statistical significance (r-pair Student test). For the magnocellular neurons of Fig. 2b, there was a statistically nonsignificant increase in average spon-
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<td>(0.896, 1.227)</td>
<td></td>
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<tr>
<td>Control</td>
<td>10</td>
<td>b</td>
<td>0.721</td>
<td>(0.662, 0.780)</td>
<td></td>
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<tr>
<td>Cool</td>
<td>10</td>
<td>b</td>
<td>0.616</td>
<td>(0.431, 0.788)</td>
<td>n.s.</td>
<td></td>
<td></td>
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<tr>
<td>Magna lum.</td>
<td></td>
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<tr>
<td>Control</td>
<td>10</td>
<td>a</td>
<td>1.407</td>
<td>(1.307, 1.507)</td>
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<tr>
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<td>10</td>
<td>a</td>
<td>0.998</td>
<td>(0.961, 1.034)</td>
<td></td>
<td>P &lt; 0.05</td>
<td>t-test population</td>
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<tr>
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<td>b</td>
<td>0.561</td>
<td>(0.452, 0.669)</td>
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<td>b</td>
<td>0.337</td>
<td>(0.297, 0.376)</td>
<td></td>
<td>P &lt; 0.05</td>
<td>t-test population</td>
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<tr>
<td>Parvo lum.</td>
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<tr>
<td>Control</td>
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<td>a</td>
<td>1.201</td>
<td>(1.008, 1.394)</td>
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<td>a</td>
<td>0.903</td>
<td>(0.643, 1.162)</td>
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<tr>
<td>Control</td>
<td>5</td>
<td>b</td>
<td>0.609</td>
<td>(0.400, 0.817)</td>
<td>n.s.</td>
<td></td>
<td>mean ind</td>
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<tr>
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<td>(0.368, 0.929)</td>
<td>n.s.</td>
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<td>0.699</td>
<td>(0.400, 0.817)</td>
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<td>mean ind</td>
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<td>a</td>
<td>1.289</td>
<td>(0.955, 1.623)</td>
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<td>P &lt; 0.05</td>
<td>Sign test population</td>
</tr>
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<tr>
<td>Control</td>
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<td>0.628</td>
<td>(0.449, 0.807)</td>
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<td>mean ind</td>
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<td>(0.474, 1.115)</td>
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<td>5</td>
<td>b</td>
<td>0.835</td>
<td>(0.210, 0.597)</td>
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<td>Sign test population</td>
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<tr>
<td>Cool</td>
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<td>b</td>
<td>0.404</td>
<td>(0.210, 0.597)</td>
<td></td>
<td>P &lt; 0.0025</td>
<td>mean ind</td>
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*In left column cells types are specified as magnocellular by “Magna” or parvocellular by “Parvo.” Studies in which contrast is modulated in luminance indicated by “lum” and in equilumiance indicated by “equilum.” Experimental condition “ec” specific for either “control” or during cooling of V1 by “cool.” Number of cells signified by “N.” The parameter analyzed signified by “par” for either (a)—intercept or (b)—the slope. The 95% confidence interval for parameters of the linear regression after logarithmic data transformation signified by “95% conf int.” Part of the data was also analyzed using the t-pair Student test and sign test for intercept or slope differences related to the individual cells. The probability of the statistical significance “sig” of the changes in the (a) or (b) parameter as an effect of V1 cooling is indicated by the (P) values: “n.s.” indicates not statistically significant. In statistical t-tests for cell populations, the responses of the individual cells to each contrast were averaged and logarithmically transformed. The confidence intervals of the linear regression parameters were then compared before and after cooling. In the tests for the means of individual values (mean ind), the contrast responses of each individual cell were also logarithmically transformed and the coefficients of the linear regression were compared before and during cooling. The t-pair Student test was performed on the population of these parameters before and during cooling.

with the probability (P < 0.05) that b is from different populations before and during cooling for color but not for luminance. Thus, in the absence of cortical inactivation, corticofugal activity produces a contrast-dependent change of the contrast gain of parvocellular neurons responding to full-field chromatic stimuli.

Recurrent projections enhance different parvocellular neurons to different extents inasmuch as some cells produced responses scarcely greater than zero to low contrast stimuli modulated in luminance (Fig. 3a) or chromaticity (Fig. 3c). This result suggests that the output of some LGN cells—at least in anesthetized animals—may be substantially dependent on corticofugal activity as well as upon retinal input and that the corticofugal projections are nonuniform with respect to the strength of their input on target cells.

Averaged responses of magnocellular and parvocellular individual neurons were also analyzed by comparing averaged coefficients of Michaelis–Menten or power functions before and during cooling of V1. We did not find statistically significant differences in these results for magnocellular and parvocellular ON- or OFF-center cells. Our control contrast-response functions were generally consistent with those of others (Sclar et al., 1990).

Averaged responses of individual magnocellular neurons were fitted with the Michaelis–Menten equation yielding a mean Rmax of 43.1 ± 8.1 (SEM)—standard error of the mean) spikes/s in control conditions and 24.5 ± 4.9 spikes/s during cooling. The difference of 18.2 ± 4.3 spikes/s is statistically significant (P < 0.01, t-pair Student test). The semisaturation contrast b and exponent n coefficients did not change significantly during cooling. Responses of individual parvocellular neurons were fitted before and during cooling using the Michaelis–Menten equation and a power function. In the control conditions, Rmax was 70.8 ± 14.4 spikes/s, during cooling Rmax was 27.7 ± 3.9 spikes/s which means that V1 inactivation decreased Rmax in a statistical significance way (P < 0.04), whereas the semisaturation contrast and n did not differ before and during cooling. Using the power function, we obtained the mean intercept a which is related to log Rmax/b and was 1.34 ± 0.08 spikes/s in controls and 0.93 ± 0.10 spikes/s during cooling. The difference 0.42 ± 0.08 spikes/s was statistically significant (P < 0.002, t-pair Student test). Cooling did not significantly change the mean slope which was 0.73 ± 0.07 in the control and 0.74 ± 0.007 during cooling. This slope equals the exponent n of the Michaelis–Menten equation for contrasts much less than the semisaturation contrast.

Inactivation of V1 did not significantly modify the spontaneous mean level of LGN activity. For example, for the ten parvocellular neurons of Fig. 2a, the mean value of spontaneous activity dropped from 42.3 ± 11.58 to 37.2 ± 10.31 spikes/s after cooling of V1. The difference of 5.1 ± 6.75 did not attain statistical significance (t-pair Student test). For the magnocellular neurons of Fig. 2b, there was a statistically nonsignificant increase in average spon-
Fig. 3. An example of averaged responses ± SEM of two parvocellular (a, c) and magnocellular (b, d) LGN neurons to drifting gratings at different contrasts before (circle) and during (squares) cooling of V1. Responses of parvocellular neurons were fitted to power functions, and responses of magnocellular were fitted to the Michaelis–Menten equation.

Cortical inactivation may also decrease a cell’s maximum response without changing the “nonlinearity” as measured by the exponent $n$ in the Michaelis–Menten equation. For example, the value of $n$ remained 1.2 for the magnocellular neuron of Fig. 3b despite a two-fold decrease in derived $R_{\text{max}}$ during cortical inactivation. For this cell, cooling caused a significant increase in the semisaturation contrast $b$ which extends the linear range of the cell’s responses to stimuli at different contrasts. However, for other magnocellular neurons (Fig. 3d), the linear response range decreases during cooling even if $n$ decreases and approximates 1, but the semisaturation contrast decreases two-fold. Moreover, the slope $b$ in the power function equation (analogous to $n$ in the Michaelis–Menten equation) for the parvocellular neurons can increase (Fig. 3a) or decrease (Fig. 3c) following cortical inactivation, but its mean value for the population does not change significantly.

Discussion

Because these experiments were carried out under anesthetic doses of sufentanil up to 8 $\mu$g/kg/h, we first consider whether such anesthesia may have altered the response properties tested. A number of long latency contextual effects believed to depend at least in part upon corticocortical recurrent projections have been...
demonstrated in V1 of the alert behaving monkey (Lamme, 1995; Zipser et al., 1996). Certain contextual effects studied by the same group are selectively suppressed by isoflurane anesthetia (Lamme et al., 1998). However, when Nothdurft et al. (1999) compared the effects of sufentanil anesthesia (5–8 μg/kg/h) on the responses of V1 neurons to contextual modulations, they found results similar to those that the same laboratory had found earlier in alert behaving animals (Knerim & Van Essen, 1992). Thus, feedback-dependent contextual modulations in V1 are largely preserved under sufentanil anesthesia. It would seem likely, although not yet proved, that the more proximal corticofugal loop would be no more severely affected than the recurrent projections to V1.

Even under sufentanil anesthesia, the corticothalamic projections enhance the contrast gain of both parvocellular and magnocellular neurons to stimuli modulated in luminance as well as to stimuli modulated in color in the equiluminant plane for parvocellular neurons. The corticofugal projections normally express a general and often robust effect on the contrast gain of LGN neurons, taking the term robust to indicate a gain in neural responsivity of at least two-fold, when the corticofugal pathways are operant. The responses of parvocellular LGN neurons are multiplicatively enhanced (as predicted by Grossberg, 1980; Koch, 1187) by descending pathways from striate cortex in a contrast-independent manner over all but the very lowest range of contrasts. The responses of magnocellular neurons are also multiplicatively enhanced by such feedback and the enhancement is largely contrast independent at contrasts above 0.2 and highly contrast dependent at lower contrasts (Fig. 2b).

What mechanisms might underlie the contrast-independent multiplicative enhancement of the responses of LGN neurons by corticofugal activity over a wide contrast range? It is necessary to explain both why the enhancement becomes largely contrast independent above certain low values of contrast and is multiplicative. We suggest that the former property may reflect the response characteristics of corticofugal neurons that project to parvocellular and magnocellular neurons and may saturate at different contrasts (Sclar et al., 1990; Albrecht & Hamilton, 1992).

If this were the case, then the corticofugal drive upon LGN neurons becomes constant above a certain contrast and the explanation for the multiplicative effect must be subcortical. In theory, a multiplicative effect can result from either a direct effect of one type of excitatory synaptic activity upon another or by withdrawal of a constant divisive effect upon target LGN neurons. We cannot exclude the possibility that corticofugal activation normally produces a disinhibitory effect (Wörgötter et al., 1998) on relay neurons by reducing shunting, that is, divisive inhibition from inhibitory interneurons within the LGN. However, we cannot ignore the possibility of multiplicative effects on the basis of excitatory inputs especially in view of pertinent anatomic results. For example, the retinal afferents to LGN relay cells terminate on proximal dendrites, whereas the vastly more numerous corticofugal afferents terminate on distal dendrites (Sherman & Koch, 1986). Moreover, although both afferent pathways to LGN relay cells use glutamate as neurotransmitter, the retinal afferents activate only ionotropic receptors, whereas the corticofugal afferents activate both ionotropic and metabotropic receptors (McCormick & von Krosigk, 1992; Sherman & Guillery, 1998).

Activation of metabotropic receptors, as would occur when V1 is active, produces a marked decrease in apparent input conductance and a corresponding increase in input resistance by reducing a K+ current in the LGN of the guinea pig (McCormick & von Krosigk, 1992). There would also be a converse lowering of input impedance of LGN cells by corticofugal activation of ionotropic receptors. However, based on the work in the guinea pig, we would expect this effect to be smaller than that due to activation of metabotropic receptors. A corresponding net increase in input impedance would be expected to increase the voltage of EPSPs generated by retinal afferents although the magnitude of this effect in the primate remains unknown. Thus, it is tempting to wonder whether activation of metabotropic receptors by corticofugal activity leads to some of the multiplicative enhancement of the contrast gain of LGN relay cells.

The corticofugal pathways also project to the perigeniculate nucleus (PGN), a thin shell of inhibitory interneurons surrounding part of the LGN, which projects both to relay cells and inhibitory interneurons within the LGN (Montero & Singer, 1985; Steriade et al., 1986). However, it is unlikely that the spatially restricted stimuli that we used to excite the classical receptive fields (RF) of LGN neurons were sufficiently large to activate PGN neurons which generally require stimulation over an area greater than the classical RF of LGN cells at common retinal eccentricities for more than minimal activation (Funke & Eysel, 1998). Moreover, the firing patterns of PGN and LGN neurons inversely correlate with each other (Funke & Eysel, 1998) suggesting a dominant role for the direct inhibitory pathway from PGN to LGN relay cells and a minimal role for a disinhibitory pathway to relay cells. Thus, inactivation of the V1 → PGN pathway would be expected to produce an increase in LGN activity, an effect we rarely observed and even then only minimally (Fig. 1b). Thus, it is more likely that the effects on LGN neurons we observed after inactivation of V1 were mediated by either the direct corticofugal pathway onto LGN relay cells or by disinhibitory effects onto relay cells via interneurons (Wörgötter et al., 1998).

The fact that our results imply exclusively excitatory modulatory effects of the corticofugal projections in our experimental situation requires comment. This preponderance of corticofugal excitation may depend upon both spatial and temporal factors. With respect to spatial factors, we know that direct activation of layer 6 cells in the cat by electrophoretic application of glutamate excites LGN cells with receptive-field centers in close retinotopic correspondence to those of striate neurons at the site of activation and inhibits LGN cells with field centers that are not in such close retinotopic correspondence (Tsumoto et al., 1978). Thus, it is not surprising that we found predominantly excitatory effects inasmuch as our stimuli were targeted to the classical receptive field for each LGN cell under study and thus preferentially excited corticofugal cells with receptive fields necessarily in retinotopic correspondence to those of LGN neurons.

Tsumoto et al. (1978) further interpret their results to imply a center-surround organization of the corticofugal system, perhaps both within the cortex and the LGN, such that excitation of a restricted region of the cortex preferentially facilitates afferent activity in the retinotopically corresponding region of the LGN while suppressing activity outside this region. If so, our results confirm the central excitatory mechanism and identify a role for it within the context of the control of contrast gain of LGN neurons but do not address the issue of corticofugal inhibition when activation of cortical and geniculate neurons are retinotopically mismatched. With respect to temporal issues, we again note that our stimuli were generally tested at 8 Hz (range 4–12 Hz), but we acknowledge that we cannot exclude the possibility that the employment of temporal frequencies outside this range might have revealed different effects.
The modulatory effects of corticofugal activity that we have inferred by selectively stimulating the classical RF while reversibly inactivating the striate cortex are strong and invite comparisons to analogous studies in other sensory systems. Comparable reductions in the responses of neurons in the medial geniculater nucleus and inferior colliculus of the mustached bat to optimally tuned auditory frequencies have been observed when the auditory cortex is inactivated (Zhang et al., 1997). Thus, strong, that is more than two-fold, enhancement of responses to optimally tuned activity within thalamic relay nuclei by corticofugal feedback may be a general feature across sensory systems. Moreover, the recurrent projections from V2 back to V1 (Payne et al., 1996) and from MT/V5 back to V3, V2 and V1 (Hupé et al., 1998) produce similarly strong effects.

Finally, our results provide a quantitative experimental basis for broad classes of models that suggest that recurrent projections from higher cortical areas can selectively enhanceafferent activity arising from lower levels so that a mutually consistent description of sensory data is iteratively achieved across successive subcortical and cortical areas (Pririmab, 1974; Milner, 1974; Harth, 1976; Grossberg, 1976, 1980; Edelman, 1978; Koch, 1987; Damasio, 1989; Mumford, 1991, 1992, 1994; Ullman, 1995; Przybylszewski, 1998; for review, see Pollen, 1999).

Acknowledgments

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References


