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Influence of Contrast on Orientation and Temporal Frequency Tuning in Ferret Primary Visual Cortex

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Alitto, Henry J. and W. Martin Usrey. Influence of contrast on orientation and temporal frequency tuning in ferret primary visual cortex. *J Neurophysiol* 91: 2797–2808, 2004. First published February 4, 2004; 10.1152/jn.00943.2003. Neurons in primary visual cortex are highly sensitive to the contrast, orientation, and temporal frequency of a visual stimulus. These three stimulus properties can be varied independently of one another, raising the question of how they interact to influence neuronal responses. We recorded from individual neurons in ferret primary visual cortex to determine the influence of stimulus contrast on orientation tuning, temporal-frequency tuning, and latency to visual response. Results show that orientation-tuning bandwidth is not affected by contrast level. Thus neurons in ferret visual cortex display contrast-invariant orientation tuning. Stimulus contrast does, however, influence the structure of orientation-tuning curves as measures of circular variance vary inversely with contrast for both simple and complex cells. This change in circular variance depends, in part, on a contrast-dependent change in the ratio of null to preferred orientation responses. Stimulus contrast also has an influence on the temporal-frequency tuning of cortical neurons. Both simple and complex cells display a contrast-dependent rightward shift in their temporal frequency-tuning curves that results in an increase in the highest temporal frequency needed to produce a half-maximum response (TF_{50}). Results show that the degree of the contrast-dependent increase in TF_{50} is similar for cortical neurons and neurons in the lateral geniculate nucleus (LGN) and indicate that subcortical mechanisms likely play a major role in establishing the degree of effect displayed by downstream neurons. Finally, results show that LGN and cortical neurons experience a contrast-dependent phase advance in their visual response. This phase advance is most pronounced for cortical neurons indicating a role for both subcortical *and* cortical mechanisms.

INTRODUCTION

A major goal in vision science is to understand how cortical circuits transform and process information supplied from the thalamus. Cortical neurons are sensitive not only to the contrast of a visual stimulus but also to other stimulus properties including orientation and temporal frequency. Determining how these properties interact to drive cortical responses is therefore an important step toward understanding the computational strategies employed by the cortex for processing visual information.

Although the firing rate of neurons in visual cortex is dependent on stimulus contrast, orientation tuning is believed to be contrast invariant (Anderson et al. 2000; Sclar and Freeman 1982; Skottun et al. 1987). Typically, the effects of contrast on orientation tuning are assessed by generating orientation tuning curves using different levels of contrast and comparing the half-width at half-height of tuning curve peaks. While half-width is an excellent measure for quantifying the breadth of orientation tuning, other features present in an orientation tuning curve may be difficult to quantify with half-width measures. For instance, half-width measures are not ideal for detecting effects of contrast on responses to null-orientation stimuli. Because many models for the generation of orientation tuning (reviewed in Shapley et al. 2003) and, in particular, contrast-invariant orientation tuning (reviewed in Miller 2003) suggest a role for inhibition to null-orientation stimuli, it is important to know the extent to which contrast affects other aspects of orientation tuning beyond measures of half-width. An alternative measure for quantifying the structure of an orientation-tuning curve is circular variance (see Ringach et al. 2002). Here, we show that measures of circular variance in ferret primary visual cortex are not contrast invariant. Rather we find an inverse relationship between circular variance and contrast, a relationship also described in a recent preliminary report for neurons in monkey visual cortex (Shapley et al. 2002).

Contrast is also known to influence the temporal-frequency tuning of neurons along the visual pathway (Albrecht 1995; Holub and Morton-Gibson 1981). For instance, the phenomenon of contrast gain control, as originally described for cat retinal ganglion cells (Shapley and Victor 1978, 1981), is characterized as a contrast-dependent shift in the temporal-frequency response function (Benardete and Kaplan 1992, 1999; Kremers et al. 1997; Usrey and Reid 2000; Yeh et al. 1995). A recent examination of the influence of contrast on visual responses in primary visual cortex to high temporal-frequency stimuli suggests that contrast affects cortical responses more than simple feedforward models of lateral geniculate nucleus (LGN) input predict and thus cortical processing must influence the relationship between contrast and temporal-frequency tuning (Kayser et al. 2001). The influence of contrast on temporal-frequency tuning of LGN and cortical neurons, however, has not been directly compared in the same study. By comparing LGN and cortical responses in the ferret, we show that much of the contrast-dependent rightward shift in high temporal-frequency responses in visual cortex can be accounted for by that present in the LGN.

METHODS

Animal preparation

Thirteen adult ferrets (*Mustela putorius furo*) of both sexes were used in this study. All surgical and experimental procedures conformed to National Institutes of Health and U. S. Department of

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Agriculture guidelines and were carried out with the approval of the Animal Care and Use Committee at the University of California, Davis. Surgical anesthesia was induced with an intramuscular injection of ketamine (40 mg/kg) and acepromazine (0.04 mg/kg). Lidocaine was applied topically or injected subcutaneously at all points of pressure and possible sources of pain. A tracheotomy was performed, and animals were placed in a stereotaxic apparatus where anesthesia was maintained with 1–1.5% isoflurane in oxygen and nitrous oxide (2:1). Body temperature was maintained at 37°C using a thermostatically controlled heating blanket. Temperature, electrocardiogran (EKG), electroencephalogram (EEG), and expired CO_2 were monitored continuously throughout the experiment. Pupils were dilated with 1% atropine sulfate, fitted with appropriate contact lenses, and focused on a tangent screen located 76 cm in front of the animal. A midline scalp incision was made and a small craniotomy was made either above the primary visual cortex or LGN.

Once all surgical procedures were complete, animals were paralyzed with vecuronium bromide ($0.2\ mg \cdot kg^{-1} \cdot h^{-1}$ iv) and ventilated mechanically. Proper depth of anesthesia was ensured throughout the experiment by monitoring the EEG for changes in slow-wave/spindle activity and monitoring the EKG and expired CO_2 for changes associated with a decrease in the depth of anesthesia.

Electrophysiological recordings and visual stimuli

Recordings were made from individual neurons in ferret primary visual cortex with tungsten in glass electrodes (Alan Ainsworth, London, UK). Spike times and waveforms were recorded to disk (with 100-μs resolution) by a PC running the Discovery software package (Datawave Technologies, Longmont, CO). Spike isolation was confirmed with off-line waveform analysis and by the presence of a refractory period as seen in the autocorrelograms (Usrey and Reid 1999, 2000; Usrey et al. 2000, 2003).

Visual responses of cortical and geniculate neurons with receptive fields between 5 and 15° eccentric were characterized quantitatively using drifting sinusoidal gratings of optimal spatial frequency. Grating stimuli were created with an AT-Vista graphics card (Truevision, Indianapolis, IN) running at a frame rate of 128 Hz. The stimulus program was developed with subroutines from a runtime library, YARL, written by Karl Gegenfurtner. Stimuli were shown on a gamma calibrated BARCO monitor. The mean luminance of the monitor was 40–50 cd/m^2. Gratings were shown for 4 s, followed by 1.6 s of mean gray. After the period of mean gray, a new grating was shown that varied in contrast, orientation, or temporal frequency. Once a complete cycle of gratings was shown, the process repeated two to four additional times.

Neurons were studied using the following sequence of stimuli. First, responses to 100% contrast gratings drifting at 4 Hz were used to generate orientation-tuning curves. Next, gratings with the preferred orientation were used to measure neural responses over a range of contrasts (1.5–100%). Once contrast response functions were determined, orientation-tuning curves were made using gratings with contrasts that spanned the cell's range of response. Finally, 100% contrast gratings of preferred orientation were used to study responses at a range of temporal frequencies (0.5–32 Hz, occasionally as high as 64 Hz). Temporal-frequency response curves were then made using drifting gratings with contrasts that spanned the cell's range of response.

Statistical analysis

When statistical analysis was required to compare two distributions, we first used Lilliefors modification of the Kolmogorov-Smirnov test to determine if the distributions in question were significantly different from normal distributions of unspecified mean and variance ($\alpha = 0.05$). If the distributions were not statistically different from normal, then a *t*-test was used to compare the means of the two populations. However, if the populations were statistically different from normal distributions, then a Wilcoxon rank sum test or a sign test was used in place of a *t*-test.

Cell classification

Cortical neurons were classified as simple cells or complex cells on the basis of the ratio of the first Fourier coefficient (f1) to mean response (simple cells: f1/mean >1.0; complex cells: f1/mean <1.0) (see Skottun et al. 1991). Subsequent analysis of neuronal responses was performed using either the cell's f1 (simple cells and LGN cells) or mean response (complex cells) with the exception of analysis related to circular variance where mean response for both simple and complex cells was used. The f1/mean was calculated without subtracting spontaneous activity. Among our population of neurons, it is worth noting that cell classification based on the f1/(mean activity minus spontaneous activity) was identical to cell classification based on the f1/mean.

Contrast response functions

Before assessing the influence of contrast on orientation and temporal-frequency tuning, contrast response functions were calculated. To quantify the contrast response function, contrast response curves were fit to a hyperbolic ratio (Albrecht and Hamilton 1982)

$$R(C) = K^*(C^n/(C^n + {C_{50}}^n))$$

where C represents the contrast levels presented during the experiment, K represents the maximal response rate, C_{50} is the contrast corresponding to 50% of the cell's maximal response, and n is a variable reflecting the cell's sensitivity. A constrained nonlinear optimization procedure (MATLAB function: fmincon; The Mathworks, Natick, MA) was used to minimize the squared error [i.e., Σ (Data-Fit)^2] when fitting contrast response functions and all subsequent data sets. To confirm our estimates of C_{50} from contrast response functions fit to a hyperbolic ratio (particularly for cells that qualitatively appeared to have more linear response functions), we also estimated C_{50} values from data interpolated with a cubic spline and found a high correlation between the two estimates (cortical neurons: $r = 0.98$, slope $= 1.07$; LGN neurons: $r = 0.96$, slope $= 1.03$).

Neuronal responses to different levels of contrast were also used to determine the relationship between contrast and onset of response as assessed by response phase; response phase was determined by Fourier analysis.

Orientation tuning

To determine the effect of contrast on orientation tuning, orientation-tuning curves were generated using several different contrast levels. The specific levels of contrast used were determined for each cell on the basis of the cell's contrast response function. The goal was to include at least one contrast from the saturating region of the contrast response function along with several contrasts located in the linear portion of the contrast response function.

To quantify the effect of contrast on orientation tuning, individual orientation-tuning curves were first fit to Gaussian distributions

$$R(\text{ori}) = K^*\exp\left(\frac{-(x-\mu)^2}{2^*\sigma^2}\right) + \text{baseline}$$

where K represents the maximum response rate, x represents the orientations used, μ represents the preferred orientation, σ represents the SD, and baseline is the DC-offset of the Gaussian distribution. This procedure allowed us to estimate the bandwidth of orientation tuning as peak half-width at half-height. The half-width at half-height is equal to 1.17σ. Gaussian fits were estimated without subtracting

spontaneous activity. Thus any effect of spontaneous activity on the Gaussian fit is included in the baseline term.

A second method, circular variance (CV), was also used to quantify the effects of contrast on orientation-tuning curves. For both simple cells and complex cells, CV was calculated using the mean firing rate of the neuron according to the following equation: CV = 1 − |R| where

$$R = \frac{\sum_k r_k e^{i2\theta_k}}{\sum_k r_k}$$

In the preceding, r_k is the mean firing rate at orientation k and θ_k is the orientation in radians. Circular variance was calculated without subtracting spontaneous activity.

Finally, we compared mean responses under different contrast conditions to examine the relationship between stimulus contrast and responses to null-orientation stimuli ($\pm 90^o$ from preferred).

Temporal-frequency tuning

To determine the influence of contrast on temporal-frequency tuning in the ferret, we calculated temporal-frequency tuning curves at high and low-contrast levels. Contrast levels were selected on the basis of the contrast response function. The high-contrast stimulus was always picked from the saturating region of the cells contrast response function and the low-contrast stimulus was taken from the linear portion of the cell's contrast response function. To quantify the effects of contrast on temporal-frequency tuning, temporal-frequency tuning curves were interpolated with a cubic spline (MATLAB function: spline; The Mathworks). This allowed us to estimate the highest temporal frequency that produced 50% of a cell's maximal response (TF_{50}). To quantify and compare TF_{50} values under high and low-contrast conditions, we calculated a contrast gain control index (CGCI) using the following equation

$$\text{CGCI} = (\text{high contrast } TF_{50} - \text{low contrast } TF_{50})/(\text{high contrast } TF_{50} + \text{low contrast } TF_{50})$$

Using this equation, a positive CGCI would indicate an increase in TF_{50} with increasing contrast, whereas a negative CGCI would indicate a decrease in TF_{50} with increasing contrast.

RESULTS

Contrast response functions

We measured the contrast response functions of 55 neurons in primary visual cortex (V1) of the adult ferret. Figure 1*A* shows four representative examples (2 simple cells and 2 complex cells) of the data. To quantify the data, each contrast response function was fit to a hyperbolic ratio equation (see METHODS). Ferret cortical neurons displayed contrast response functions similar to what is commonly reported in monkey and cat V1—an initial sharp increase in response at low contrasts followed by a saturating nonlinearity prior to 100% contrast (Albrecht and Hamilton 1982). On average, V1 neurons reached 50% of their maximal response (C_{50}) at 16.7 ± 1.5% contrast (Fig. 1, *B* and *C*), with complex cells displaying

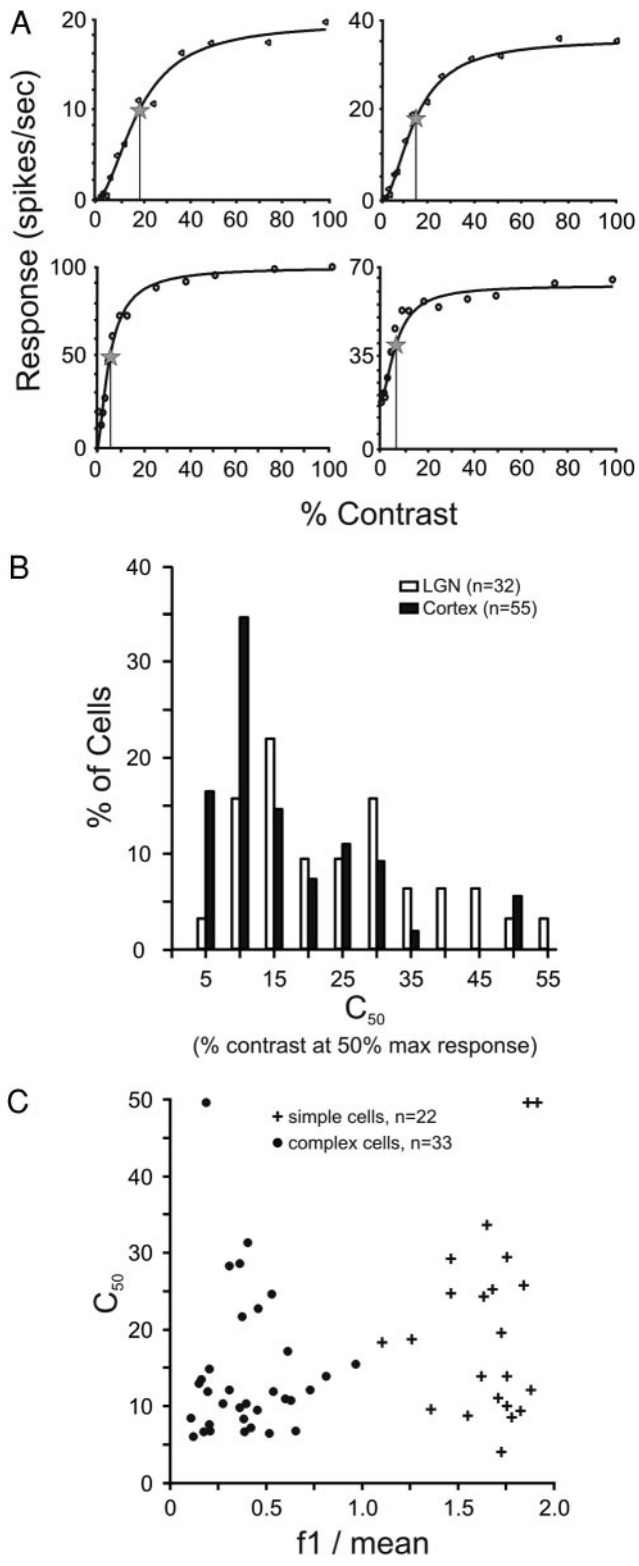


FIG. 1. Contrast response functions in ferret visual cortex. *A*: contrast response functions for four representative cells: 2 simple cells (*top*) and 2 complex cells (*bottom*). —, fits to a hyperbolic ratio (see METHODS); ⋆, the estimated contrast needed to achieve a half-maximum response (C_{50}, see METHODS). *B*: histogram showing the distribution of C_{50} values among 55 cortical neurons and 32 lateral geniculate nucleus (LGN) neurons. The average C_{50} for cortical neurons was less than that for LGN neurons [16.7 ± 1.5% (mean ± SE) vs. 24.7 ± 2.4%, respectively). *C*: scatter plot showing the relationship between the f1/mean ratio and C_{50} for each cortical neuron. +, simple cells; ●, complex cells. On average, simple cells have a greater C_{50} than complex cells (20.4 ± 2.8 vs. 14.3 ± 1.7%, respectively). While the 2 populations are significantly different ($P = 0.02$), the distributions are largely overlapping.

slightly lower C_{50s} than simple cells (14.3 ± 1.7 vs. 20.4 ± 2.8%, respectively; $P = 0.02$).

Because there are significant transformations in visual responses and receptive field structure across the thalamocortical synapse (Hubel and Wiesel 1962; Reid and Alonso 1995), we compared contrast response functions of LGN and V1 neurons. To make this comparison, we recorded from 32 neurons in layers A and A1 of the LGN. As was the case for our population of V1 neurons, LGN neurons typically displayed a saturating nonlinearity prior to 100% contrast. On average, the C_{50} for our population of LGN neurons (mean $C_{50} = 24.7 \pm 2.5\%$) was greater than that of simple cells (20.4 ± 2.8%, $P = 0.19$) and complex cells (14.3 ± 1.7%, $P < 0.01$). Thus there appears to be a progressive decrease in C_{50} as visual information is processed in the LGN and V1.

Effect of contrast on orientation tuning in V1

Orientation tuning is a prominent feature of neurons in ferret V1. For all neurons recorded from in this study, we generated orientation-tuning curves first using 100% contrast sine wave gratings of optimal spatial and temporal frequency. To obtain a reliable measure of tuning width, responses from each neuron were fit to a Gaussian equation using a constrained nonlinear optimization method (see METHODS). Orientation-tuning bandwidth was then determined by estimating the half-width of tuning curve peaks at half-maximum response (see METHODS). On average, simple cells were more tightly tuned than complex cells (Fig. 2*B;* simple cell mean half-width = 16.6 ± 1.1°; complex cell mean half-width = 23.7 ± 2.2°). This difference was significant ($P < 0.01$) and has been observed previously in other species (see Table 1 in DeValois et al. 1982; Ringach et al. 2002). However, because the population distributions of half-width at half height for simple cells and complex cells are largely overlapping (Fig. 2*B*), sharpness of orientation tuning is not a strict predictor of cell type.

In cat and monkey, orientation-tuning bandwidth of V1 neurons is invariant to stimulus contrast (Anderson et al. 2000; Sclar and Freeman 1982; Skottun et al. 1987). To determine whether or not orientation tuning of V1 neurons in the ferret is similarly contrast invariant, we generated several additional orientation-tuning curves using a range of contrasts. Again, the half-width at half height was estimated for each contrast presented. Figure 3*A* shows orientation-tuning curves of six representative V1 neurons under different levels of contrast. In each case, the tuning bandwidth of these neurons remained constant with different levels of contrast.

To quantify the relationship between contrast and orientation-tuning bandwidth, we plotted Gaussian half-width versus stimulus contrast for each neuron and performed a linear regression to estimate the correlation between the two variables (Fig. 3*B, inset*). If the tuning half widths from our sample of neurons were systematically influenced by contrast, then the slope of the best-fitting linear equation should be different from zero. Figure 3*B* shows results from this analysis for all of the neurons in our sample collectively. The mean slope for the entire population of V1 neurons was 0.0016 ± 0.01. There was no difference between simple and complex cells ($P = 0.94$). Accordingly, the average half-width of a typical V1 neuron changes by only 0.08° when contrast changes by 50% (e.g., 5–55% contrast).

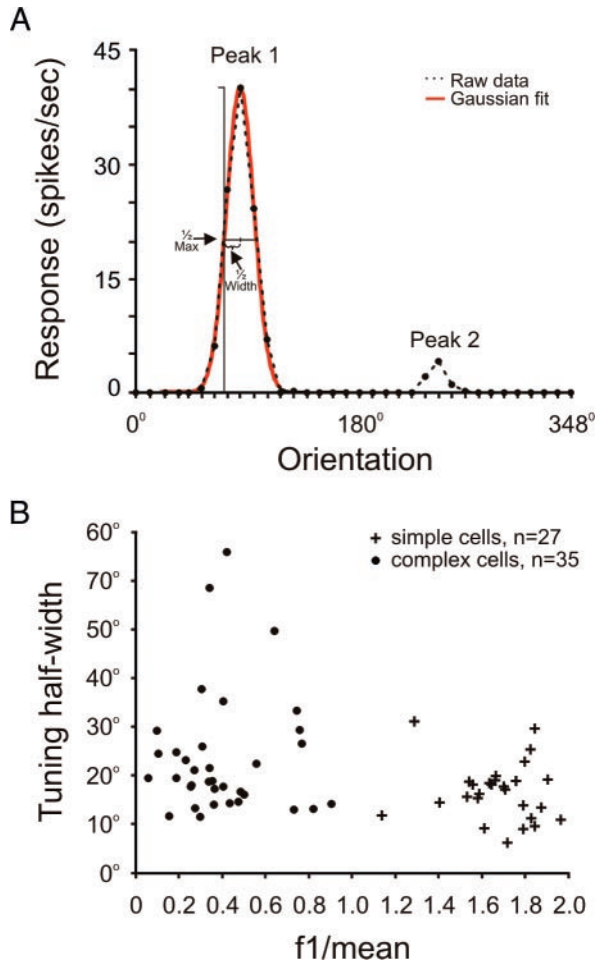


FIG. 2. Orientation-tuning bandwidth of cortical neurons at 100% contrast. *A*: bandwidth of orientation tuning was estimated by fitting the data to a Gaussian distribution (see METHODS). Measured responses are indicated with filled black circles; the Gaussian fit is indicated in red. Note that only the largest peak (preferred direction) in a tuning curve was fit to a Gaussian distribution. *B*: scatter plot showing the relationship between the f1/mean ratio for each neuron and the tuning half-width (peak half-width at half-maximum response, or σ *1.1774). crosses, simple cells; black circles, complex cells. On average, simple cells have narrower peaks in their orientation-tuning curves [16.6 ± 1.1° (mean ± SE)] than complex cells (23.7 ± 2.2°).

Because most V1 neurons display a nonlinear contrast response function, it is possible that orientation-tuning bandwidth *is* influenced by contrast but only in the nonsaturating region of the contrast response curve. If this was the case, then including several contrasts in the saturating region of a given neuron could significantly reduce the apparent effect of contrast on orientation tuning. To exclude this possibility, we took the highest contrast data point (saturating, high contrast) and plotted it against the lowest contrast data point (nonsaturating, low contrast) for each neuron (Fig. 3*C*). Analysis by *t*-test showed that the two populations were not significantly different from each other (simple cells, $P = 0.85$, complex cells, $P = 0.90$). As can be seen in Fig. 3*C*, most neurons cluster around equality. Therefore even when taking into account the nonlinear nature of the contrast response function of most V1 neurons, the bandwidth of orientation tuning, as assessed by half-width at half height, is unaffected by stimulus contrast.

A recent report suggests that the orientation tuning of cortical neurons may not be as invariant to stimulus contrast as

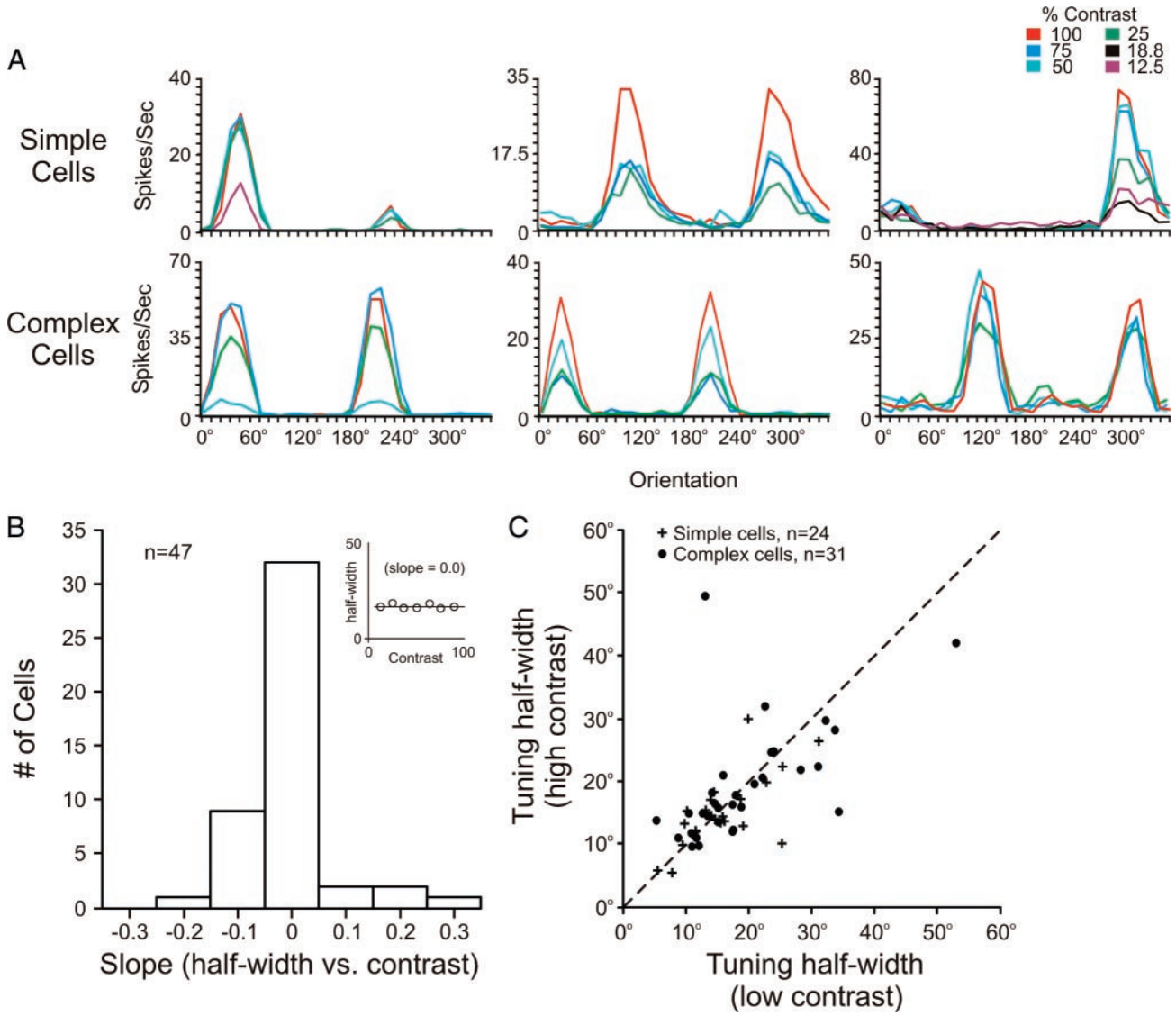


FIG. 3. Cortical neurons display contrast-invariant orientation tuning when assessed with bandwidth measures. *A*: orientation-tuning curves for 3 simple cells (*top*) and 3 complex cells (*bottom*) using different levels of contrast. Simple cell responses are plotted with respect to the first harmonic (f1) of measured responses; complex cell responses are plotted with respect to their mean response (see METHODS). Gaussian fits are not shown. *B*: histogram showing the relationship between tuning half-width and contrast for 47 cortical neurons. Values along the *x* axis—slope (half-width vs. percent contrast)—were determined by performing linear regression analysis on estimates of tuning half-width over a range of contrasts (see inset for example). The mean slope was 0.0016 ± 0.01 (mean ± SE), indicating no effect of contrast on tuning half-width. The number of cells contributing to *B* is slightly lower than that of *C* as only cells tested with a minimum of 4 contrast levels are included. *C*: scatter plot showing the relationship between tuning half-width at high contrast vs. tuning half-width at low contrast [high contrast = 92.9 ± 16.1% (mean ± SD); low contrast = 21.5 ± 14.4%]. +, simple cells; ●, complex cells. Neither population showed an effect of contrast on tuning half-width.

originally proposed. Specifically, when using circular variance to quantify orientation selectivity in macaque V1, Shapley and colleagues (2002) found an inverse relationship between contrast and circular variance. To determine whether or not a similar relationship holds for neurons in ferret V1, we calculated circular variance (see METHODS) for the same set of neurons used to examine the influence of contrast on orientation tuning half-width. Similar to results in the macaque, we found an inverse relationship between contrast and circular variance (Fig. 4). As shown in Fig. 4*A*, circular variance was significantly greater at low contrasts compared with high contrasts for both simple cells ($P < 0.02$) and complex cells ($P < 0.003$). To quantify the relationship between contrast and circular variance, we plotted circular variance versus stimulus contrast and fit the relationship to a linear equation (Fig. 4*B*). If circular variance was systematically influenced by contrast, then the slope of the best-fitting linear equation should be different from zero. Results show that the mean slope of circular variance versus contrast was significantly less than zero (Fig. 4*B;* mean $= -0.0012 \pm 3 \times 10^{-4}$; $P < 0.0001$). Although an average slope of -0.0012 may not seem striking, it should be noted that the average circular variance under high-contrast conditions was 0.41. Accordingly, if contrast were to change by 50%, then mean circular variance would change by 14%, given a slope of -0.0012.

Changes in circular variance can result from several differ-

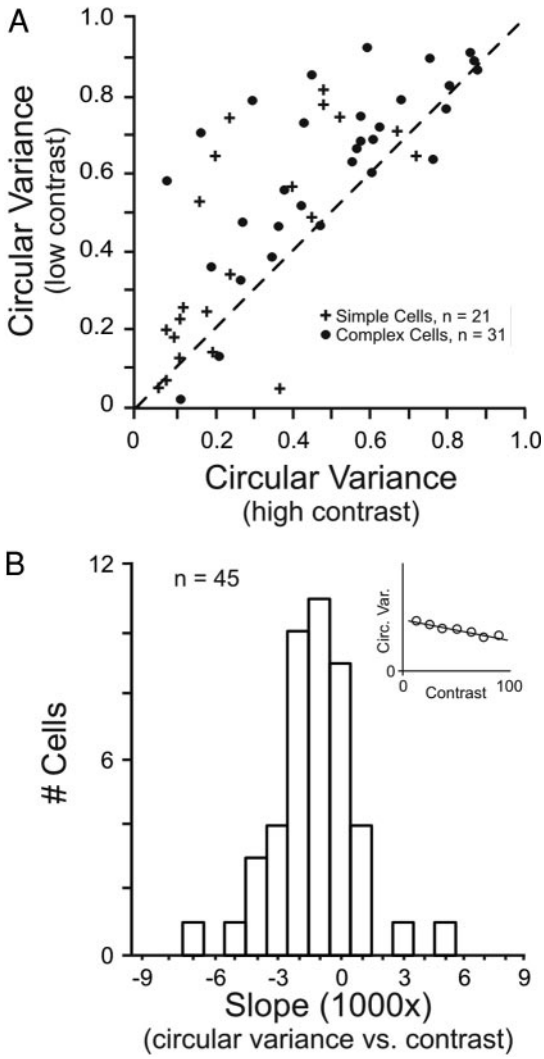


FIG. 4. Circular variance is inversely related to stimulus contrast. *A*: scatter plot showing the relationship between circular variance at low contrast versus circular variance at high contrast. Simple cells are indicated with crosses; complex cells indicated with filled black circles. Overall, circular variance was significantly greater at low contrasts (simple cells: $P < 0.02$; complex cells: $P < 0.003$). *B*: histogram showing the relationship between circular variance and contrast for 45 cortical neurons. Values along the *x* axis—slope (circular variance vs. percent contrast)—were determined by performing linear regression analysis on measures of circular variance over a range of contrasts (see *inset* for example). The mean slope ($-0.0012 \pm 3 \times 10^{-4}$; mean ± SE) was significantly <0 ($P < 0.0001$). The number of cells contributing to *B* is slightly lower than that of *A* as only cells tested with a minimum of 4 contrast levels are included.

ent changes in a Gaussian distribution (Fig. 5). For instance, a contrast-dependent decrease in circular variance could result from a contrast-dependent decrease in the bandwidth of orientation tuning (Fig. 5*A*). This possibility, however, is ruled out as cortical neurons display contrast-invariant orientation tuning, as assessed with bandwidth measures. A contrast-dependent decrease in circular variance could also result from a contrast-dependent decrease in the ratio of null orientation to preferred orientation activity. Two possible causes for a decrease in this ratio are a contrast-dependent increase in preferred orientation activity (Fig. 5*B*) in the presence of a nonzero DC-offset (compare Fig. 5, *B* and *D*) and/or a contrast-dependent suppression of null-orientation activity (Fig. 5*C*). Because it is widely accepted that contrast increases preferred orientation responses, the real question is whether or not contrast affects null-orientation responses and the DC offset.

To determine the cause(s) of the contrast-dependent decrease in circular variance, we first examined the relationship between contrast-dependent change in circular variance and contrast-dependent change in the ratio of null orientation to preferred orientation activity (Fig. 6). Among our population of cortical neurons, there was indeed a contrast-dependent shift in the ratio of null orientation to preferred orientation activity ($\text{mean}_{(\text{low contrast})} = 0.14$, $\text{mean}_{(\text{high contrast})} = 0.08$, $P < 0.05$). Further, there was a significant positive correlation between change in this ratio and change in circular variance ($r = 0.78$; $P < 0.001$), a correlation further improved by comparing change in the square root of null to preferred orientation activity, $(\text{null/preferred})^{0.5}$, and change in circular variance (Fig. 6; $r = 0.91$; $P < 0.0001$).

Within our dataset, we did not find a significant effect of contrast on null-orientation activity, as assessed with the DC offset ($\text{mean}_{(\text{high contrast})} = 2.03 \pm 0.49$ spikes/s, $\text{mean}_{(\text{low contrast})} = 2.16 \pm 0.45$ spikes/s; $P = 0.84$). Even when taking into account possible effects of changes in spontaneous activity between data collected under low- and high-contrast conditions, we did not find a significant influence of contrast on the DC-offset (Fig. 7*A;* $\text{mean}_{(\text{low contrast})} = -0.47 \pm 0.39$ spikes/s, $\text{mean}_{(\text{high contrast})} = -0.59 \pm 0.49$ spikes/s, $P = 0.86$). Based on these results, we conclude that the contrast-dependent change in circular variance is the result of a change in the ratio of null orientation to preferred orientation activity that is driven by a contrast-dependent increase in preferred orientation responses and not a contrast-dependent decrease in null-orientation responses.

Although we did not find evidence for a contrast-dependent suppression of null-orientation responses, we did find evidence for null-orientation suppression, in general. This suppression, however, was best measured in cells with reasonable levels of spontaneous activity. As shown in previous studies using extracellular recordings (Ramoa et al. 1986; Sclar and Freeman 1982), low levels of spontaneous activity can mask null-orientation suppression via a rectifying nonlinearity (that is, suppression cannot decrease firing rate <0). After excluding cells from our data set with spontaneous activity <1 spike/s and combining both high and low-contrast conditions, an ANOVA revealed null-orientation suppression, as the DC offset minus spontaneous activity was significantly less than zero (Fig. 7*B;* mean $= -1.52$ spikes/s, $P < 0.05$). Even for the population as a whole, an examination of null-orientation activity uncovered a linear relationship between spontaneous activity and DC offset that was consistent with null-orientation suppression. As shown in Fig. 7*C*, although the majority of cells displayed low levels of spontaneous activity, the best-fitting linear relationship between DC offset and spontaneous activity was below the line of unity for both high and low-contrast conditions. This result indicates that spontaneous activity grows faster than the DC offset, an effect consistent with null-orientation suppression.

Temporal-frequency response functions

In cat and monkey, LGN neurons are able to follow higher temporal frequencies than V1 neurons (Hawken et al. 1996; Movshon et al. 1978; Orban et al. 1985). To compare the

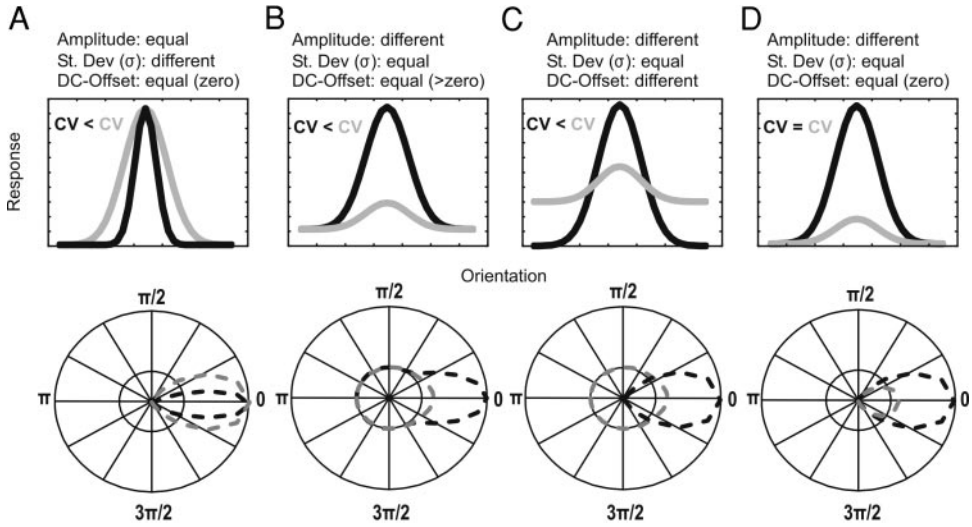


FIG. 5. *Top*: orientation tuning curves and factors that influence circular variance (CV). Gaussian distributions; *bottom*: corresponding polar plots. *A*: CV is influence by the SD (σ) of a Gaussian distribution: a decrease in the SD (a value used to determine peak half-width at half-height, see METHODS) will lead to a decrease in circular variance. *B*: in the presence of a DC offset, an increase in the amplitude of a Gaussian distribution will lead to a decrease in circular variance. *C*: CV is influenced by the DC offset of a Gaussian distribution: a decrease in the DC offset will lead to a decrease in the circular variance. *D*: CV is not affected by a change in the amplitude of a Gaussian distribution, provided the DC offset is 0.

temporal-frequency tuning properties of LGN and cortical neurons in the ferret, we recorded from 32 LGN neurons and 32 cortical neurons while presenting cells with drifting sine-wave gratings of varying temporal frequency. Temporal-frequency response functions were interpolated with a cubic spline to allow an estimate of the highest temporal frequency that would elicit a half-maximum response (TF_{50}, Fig. 8*A*). As expected, TF_{50} values were greater for LGN neurons than for cortical neurons (mean LGN $TF_{50} = 19.8 \pm 2.9$ cycles/s, mean cortical $TF_{50} = 5.6 \pm 0.5$ cycles/s, Fig. 8*B*) supporting the view of low-pass filtering between LGN and cortex (Hawken et al. 1996; Movshon et al. 1978; Orban et al. 1985). Among cortical neurons, TF_{50} values did not differ significantly between simple and complex cells (mean: 6.4 ± 3.1 vs. 5.5 ± 2.4 cycles/s, respectively, $P = 0.459$).

Influence of contrast on temporal-frequency tuning

Stimulus contrast is known to influence the temporal-frequency tuning of cortical neurons (Albrecht 1995; Holub and Morton-Gibson 1981). For instance, contrast gain control—as originally reported for retinal ganglion cells of cats (Shapley and Victor 1978, 1981)—can be described as an increase of high temporal-frequency responses relative to low temporal-frequency responses as contrast increases. Although contrast gain control exists in the retina and LGN, recent proposals suggest that additional cortical nonlinearities could explain the contrast-dependent improvement in cortical responses to high temporal-frequency stimuli (Carandini et al. 1997; Kayser et al. 2001). If this is indeed the case, then contrast induced rightward shifts in temporal-frequency tuning should, on average, be greater for cortical neurons than for LGN neurons. We therefore measured the influence of contrast on temporal-frequency tuning for 32 cortical neurons and 32 LGN neurons. Representative examples of temporal-frequency response functions under different contrast conditions are shown in Fig. 9*A*. Figure 9, *B* and *C*, shows TF_{50} values under high- and low-contrast conditions with points above unit slope indicating cells that display a contrast-dependent increase in TF_{50}. Among our population of cortical and LGN neurons, TF_{50} values calculated using high-contrast stimuli were, on average, greater than TF_{50} values using low-contrast stimuli (cortical neurons, $P < 0.05$; LGN neurons, $P < 0.05$). While our population of LGN neurons included both X and Y cells, it is worth noting that we only classified a subset of the LGN neurons and therefore cannot comment on whether the two cell types differ in the extent to which they experience a contrast-dependent shift in temporal-frequency tuning as has been reported in cat (Sclar 1987).

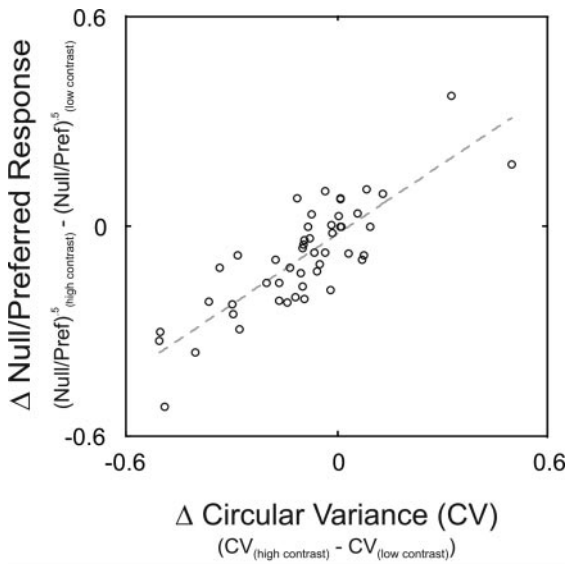
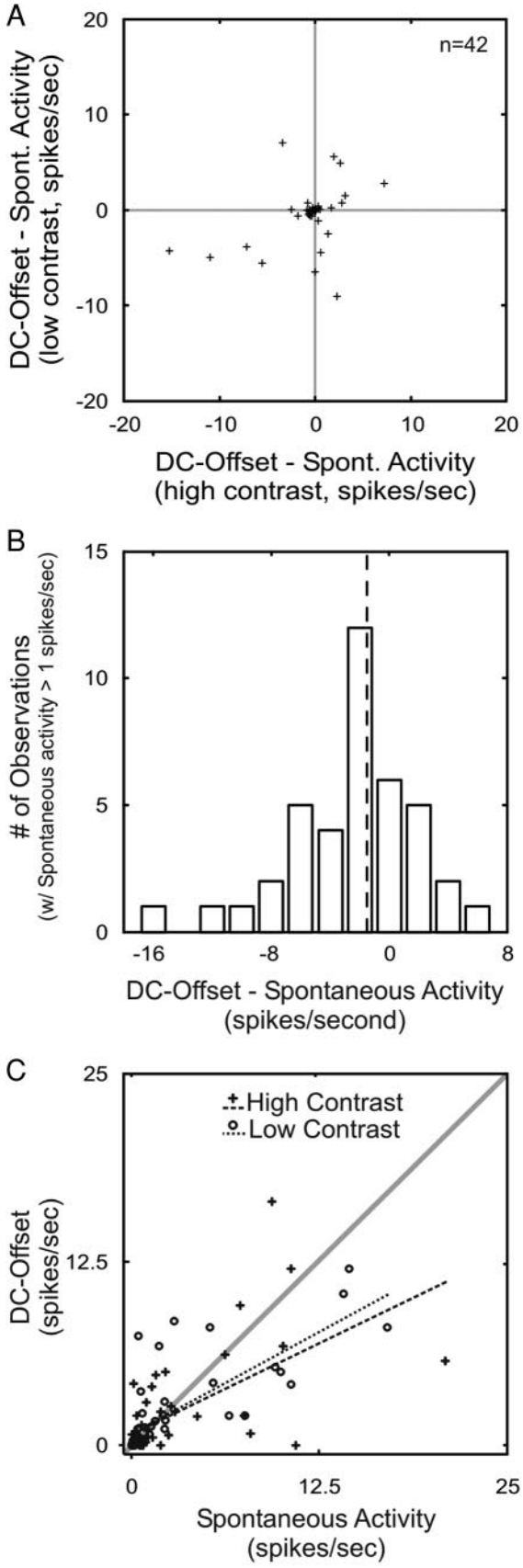


FIG. 6. Relationship between change in circular variance and change in the ratio of null orientation to preferred orientation responses. Results show a significant positive correlation ($r = 0.82$; $P < 0.0001$) between the 2 measures.

To quantify and compare the contrast-dependent shift in temporal-frequency tuning between LGN and cortical neurons, we calculated a contrast gain control index (CGCI, see METHODS), whereby positive CGCI values indicate an increase in TF_{50} with increasing contrast and negative CGCI values indicate a decrease in TF_{50} with increasing contrast. Figure 9*D* shows the distribution of CGCI values for our set of cortical and LGN neurons. Mean CGCI values were similar for cortical neurons (CGCI $= 0.14 \pm 0.05$) and LGN neurons (CGCI $= 0.22 \pm 0.04$) and analysis via *t*-test shows that the two populations are statistically indistinguishable from each other ($P = 0.24$). According to results of this analysis, the contrast-depen-



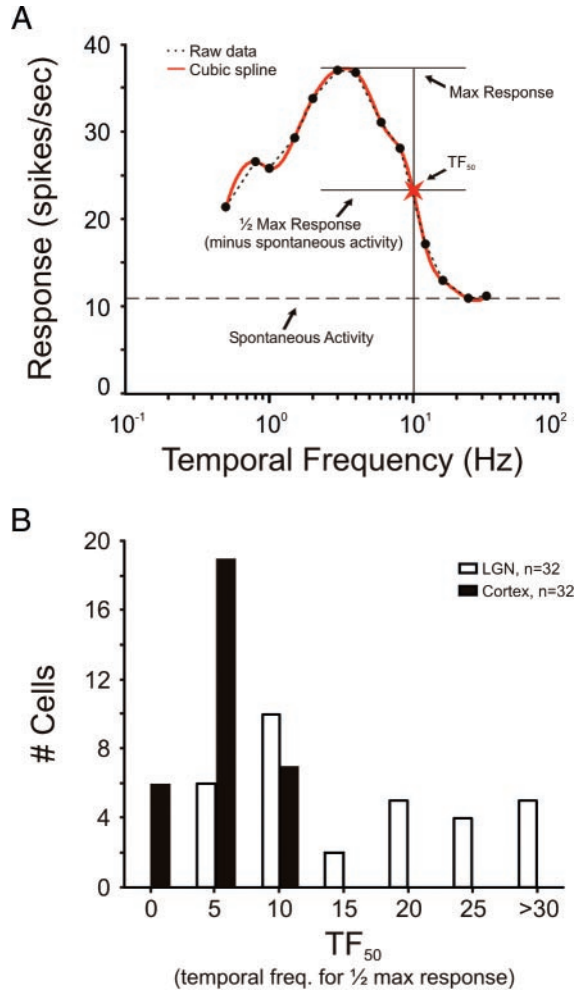


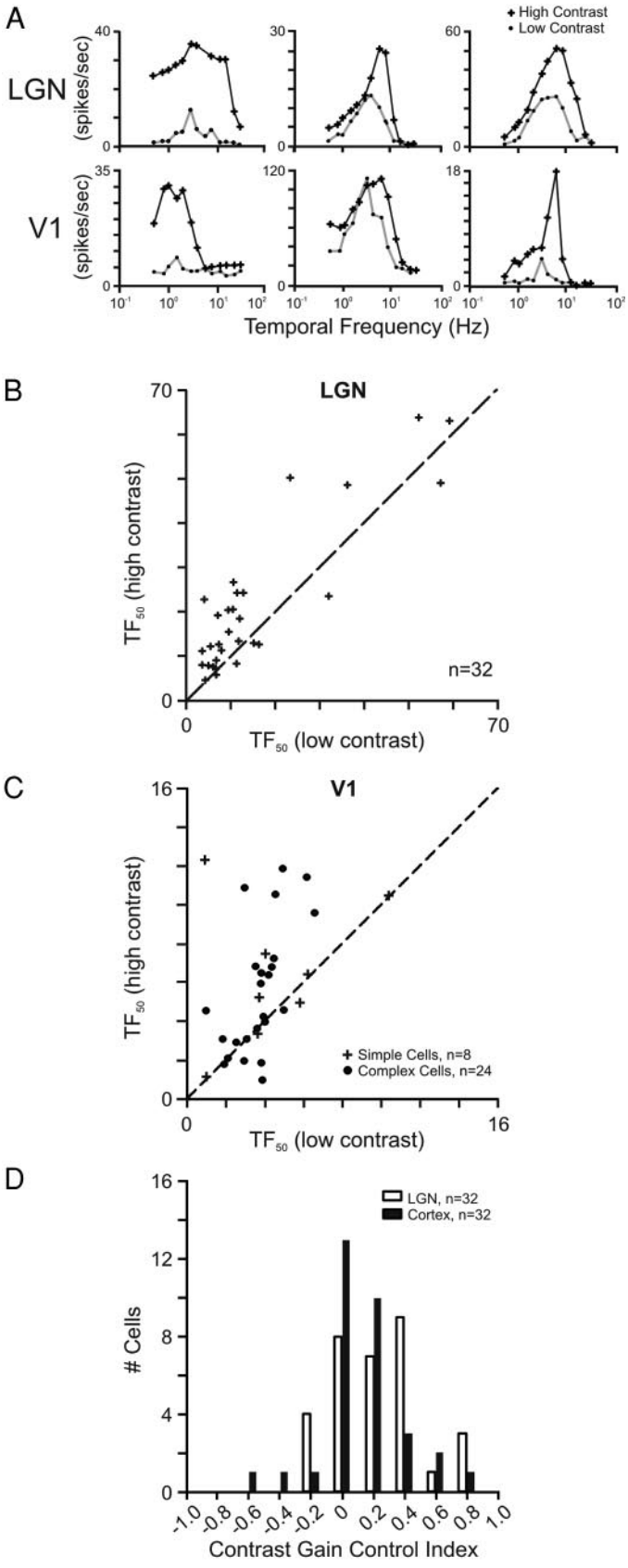
FIG. 8. Temporal-frequency tuning in the cortex and LGN. *A*: representative example of a temporal-frequency tuning curve illustrating how the TF_{50} (the highest temporal frequency to achieve a half-maximum response) was determined. Temporal-frequency tuning curves were interpolated with a cubic spline (red); raw data are shown in black. *B*: histogram showing the distribution of TF_{50} values for 32 cortical neurons and 32 LGN neurons. On average, TF_{50} values were greater for LGN neurons than for cortical neurons [19.8 ± 2.9 (SE) vs. 5.6 ± 0.5 cycles/°].

dent shift in TF_{50} in the cortex does not necessarily require additional cortical processing.

Influence of contrast on response latency

Finally, we investigated the effect of contrast on the response latency of visual neurons in the ferret. Previous studies in cat and monkey have suggested that visual neurons have a reduced response latency at high-contrast levels compared with

FIG. 7. Cortical neurons display contrast-invariant, null-orientation suppression. *A*: scatter plot showing the relationship between DC offset minus spontaneous activity under low and high-contrast conditions. There is not a significant effect of contrast on this measure of null-orientation suppression ($P = 0.84$). *B*: histogram showing the extent of null-orientation suppression, as indicated by measures of DC offset minus spontaneous activity, among cortical neurons with spontaneous activity levels >1 spikes/s. As a population, this measure of null-orientation suppression was significantly <0 ($P < 0.05$). *C*: scatter plot showing the relationship between DC offset and spontaneous activity. Linear regression (- - -) indicates suppression of null-orientation responses for both low- and high-contrast stimuli.



low-contrast levels. This effect has been measured in retinal ganglion cells (Benardete et al. 2002; Shapley and Victor 1978, 1981), LGN cells (Kremmers et al. 1997; Saul and Humphrey 1990; Sclar 1987), and simple cells (Albrecht 1995; Carandini and Heeger 1994; Dean and Tolhurst 1986; Reid et al. 1992) as a phase advance of responses to grating stimuli at high contrasts relative to low contrasts. In other words, these cell types respond progressively earlier in the stimulus cycle when presented with sine wave gratings at high contrasts relative to low contrasts. To determine the influence of contrast on the phase of LGN and cortical simple cell responses, we used data collected to measure contrast response functions and fit the relationship between log contrast and response phase to a linear polynomial.

As was the case for TF_{50} values, many but not all, cortical and LGN neurons display response phase that is dependent on contrast (Fig. 10*A*). To quantify the relationship between response phase and contrast, we first plotted response phase versus log contrast for each neuron and fit the relationship to a linear equation (Fig. 10B, inset). If response phase was systematically influenced by contrast, then the slope of the best-fitting linear equation should be different from zero. Although both the LGN and V1 populations contain many examples of neurons with slopes equal to zero (i.e., no influence of contrast on response latency), both populations are skewed toward positive values and have mean slopes that are significantly greater than zero (Fig. 10*B;* LGN $P < 0.01$; V1 $P < 0.01$). The average slope of the relationship between response phase and log contrast was 0.49 ± 0.101 for LGN neurons and 1.03 ± 0.23 for cortical neurons. This corresponds to a shift of 13.2% of a cycle for the LGN neurons and a shift of 27.0% of a cycle for the cortical neurons following a 50% change in contrast. Finally, a comparison of the phase advance exhibited by our population of LGN and cortical neurons reveals that phase advance in the cortex is significantly greater in magnitude than in the LGN ($P < 0.01$). While the two populations are partially overlapping, these observations indicate that cortical processing can influence phase advance beyond that present in the LGN, as has been suggested from theoretical work (Carandini et al. 1997; Chance et al. 1998; Kayser et al. 2001).

DISCUSSION

The goal of this study was to determine the influence of contrast on the response properties of neurons in ferret primary visual cortex. We show that neurons in primary visual cortex of the ferret exhibit contrast-invariant orientation tuning as as-

FIG. 9. Effect of contrast on temporal-frequency tuning. *A*: temporal-frequency tuning curves for 3 representative LGN neurons (*top*) and 3 representative cortical neurons (*bottom*). Gray points represent neural responses at low contrast; black points represent responses at high contrast. *B* and *C*: scatter plots showing the relationship between high-contrast TF_{50} and low-contrast TF_{50} for 32 LGN neurons [*B*, high contrast = 86.9 ± 18.9% (mean ± SD); low contrast = 23.6 ± 11.3%] and 32 cortical neurons (*C*, high contrast = 95.9 ± 11.1%; low contrast = 18.5 ± 11.5%). Both LGN and cortical neurons have greater TF_{50s} at high contrast relative to low contrast ($P < 0.05$ for both populations). *D*: histogram showing the distribution of contrast gain control index (CGCI) values for LGN and cortical neurons. The CGCI was calculated as $(TF_{50\ \text{high contrast}} - TF_{50\ \text{low contrast}})/(TF_{50\ \text{high contrast}} + TF_{50\ \text{low contrast}})$. Positive values indicate an increase in TF_{50} as contrast increases. Mean CGCI values were similar for cortical and LGN neurons [0.136 ± 0.05 (mean ± SE) vs. 0.217 ± 0.04, respectively].

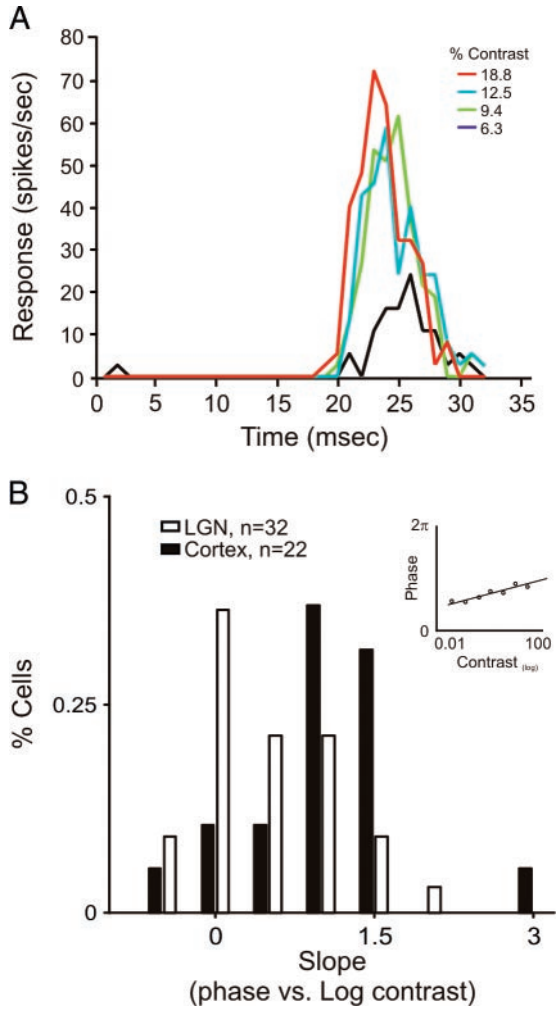


FIG. 10. Contrast induces a phase advance in the timing of responses for LGN neurons and cortical simple cells. *A*: representative example of the responses of a simple cell presented with sine-wave gratings of different contrasts. Response timing of the cell advanced as contrast levels increased. *B*: histogram showing the relationship between timing of response and contrast for 22 simple cells and 32 LGN neurons. Values along the *x* axis—slope (phase vs. contrast)—were determined by performing linear regression analysis on measures of response phase over a range of contrasts [see *inset* for example; cortex range: high contrast = 21.3 ± 13.3% (mean ± SD), low contrast = 13.23 ± 9.9%; LGN range: high contrast = 27.2 ± 15.4%, low contrast = 15.6 ± 10.1%]. The mean slope (phase vs. contrast) was significantly >0 for both populations ($P < 0.01$) with simple cells showing greater phase advance, on average, than LGN neurons.

sessed by measures of Gaussian half-width at half-maximum response. Contrast does, however, influence the structure of orientation-tuning curves as measures of circular variance decrease with increasing contrast. A similar effect of contrast on circular variance has been described in a recent preliminary report for neurons in monkey V1 (Shapley et al. 2002), indicating that this property of visual processing is shared across species. In the ferret, we show that the change in CV is driven by an increase in preferred orientation activity at high contrast and is not related to changes in orientation-tuning bandwidth or changes in activity at null orientations. We also show that V1 neurons in ferret display a contrast-dependent rightward shift in the high temporal-frequency stimuli that elicit a half-maximum response. Although past efforts have suggested that this contrast-dependent shift could rely on intracortical mechanisms (Carandini et al. 1997; Kayser et al. 2001), results from the present study show that the degree of shift experienced by cortical neurons is similar in magnitude to that of LGN neurons. Thus the effect of contrast on temporal-frequency tuning in ferret cortex appears to reflect the response profiles of feed-forward inputs from the thalamus. Finally, our results demonstrate a significant increase in the contrast-dependent phase advance of cortical neurons compared with LGN neurons. In the following sections, we discuss the paradoxical findings of contrast-invariant orientation tuning and contrast-dependent changes in circular variance; we also consider potential neural mechanisms to account for the effects of contrast on cortical responses.

Contrast response function and orientation tuning

Our results confirm those of previous studies showing no relationship between stimulus contrast and bandwidth of orientation tuning (Anderson et al. 2000; Sclar and Freeman 1982; Skottun et al. 1987). However, using an alternative measure—circular variance—to quantify orientation selectivity (Ringach et al. 2002), we found an inverse relationship between circular variance and contrast similar to that recently reported for cortical neurons in the macaque monkey (Shapley et al. 2002).

Circular variance is a measure that reflects how well a neuron's orientation tuning curve, when plotted in polar coordinates (as in Fig. 5, *bottom*), approximates a circle. If an orientation-tuning curve is best described with only a DC offset (e.g., orientation tuning of an LGN neuron), circular variance will equal one. As neurons become more sharply tuned for orientation, circular variance decreases. At the extreme, neurons that respond only to a single orientation have a circular variance of zero. In general, changing the amplitude of an orientation tuning curve will have no influence on circular variance, provided the ratio of null response to preferred response remains constant. For cortical neurons, a constant ratio would be seen for neurons that either lack orientation selectivity (i.e., null response/preferred response = 1) or lack a DC-offset (i.e., null response/preferred response = 0).

In the present study, we show that the contrast-dependent decrease in circular variance results from contrast-dependent changes in the ratio of null/preferred orientation responses. Although contrast has been shown to suppress null-orientation responses in cat (Sclar and Freeman 1982)—an effect that would change the ratio of null/preferred orientation responses in the direction necessary to produce a decreased circular variance—we found no evidence for contrast-dependent suppression in the ferret. Instead, results show that change in circular variance is primarily caused by an increase in the amplitude of the orientation-tuned response at high contrasts in the presence of a contrast invariant DC offset (see Fig. 5*B*).

Models and mechanisms

Contrast invariant orientation tuning is difficult to explain purely on the basis of feed-forward input from the LGN (see Ferster and Miller 2000; Miller 2003; Sompolinsky and Shapley 1997). Feed-forward models that lack inhibition or suppression predict that the bandwidth of orientation tuning should broaden with increasing levels of contrast. In such models,

simple cells—the primary target of thalamic afferents—can reach spike threshold by receiving either weak excitation from many LGN neurons, as would occur with a low-contrast stimulus oriented optimally along the length of the receptive field, or strong excitation from just a few LGN neurons, as would occur with a high-contrast stimulus oriented orthogonal to the long axis of the receptive field.

By adding inhibition to feed-forward models, however, contrast invariant orientation tuning can be obtained. In particular, an evolving model by Miller and colleagues predicts that cortical simple cells will display contrast invariant orientation tuning if they receive feed-forward excitation from LGN neurons with appropriately overlapping receptive fields and feed-forward untuned inhibition that scales with contrast (Miller 2003; Troyer et al. 1998, 2002; K. D. Miller, personal communication). Results from a number of studies provide support for the first component of the model (Ferster 1988; Hirsch et al. 1998; but see Borg-Graham et al. 1998). We believe results from the present study may provide partial support for the second component. In particular, we report suppression of spiking activity to null-orientation stimuli. Although this extracellular measure of suppression is contrast invariant, the following argument can be made that the intracellular inhibition that contributes to the measure actually scales with contrast. Individual layer 4 neurons receive feedforward excitatory input from the LGN that can be thought of as containing two components—an orientation-tuned Gaussian and an untuned DC offset. If we accept the view that the orientation-tuned Gaussian and DC offset both scale with contrast, then there would seem to be a requirement for an untuned source of inhibition that scales similarly with contrast. This untuned inhibition would serve to cancel out the untuned excitation and allow the cell to maintain a constant level of spiking activity to null-orientation stimuli over a range of contrasts. Although the specific source(s) of untuned inhibition needed for contrast invariant orientation tuning has yet to be determined, recent studies in cat and ferret report the existence of untuned layer 4 neurons that are either known (Hirsch et al. 2003) or suspected (Usrey et al. 2003) inhibitory neurons. Untuned inhibition could also result from inhibition from a large population of neurons wherein each individual inhibitory neuron is tuned to orientation, but the population as a whole is untuned to orientation. Finally, it should be noted that untuned inhibition is likely to be a general property of V1 neurons across species, as reports describe null-orientation suppression in cat (Sclar and Freeman 1982) and both tuned and untuned suppression in macaque monkey (Ringach et al. 2003).

In addition to the mechanisms described in the preceding text, consideration should also be given to the influence of synaptic depression on contrast-invariant orientation tuning. A number of studies, both in vitro and in vivo, have shown that thalamocortical synapses experience synaptic depression (Carandini et al. 2002; Chung and Nelson 2002; Freeman et al. 2002; Gil et al. 1999; Stratford et al. 1996). Thus as firing rates of thalamic neurons increase, as would occur with increasing contrast, excitatory postsynaptic potentials (EPSPs) decrease. Because thalamic neurons lack orientation selectivity, synaptic depression that accompanies increases in contrast should reduce the input conductance of layer 4 neurons at all orientations—an effect similar in spirit to the negative DC offset provided by inputs from untuned inhibitory neurons (as described in the preceding text). Although direct evidence for, or against, synaptic depression in the construction of contrast-invariant orientation tuning is lacking, recent modeling efforts conclude that synaptic depression neither creates nor necessarily degrades contrast-invariant orientation tuning in primary visual cortex (Carandini et al. 2002; Kayser et al. 2001).

Finally, neurons along the visual pathway are known to experience a decreased latency or phase advance in visual responses as stimulus contrast increases (Albrecht 1995; Carandini and Heeger 1994; Dean and Tolhurst 1986; Reid et al. 1992; Saul and Humphrey 1990; Sclar 1987; Shapley and Victor 1978, 1981; see Fig. 2 of Kayser et al. 2001). Although recent arguments have suggested that phase advance is likely to be greater in the cortex than in the LGN (Carandini et al. 1997; Chance et al. 1998; Kayser et al. 2001), this idea had not previously been tested in the same study. Our results in the ferret now demonstrate that cortical neurons do, on average, display a greater contrast-dependent phase advance than LGN neurons. Modeling efforts suggest that the increased phase advance could result from cortical synaptic depression (Chance et al. 1998) and/or a combination of geniculocortical synaptic depression, intracortical synaptic depression, spike-rate adaptation, and stimulus-induced conductance increases that decrease the membrane time constant (Kayser et al. 2001). If cortical synaptic depression is found to play a role, then synaptic depression, as a general mechanism, may likely contribute to the contrast-dependent phase advance exhibited by LGN neurons. Indeed, retinogeniculate synapses, like thalamocortical synapses, are known to experience synaptic depression (Chen and Regehr 2003; Chen et al. 2002).

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