Contrast dependence of center and surround integration in primary visual cortex of the cat

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The magnitudes of spike responses of area 17 (striate cortex, area V1) neurons to stimulation of their classical receptive fields were reduced (suppressed) when the stimuli extended into the silent surround regions. We found that when optimally oriented sine-wave drifting grating patches extended into the distant parts of silent surround regions, over 35% of V1 neurons showed a 'counter-suppression', that is, a reduction in the magnitude of suppression. The magnitudes of both the suppression and the counter-suppression effects were dependent on stimulus contrast, that is, with a decrease of contrast the magnitude of suppression decreased, while the magnitude of counter-suppression increased. Overall, the surround modulation tended to be clearly suppressive at high contrast and less suppressive or even facilitatory at low contrast. The contrast-dependent effects described here appear to represent one of the fundamental properties of neurons in the mammalian visual system. These properties allow improvement of recognition (high contrast) or detection (low contrast) of visual objects under varying conditions. Putative changes of center and surround mechanisms at low contrast are discussed.

Keywords: iso-oriented drifting gratings, stimulus contrast, surround suppression, counter-suppression, facilitation, single unit recordings


Introduction

Stimulation of parts of visual space surrounding the classical receptive field (CRF) of single neurons in mammalian primary visual cortex (striate cortex, area 17, area V1) can dramatically modulate the magnitude of spike responses evoked by CRF stimulation. When the CRFs and the silent surrounds are concurrently stimulated with iso-oriented gratings the effects are usually reported to be suppressive (Akasaki, Sato, Yoshimura, Ozeki, & Shimegi, 2002; Bardy, Huang, Wang, FitzGibbon, & Dreher, 2006; Li & Li, 1994; Sadakane, Ozeki, Naito, Akasaki, Kasamatsu, & Sato, 2006; Walker, Ohzawa, & Freeman, 2000; for review of earlier publications, see Allman, Miezin, & McGuinness, 1985). However, optical imaging studies of responses of area 17 neurons to stimuli presented in the region well beyond the CRFs, suggest that stimulation of the silent surround generates both excitatory and inhibitory subthreshold activities (Toth, Rao, Kim, Somers, & Sur, 1996). Indeed, depending on the relative contrast between the CRF and its surround, the effects of stimulation of silent surrounds on the magnitude of spike responses of area 17 neurons can be either...
suppressive or facilitatory (see also Mizobe, Polat, Pettet, & Kasamatsu, 2001; Polat, Mizobe, Pettet, Kasamatsu, & Norcia, 1998; Sengpiel, Sen, & Blakemore, 1997). Furthermore, although the surround effects revealed by large iso-oriented gratings are rarely facilitatory, it has been reported that in cat’s area 17 suppression induced by stimulation of the proximal or ‘near’ silent surround (<5° from the CRF) is counterbalanced by the ‘disinhibition’ or ‘counter-suppression’ when the distal or ‘far’ surround (usually >5° from the CRF) is stimulated (Li & Li, 1994). However, the phenomenon of counter-suppression originating from the distal parts of the silent surround has not been reported in many relevant subsequent studies of area V1 and one of the present study was reinvestigation of this issue.

The extent of the excitatory spatial summation of excitation in the receptive fields (RFs) of V1 neurons in domestic cats (Sadakane et al., 2006; Sengpiel et al., 1997) and macaque monkeys (Kapadia, Westheimer, & Gilbert, 1999; Sceniak, Ringach, Hawken, & Shapley, 1999) appears to depend on stimulus contrast and is on average twice as large at low contrast as that at high contrast. This extension of spatial summation of excitatory signals into the visual space immediately surrounding the CRF suggests a rebalance between subthreshold excitation and inhibition originating in the region. Furthermore, it has been demonstrated previously that at low contrast the spatial extent of the silent surround is far greater than the extent of the excitatory summation area—in many cases it can extend beyond 13° of visual angle (cat: Li & Li, 1994; Mizobe et al., 2001; macaque monkey: Levitt & Lund, 2002). It is not yet known to what extent single cortical neurons integrate the information over a large part of the visual field at various stimulus contrasts. Thus, using single patches of optimized drifting sine-wave luminance gratings we investigated the effect of stimulus contrast on spatial integration over a large area (up to 28° in diameter) surrounding the CRF of individual area 17 neurons. Preliminary results have been published in form of an abstract (Wang, Bardy, Huang, FitzGibbon, & Dreher, 2007).

**Materials and methods**

**Animal preparation**

Nine normal adult cats of either sex, weighing 2.5–4.0 kg, were used. All procedures were performed in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, revised 1985) and were approved by the Animal Care Ethics Committee of the University of Sydney. Standard animal preparation procedures for extracellular recording were used (Bardy et al., 2006; Huang, Wang, & Dreher, 2007; Wang, Waleszczuk, Burke, & Dreher, 2000). Briefly, the animals were initially anaesthetized with 2.5–5.0% halothane and a 70:30 mixture of N2O and O2. A surgical level of anesthesia was maintained with 1.5–2.5% halothane in the same gaseous mixture while the surgery, intravenous and tracheal cannulation and bilateral cervical sympathectomy were performed. A small craniotomy was positioned over the site of area 17 where the central visual field is represented. During the recording session the level of halothane was reduced to 0.5–1.0% and the animal was paralyzed with a continuous i.v. infusion of gallamine triethiodide (7.5–10 mg kg⁻¹ h⁻¹; Sigma Aldrich, USA) in a 50:50 mixture of 5% dextrose and Hartmann’s Solution (sodium lactate) and artificially ventilated. Peak expired-CO2 was monitored and kept close to 4.0%. The electroencephalogram (EEG) and heart rate were recorded continuously for monitoring anaesthetic level. The level of halothane was adjusted when necessary to maintain slow-wave synchronized activity (0.5–4 Hz) in the EEG and heart rate below 220 beats/min. The animal’s body temperature was regulated by an automatically controlled heating blanket and kept at 37°C.

Antibiotics (Amoxicillin, 75 mg; 150 mg ml⁻¹, Norbrook Laboratories, Newry, UK), dexamethasone phosphate (4 mg; 5 mg ml⁻¹, Troy Laboratories, Smithfield, NSW, AU) and atropine sulfate (0.3 mg; 0.6 mg ml⁻¹, Apex Laboratories, Somersby, NSW, AU) were administered i.m. daily. The pupils were dilated with 1% atropine sulfate (Sigma Pharmaceuticals, Clayton, VIC, AU) and the nictitating membranes were retracted with 0.2% phenylephrine hydrochloride (10%, Chauvin Pharmaceuticals, Kingston- Upon-Thames, Surrey, UK). The corneas were protected with zero-power air-permeable contact lenses and 3 mm artificial pupils were placed in front of the eyes. Correcting lenses were used to bring the eyes into focus on a viewing tangent screen 57 cm in front of the eyes.

To reconstruct the recording electrode penetrations, electrolytic lesions were made at the end of each electrode penetration (typically 5–7 μA for 10 s). At the end of the experiment the animals were deeply anaesthetized by an overdose of pentobarbitral sodium (60 mg kg⁻¹ i.v.; 325 mg ml⁻¹, Lethabarb®, Virbac Australia, Peakhurst, NSW, AU) and perfused transcardially with warm (37°C) physiological saline followed by 4% paraformaldehyde in 0.1 M phosphate buffer. The brains were stored in 30% sucrose in 0.1 M phosphate buffer for cryoprotection then stereotactically blocked, coronally sectioned at 50 μm on a freezing microtome, mounted on slides and stained with Cresyl Violet for Nissl substance. Penetrations were reconstructed from brain sections with the aid of a computer morphometry program (Magellan software).

**Visual stimuli and recording neuronal activity**

Visual stimuli were generated by a VSG-5 stimulus system (Cambridge Research System, Cambridge, UK) and were presented on a CRT monitor (Barco, Belgium). Single neurons in area 17 were recorded extracellularly
using stainless steel microelectrodes (11 MΩ; FHC, Bowdoin, ME, USA). RFs of area 17 neurons were first mapped with hand-held light slits and black bars. RF properties (orientation-tuning, temporal and spatial frequency profiles) to stimuli presented via the dominant eye were then examined quantitatively by presenting a series of sinusoidally modulated luminance gratings. The contrast response function was then tested using the optimal stimulus size obtained at high contrast. Once the optimal stimulus for an individual neuron was determined, the center of the CRF was reassessed to ensure the accuracy of its location. This was done by using a series (usually 49 or 7 × 7) of single small drifting grating patches (0.5–1° in diameter) pseudo-randomly presented over the RF.

We examined size tunings with single drifting gratings optimized for individual cells. For each of 57 cells tested at two or more contrasts, a high and a low contrast were selected, based on the contrast response function of an individual cell, that elicited ~80% and ~40%, respectively, of the maximal response. The mean luminance of all stimuli was kept constant at 8 cd m⁻² as was the background luminance of the stimuli. Each stimulus cycle consisted of an initial period of 1 s stationary grating stimulation followed by 3 s drifting grating stimulation and then a 1 s blank before the next stimulus cycle. Stimuli of different sizes were pseudo-randomly presented and typically ranged from 0.5° to 28° in diameter in 10 or 12 logarithmic steps. Usually, each size-tuning profile was constructed from 2 blocks of stimuli, each with 6 repetitions. Contrast was defined as (Lmax - Lmin)/(Lmax + Lmin).

Data analysis

The cells were classified as ‘simple’, if the first harmonic (F1) of their spike responses to sine-wave gratings was greater than the mean firing rate (F0) of the response (F1/F0 ratio >1), or ‘complex’, if F1/F0 ratios were <1 (cf. Bardy et al., 2006; Skottun, De Valois, Grosof, Movshon, Albrecht, & Bonds, 1991). For simple cells, the size-tuning curves were based on the first harmonic (F1) of the responses to the optimized gratings, while for complex cells the mean firing rate (F0) of the response was used. Each size-tuning curve was fitted using a Supplementary Difference of Gaussians (3G) model.

The model is defined as

\[ f(s) = K_c \cdot G_c(s) - K_s \cdot G_s(s) + K_{cs} \cdot G_{cs}(s), \]

where

\[ G_c(s) = \left( \frac{2}{\sqrt{\pi}} \int_0^s e^{-y/w_c^2} dy \right)^2, \]

\[ G_s(s) = \left( \frac{2}{\sqrt{\pi}} \int_0^s e^{-y/w_s^2} dy \right)^2, \]

\[ G_{cs}(s) = \left( \frac{2}{\sqrt{\pi}} \int_0^s e^{-y/w_{cs}^2} dy \right)^2, \]

and

\[ G_{cs}(s) = \left( \frac{2}{\sqrt{\pi}} \int_0^s e^{-y/w_{cs}^2} dy \right)^2, \]

in which \( s \) is stimulus diameter, \( K_c \) and \( w_c \) are the strength and space constant of the center, and \( K_s \) and \( w_s \) are the strength and space constant of the suppressive surround (cf. Cavanaugh, Bair, & Movshon, 2002). \( K_{cs} \) and \( w_{cs} \) are the strength and space constant of the excitatory counter-suppressive surround.

Where there is no counter-suppression (\( K_{cs} = 0 \)) the model is the conventional Difference of Gaussians (2G) model. In a small number of cases where \( K_{cs} \) was small, for example, \( K_{cs} < 0.01 \) or there was no detectable counter-suppression, \( K_{cs} \) was set to zero for the fitting process to avoid overestimating the presence of counter-suppression.

The fitting procedures were carried out using the MATLAB optimization procedures in which we constrained \( w_c < w_s < w_{cs} \). We accessed the goodness of each fit by calculating the mean fraction error (cf. Sceniak, Hawken, & Shapley, 2001) defined as

\[ e = \frac{1}{N} \sum_{i=1}^{N} \frac{(f_i - R_i)^2}{(\bar{f} + \bar{R})^2}, \]

where \( f_i \) and \( R_i \) are the expected response, \( f \), and experimental response, \( R \), to the \( i \)th stimulus size respectively. The fit error in the present study ranged from 0.0015 to 0.38 with median error of 0.023.

The empirical RF size or \( w_{opt} \) of individual cells was measured from their fitted size-tuning curves and was defined as the stimulus size that produced a maximum response (\( R_{max} \)) before the apparent surround suppression. \( R_{max} \) also signals the start of the surround suppression, which reaches its greatest extent at the succeeding minimum responses (\( R_{min} \)). In some cells, a further extension of stimulus size into the far surround may lead to an increase rather than a further decrease in the magnitude of response. This increase in the magnitude of the CRF generated spike response accompanying an extension of stimuli into the far silent surround is termed here a ‘counter-suppression’. The maximum counter-suppression was identified as the highest response (\( R_{cs} \)) reached after \( R_{min} \) or at the largest stimulus diameter (28°).

The magnitudes of the suppression and counter-suppression were taken as (\( R_{max} - R_{min} \)) and (\( R_{cs} - R_{min} \)) respectively. For the purpose of comparing the strength of suppression and counter-suppression in different neurons we used three normalized terms. The ‘Suppression Index’ (SI) is defined as:

\[ (R_{max} - R_{min})/R_{max}, \]
The ‘Counter-Suppression Index’ (CSI) is defined as:

\[
\frac{(R_{cs} - R_{min})}{R_{max}},
\]

(7)

In order to quantify the suppressive or ‘facilitatory’ effects of large field integration we introduced a ‘Relative Integrated Response’ (RIR), defined as:

\[
\frac{(R_{ds} - R_{max})}{R_{max}},
\]

(8)

where \(R_{ds}\) is the response elicited when the distal part of the surround is stimulated concurrently with the CRF. \(R_{ds} = R_{min}\) for cells showing suppression-only and \(R_{ds} = R_{cs}\) for cells showing both suppression and counter-suppression. The effect is considered facilitatory if \(RIR > 1\) or suppressive if \(RIR < 1\). When there was no detectable surround suppression at a given (usually low) contrast (e.g. Figure 1F at a contrast of 11\%) the maximum center response was taken to be the response to the stimulus size estimated by center excitatory space constant (\(w_c\)) given the empirical agreement between \(w_{opt}\) and \(w_c\) (see Results).

To relate the empirical measurements to the parameters derived from Gaussian functions, we used the ratio of suppressive area to the combined excitatory center and counter-suppression areas

\[
SI = \frac{(K_s \cdot w_s)}{(K_c \cdot w_c + K_{cs} \cdot w_{cs})},
\]

(9)

as a suppression estimate. Where there is no counter-suppression, \(K_{cs} = 0\), \(SI = \frac{(K_s \cdot w_s)}{(K_c \cdot w_c)}\), which is the same as the suppression estimate for the conventional 2G-model (Sceniak et al., 1999).

Similarly, the ratio of counter-suppression area to center excitatory area

\[
CSI = \frac{(K_{cs} \cdot w_{cs})}{(K_c \cdot w_c)},
\]

(10)

is used as a counter-suppression estimate.

Statistical analyses were performed using the ‘Prism 4 statistic package’ (GraphPad Software, San Diego, CA, USA). We used Mann–Whitney \(U\) test to assess the significance of the suppression and counter-suppression effects recorded for individual cells. The Wilcoxon matched-pairs signed-ranks test was used for pair-comparisons of SIs, CSIs and the RIRs measured at high and low contrasts. Unless otherwise stated in the text it can be assumed that the Wilcoxon matched-pairs signed-ranks test was used. \(\chi^2\) test and nonparametric correlation (Spearman) were also used for assessing the significance of differences between distributions and the relationship between two sets of data respectively. In addition, a \(\chi^2\) test for trend was used for assessing significance in trend. For all tests, a two-tailed criterion was used and a significance level of \(p < 0.05\) was adopted. Mean values given in the text are accompanied by the standard error of the mean (i.e. mean ±SEM). Median values were used when the mean was skewed towards to the value of a few outlying data points.

![Figure 1](image-url)
Results

Size-tuning properties of 57 cells were examined at two (low and high) or more stimulus contrasts. The CRFs of all but three cells were located within 10° eccentricity from the area centralis. Just over half of the cells (51%, 29/57) were identified as simple cells since the first harmonic (F1) of the responses was greater than the mean firing rate (F0) of the responses (F1/F0 > 1). The other half of the sample was identified as complex cells since the F1/F0 ratio of their responses was less than 1 (F1/F0 < 1, cf. Bardy et al., 2006; Skottun et al., 1991).

At high stimulus contrasts, almost all (95%, 54/57) neurons in our sample showed various degrees of suppression (their SIs ranged from 0.01 to 0.96) in their spike responses generated by CRF stimulation, when the silent surround was stimulated concurrently with the CRF (Figures 1A–1F, filled squares). Mean suppression index for the whole sample was 0.44 (±0.04). We also observed that at high stimulus contrast, a substantial proportion of cells (37%, 21/57) exhibited not only a clear suppression when stimuli extended into the near surround but also a counter-suppression when the stimuli extended into the far region of the surround (up to 28° in diameter). Mean strength of counter-suppression was 0.24 (±0.04). In a large proportion of cells, the changes in magnitudes due to suppression (91%; 49/54) as well as those due to counter-suppression (43%; 9/21) were statistically significant (p < 0.05, Mann–Whitney U test).

Stimulus size-tuning and stimulus contrast

A majority of cells exhibiting either suppression-only (73%, 24/33) or suppression and counter-suppression (71%, 15/21) at high contrast also showed either suppression or suppression and counter-suppression at low contrast (Table 1). Thus, area summation profiles of these cells were unaffected irrespective of stimulus contrasts tested although suppression tended to decrease and/or counter-suppression to increase at low contrast.

We also observed that in some high contrast suppression-only cells (27%, 9/33), at low contrast not only suppression became weaker but also counter-suppression emerged (3 cells, e.g. Figure 1C) or no surround suppression was revealed (6 cells, e.g. Figures 1E and 1F). Similarly, four high contrast suppression and counter-suppression cells (19%, 4/21) showed no suppression at all or summation-only at low contrast. On the other hand, fewer cells (10%, 2/21) showing suppression and counter-suppression at high contrast became suppression-only at low contrast.

For three high contrast summation-only cells one cell also exhibited summation only at low contrast and the other two cells showed either weak suppression (1 cell) or suppression and counter-suppression (1 cell) when tested at low contrast.

<table>
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<tr>
<th>Number</th>
<th>Suppression</th>
<th>Counter-suppression</th>
</tr>
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<tbody>
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<td>of cells</td>
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</tr>
<tr>
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<td>✓</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>54</td>
</tr>
</tbody>
</table>

Table 1. Number of cells showing suppression and/or counter-suppression at high and low contrasts. Cells in the first column show all the features indicated by ticks (✓) in the same row. *: Minimum response taken at the plateau of the response (e.g. Figure 1E at a contrast of 10%).

Thus, it is likely that, at low contrast, subthreshold signals originating from the surround are less suppressive or even excitatory when the distal surround is stimulated. Table 1 lists all cells tested and the number of cells showing suppression and/or counter-suppression at high and/or low contrasts.

Consistent with previous studies (cat: Sadakane et al., 2006; Tailby, Solomon, Peirce, & Metha 2007; macaque monkey: Cavanaugh et al., 2002; Kapadia et al., 1999; Sceniak et al., 1999; Tailby et al., 2007) we also observed an increase in summation area at low contrast. The empirical RF size, \(w_{\text{opt}}\), or excitatory space constants, \(w_c\), was on average 1.33 or 1.41 times those measured at high contrast. The increase was very similar to that (1.36) reported previously in the cat (Tailby et al., 2007) but substantially smaller than that in macaques (~2.5 times; Cavanaugh et al., 2002; Kapadia et al., 1999; Sceniak et al., 1999). The difference might be due to the range of contrasts used. It is possible that by using only two contrasts, our estimate of summation area expansion with reduction in contrast is lower than those observed in studies employing a larger range of contrasts.

Strength of suppression and counter-suppression at high and low contrasts

At high contrast the distribution of SIs of suppression-only cells was significantly different (\(\chi^2 = 25.6, df = 4, p < 0.0001\)) from that of cells exhibiting both suppression and counter-suppression. Indeed, some suppression-only cells, but none of the suppression and counter-suppression cells, exhibited very strong surround suppression (SI > 0.8, Figure 2A). Although at high contrast the mean SI (0.51 ± 0.05, \(n = 33\)) of suppression-only cells was higher than
that (0.40 ± 0.05, n = 21) of cells showing both suppression and counter-suppression, nevertheless, the difference between the two groups was not significant (p = 0.18, Mann–Whitney U test). Furthermore, there was no significant correlation between SIs and CSIs for cells that exhibited both suppression and counter-suppression (Spearman r = 0.10, p = 0.68, n = 21, Figure 2B).

In addition to broadening of the size-tuning curves, lowering the contrast resulted in changes in the strength of suppression and counter-suppression. Figures 3A and 3C show the distributions of SIs and CSIs at low and high contrasts respectively. It is apparent from Figure 3A that almost all cells (95%; 54/57) showed some surround suppression at high contrast but at low contrast a smaller proportion of cells exhibited surround suppression (81%; 46/57). Although the distributions of SIs at low vs. high contrast were not statistically different (χ² = 10.83, df = 5, p = 0.055, n = 57), a paired comparison of SIs revealed significantly (p < 0.0001) smaller SIs at low contrast (0.33 ± 0.04) vs. those at high contrast (0.44 ± 0.04; Figure 3B).

At low contrasts there was a significant (χ² = 8.35, df = 2, p = 0.015, n = 25, based on 3 categories: 0.21–0.60, >0.61) increase in the number of cells that exhibited relatively strong counter-suppression (Figure 3C). It appears that at low contrast, at least in some cells, the subthreshold excitatory influence from the surround overwhelmed the suppressive influence and, thus, no surround suppression was revealed in their spike responses (Figure 3C; see also Figures 1E and 1F). A paired comparison of CSIs at low and high contrasts (Figure 3D; n = 22, including 5 cells having zero CSI at either high or low contrast and 2 cells showing a plateau, or SI = 0, before reaching a new high) revealed that CSIs were significantly (p = 0.004) greater at low contrast (0.38 ± 0.06) than those at high contrast (0.19 ± 0.04).

The contrast-dependent effect on suppression and counter-suppression reported above was found in cells identified as either simple or complex (Figures 3B and 3D) and cells in different laminar locations (Figure 4). As indicated in Figure 3B, simple and complex cells did not differ significantly in the strength of surround suppression at either low (p = 0.98, Mann–Whitney U test) or high contrast (p = 0.58). Both simple and complex cells showed a significant and similar reduction in the strength of surround-suppression at low contrast (Figure 3B, p < 0.001). Mean SI decreased from 0.41 (±0.05, n = 29) at high contrast to 0.32 (±0.05) at low contrast for simple cells and from 0.45 (±0.06, n = 28) to 0.34 (±0.06) for complex cells.

Although at high contrast the mean counter-suppression index (0.24 ± 0.07, n = 13) of simple cells was higher than that of complex cells (0.12 ± 0.04, n = 9) they are not significantly different from each other (p = 0.22, Mann–Whitney U test). Both simple and complex cells showed a substantial increase in counter-suppression at low contrast (0.39 ± 0.07 and 0.37 ± 0.011 respectively). The increase is statistically significant (p = 0.008) for complex cells but not significant (p = 0.08) for simple cells.

At high contrast the mean strength of suppression varied from 0.38 (±0.07) to 0.47 (±0.07) for cells located in supragranular layers (L2–3, n = 18), granular layer (L4, n = 14) and infragranular layers (L5–6, n = 25) and the differences were not significant (Figure 4A, p > 0.41). However, they all exhibited a significant reduction (p < 0.05) in surround suppression at low contrast with mean SIs ranging from 0.27 (±0.07) to 0.37 (±0.06). At high contrast the strength of counter-suppression varied across different laminae. Cells located in lamina 4 showed the highest mean CSI (0.27 ± 0.08, n = 5), more than two times the lowest mean CSI (0.10 ± 0.04, n = 5, lamina 6). However, possibly due to the small sample size in each lamina, the difference was not statistically significant (p > 0.10, Mann–Whitney U test).Irrespective of their laminar locations most cells exhibited an increase in the strength of counter-suppression at low contrast (Figure 4B).
For 15 cells showing surround suppression and counter-suppression at both low and high contrasts, the strength of suppression at low contrast was on average 0.29 times lower and the strength of counter-suppression 2.49 times greater than that seen at high contrast. The two trends, although not significantly correlated (Figure 5A, Spearman $r = -0.01, p = 0.96$), were strongly and significantly ($p = 0.0002$) opposed to each other. In these cells, the increase in counter-suppression (Figure 5B) and the decrease in suppression (Figure 5C, filled triangles) at low contrast were independent of the increase in empirical RF size found at low contrast. On the other hand, for cells showing only surround suppression at both low and high contrasts, the reduction in surround suppression at low contrast was significantly related to enlargement of RF size (Figure 5C, Spearman $r = -0.44, p = 0.03, n = 24$).

Contrast-dependent effect and model estimates

When using the suppression estimates ($S_{L}$) calculated by the parameters derived from model functions (see Materials and methods) to assess the contrast effect on surround suppression, we found that mean $S_{L}$ at low contrast ($0.77 \pm 0.06, n = 57$) was very similar to that at high contrast ($0.71 \pm 0.05, n = 57$). Thus, surround suppression seemed unaffected at low contrast (see also Sceniak et al., 1999). Both excitatory ($K_{e}$) and suppressive

Figure 3. Frequency distributions of suppression and counter-suppression indices at low and high contrasts and comparison of these two indices at high contrast with those at low contrast. (A) Most cells (54/57) at high contrast exhibited surround suppression. The distribution of suppression indices (A) and a direct comparison for individual cells (B) at low and high contrasts indicate that the suppression indices at low contrast are usually substantially smaller than those at high contrast. In some cells suppression index was reduced to zero. (C, D) A smaller proportion of cells (25/57) exhibited counter-suppression at low and/or high contrasts. There is a clear trend towards an increase in the strength of counter-suppression at low contrast. Numbers of cells showing a significant suppression and/or counter-suppression are indicated by a leveled line with an asterisk and the numbers inside bars. Arrows indicate the mean values at given measurements.

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When using the suppression estimates ($S_{L}$) calculated by the parameters derived from model functions (see Materials and methods) to assess the contrast effect on surround suppression, we found that mean $S_{L}$ at low contrast ($0.77 \pm 0.06, n = 57$) was very similar to that at high contrast ($0.71 \pm 0.05, n = 57$). Thus, surround suppression seemed unaffected at low contrast (see also Sceniak et al., 1999). Both excitatory ($K_{e}$) and suppressive
(Ks) strengths were reduced significantly at low contrast (p < 0.002) and were respectively 0.32 (median) and 0.36 (median) of their strengths at high contrast. The reduction in Kc was greater (p = 0.01, n = 57) than the reduction in Ks. The lack of a predominant reduction in SIE and Ks makes it unlikely that they are responsible for the observed reduction in surround suppression at low contrast.

Both excitatory, wc, and suppressive, ws, space constants derived from model functions (Equations 1–4) increase significantly (p < 0.015) at low contrast and were 1.29 and 1.16 times respectively compared to those at high contrast. While changes in wc and ws were not closely correlated (Spearman r = 0.17, p = 0.23, n = 54, excluding 3 cells with Ks = 0) at low contrast the overlap between excitatory and suppressive space (1.66 ± 0.18), defined as ws/wc, was substantially larger (p = 0.05), that is the ratio between the two was smaller, than that (2.04 ± 0.24) at high contrast (Figure 6A). It is possible that an increased spatial overlap of wc and ws at low contrast undermines the apparent suppression of response beyond the CRF as observed in the present study. However, when relating the difference between overlapping excitatory and suppressive space at low and high contrasts to the difference between SIs at low and high contrasts we did not find a clear correlation between the two (Spearman r = 0.13, p = 0.33, n = 54, Figure 6B). Consistent with a previous report (Sceniak et al., 1999) we also found that the increase of wc at low contrast was closely correlated (Spearman r = 0.67, p < 0.0001, n = 44, Figure 6C) with the increase of empirical RF size, wopt, for cells exhibiting surround suppression at both low and high contrasts. On the other hand, the contrast effect evaluated by the suppression estimate (SIe) was not related to that measured by the suppression index (SI) as shown in Figure 6D (Spearman r = -0.01, p = 0.96, n = 44). Furthermore, we did not observe a close correlation between a decrease in suppression index (SI) at low contrast and an increase in wc for either suppression-only cells (Spearman r = -0.14, p = 0.51, n = 24) or counter-suppression cells (Spearman r = 0.13, p = 0.64, n = 15).

At both low and high contrasts the excitatory counter-suppressive space constant, ws, was usually larger, on average 3.0 and 2.2 times that of wc and ws respectively. In most cells exhibiting surround suppression and counter-suppression at both low and high contrasts (80%, 12/15) ws was enlarged at low contrast. However, the extent of overlap of excitatory counter-suppressive space with either center excitatory space (ws/ws) or suppressive space (ws/ws) was similar (p > 0.89 in both cases) regardless of the stimulus contrast used (Figures 6E and 6F).

Further analysis of model estimates for counter-suppression revealed that the counter-suppression strength, Kcs, and area, Kcs ∗ ws, were significantly weaker at low contrast (p < 0.015 in both cases). The reductions were similar (median: 0.66 for Kcs and 0.46 for Kcs ∗ ws) to those of center excitation (median: 0.67 for Kc and 0.51 for Kc ∗ wc) as well as those of surround suppression (median: 0.62 for Ks and 0.49 for Ks ∗ ws). Neither of these changes in Kcs and area, Kcs ∗ ws, were correlated with a change in CSI (Spearman, r = -0.45, p = 0.09, n = 15). CSIe calculated from model parameters (see Materials and methods) also varied at low contrast. However, in only about half the sample (47%, 7/15) CSIe increased. We did not find a significant correlation between changes in CSIe and those in CSI (Spearman, r = -0.35, p = 0.19, n = 15, Figure 6G).

**Suppression and facilitation from ‘far’ surround**

The magnitude of counter-suppression was usually smaller than the magnitude of suppression for most cells exhibiting both suppression and counter-suppression at low and high contrasts. Thus, the overall modulatory
Figure 6. Changes in spatial overlap of excitatory, suppressive and counter-suppressive space at low contrast and the relationships between model estimates and measured suppression or counter-suppression. (A) For 54 cells with a suppressive space constant more than zero the ratio of suppressive space to excitatory space was reduced at low contrast, indicating a greater overlap between excitatory and suppressive space. However, the difference in the degree of overlap was not directly related to the difference in the strength of suppression between low and high contrast (B). For cells exhibiting suppression the increase in empirical receptive field size at low contrast was similar to and significantly correlated with the increase of excitatory space constant (C). As shown in (D) changes in the suppression estimate calculated from model functions at low contrast were not related to the decreases in the measured strength of suppression. The ratios of counter-suppressive space constant to either excitatory or suppressive space constant at low contrast were similar to those at high contrast (E, F). Changes in the counter-suppression estimate at low contrast were not related to the increases in the measured strength of counter-suppression (G). Arrows indicate the means (A, C) and the medians (E, F) values for given measurements. Solid lines are regression lines.

effect when the near and far parts of the silent surrounds were stimulated was still suppressive. However, there was a small group of cells in which the magnitude of counter-suppression was greater than the magnitude of suppression (cf. Figure 1D); a phenomenon that was more often revealed at low contrast. Thus, in these cells the overall effect of stimulation of both proximal and distal surrounds was facilitatory to the CRF generated spike responses. To estimate the strength of responses integrated over a large visual space in relation to the CRF generated spike
responses we calculated a Relative Integrated Response (RIR, see Materials and methods) for cells showing both suppression and counter-suppression at high and/or low contrasts (25 cells; filled diamonds in Figure 7A) and cells exhibiting suppression only at high, but not at low, contrasts (6 cells; open triangles in Figure 7A) as well as other cells (26 cells; asterisks) including those showing suppression-only at both contrasts (24 cells). Although at low contrast there was a systematic increase in the RIRs (Figure 7A), in a majority of the sample cells the net influence from stimulation of combined near and far surrounds was still suppressive. Overall, the mean RIR at high contrast (-0.31 ± 0.06) was significantly (p < 0.0001, n = 57) lower than that at low contrast (-0.03 ± 0.10). The same data plotted as a bar graph in Figure 7B demonstrates a shift of the RIRs to less suppression or even facilitation at low contrast and this trend was statistically significant (χ² = 6.41, df = 1, p = 0.01, n = 57, χ² test for trend).

### Discussion

#### Suppressive and counter-suppressive regions in the extraclassical receptive fields of area 17 neurons

We have found that stimulation of silent surrounds in the receptive fields of area 17 neurons with high contrast iso-oriented sine-wave gratings results in a very substantial reduction in the magnitude of spike responses generated by stimulation of the CRFs. Our results are consistent with numerous earlier reports in both cats (Akasaki et al., 2002; Bardy et al., 2006; Li & Li, 1994; Sengpiel et al., 1997; Walker et al., 2000) and macaque monkeys (Cavanaugh et al., 2002). The magnitude of the surround suppression observed in the present study (mean 44%) is within the range reported previously by other research groups (Akasaki et al., 2002; Jones, Andolina, Oakely, Murphy, & Sillito, 2000; Sengpiel et al., 1997; Tailby et al., 2007; Walker et al., 2000).

Even at high contrasts 37% of cells in our sample showed some reduction in the magnitude of suppression (counter-suppression) when the far surround was stimulated with the iso-orientated gratings. The counter-suppression was usually apparent with stimuli of >10° in diameter and was present among cells with various degrees of surround suppression strength. Thus, it appears that the large grating patches of intermediate mean luminance generate some appreciable excitatory subthreshold activity. We also found that the relative strength of both surround suppression and counter-suppression was contrast-dependent: suppression decreased when the contrast was low, whereas counter-suppression decreased when the contrast was high. Furthermore, a facilitatory effect of large field stimulation was more often observed at low rather than high contrast.

Most studies examining the effects of stimulation of silent surrounds in the RFs of mammalian area 17 neurons did not report the presence of a counter-suppressive effect (see Introduction for details). This may be partly due to the fact that the stimuli used in those studies (subtending ≤10° of visual angle) might not have been large enough to...
cover the far surround (macaque monkey: Jones et al., 2000; Sceniak et al., 2001; cat: Sengpiel et al., 1997) and/or the counter-suppression effect was rare and/or weak (DeAngelis, Freeman, & Ohzawa, 1994; Sadakane et al., 2006; Walker et al., 2000). Furthermore, although we observed a counter-suppression effect in a relatively large proportion of cells using very large, high contrast stimuli, the counter-suppression was usually substantially weaker than the surround suppression. We also note that in the studies in which intermediate luminance values (range 3–8.3 cd m\(^{-2}\)) were used (cat: Li & Li, 1994; the present study; macaque monkey: Kapadia et al., 1999) counter-suppression or even surround facilitation was more apparent.

Li and Li (1994) reported that only ~10% of the cells recorded from area 17 of anaesthetized cats showed disinhibition (counter-suppressive effects) as the stimuli became wider or longer. The proportion is thus much smaller than the proportion of cells showing counter-suppression seen in the present study when the large grating patches encroached the far surround region. Li and Li (1994) varied independently the length and width of grating slits and thus their results cannot be directly compared with ours. However, part of the discrepancy between the reported proportions of cells whose RFs contained disinhibitory regions may arise from the fact that we included cells exhibiting weak counter-suppression effects. Indeed, in our sample nearly half of the cells that exhibited counter-suppression had a CSI ≤ 15% and for most of these the counter-suppression was significant only at low contrast. By comparison, most of area 17 cells tested by Li and Li (1994) seemed to have a CSI > 15% (see their Figures 3F and 4F). Thus, it is possible that some of their suppression-only cells might have shown a counter-suppression effect at low contrast.

Subcortical and cortical contributions to suppression and counter-suppression in area 17

The suppression observed in area 17 neurons when the silent surrounds are stimulated exhibits very similar properties to those observed in their principal dorsal thalamic input neurons, in the lateral geniculate nucleus (LGN; Levick, Cleland, & Dubin, 1972; Li & He, 1987; Naito, Sadakane, Okamoto, & Sato; 2007; Nolt, Kumbhani, & Palmer, 2004, 2007). Overall, studies of the spatial properties of retinal ganglion cells (RGCs) and LGN neurons suggest strong subcortical contributions to the spatial properties of cortical neurons. This includes contrast-dependent center–surround interactions (Krüger & Fischer, 1973a), spatial summation (Kaplan, Marcus, & So, 1979; Nolt et al., 2004; Solomon, White, & Martin, 2002), suppression of responses at spatial frequencies above those to which the classical, antagonistic surrounds are responsive (Nolt et al., 2007), as well as contextual response modulation (Sadakane et al., 2006). It has been controversial whether (Sillito, Cudeiro, & Murphy, 1993; Sun, Chen, Huang, & Shou, 2004) or not (Bonin, Mante, & Carandini, 2005) surround suppression is tuned to stimulus orientations in cat LGN. By directly comparing the results from cat LGN and those from VI in the same experiment Naito et al. (2007) found that orientation tuning of surround suppression in LGN was comparable to that in VI. Thus, it is likely that, at least in the cat, changes in surround suppression in LGN would be manifested in VI (cf. Ozeki et al., 2004).

The disinhibitory or counter-suppressive effects observed by us in area 17 also have their counterparts in cat RGCs (Ikeda & Wright, 1972a) and LGN neurons (Li & He, 1987). The disinhibitory effects observed when the far surrounds of RGCs (Ikeda & Wright, 1972a; Li, Pei, Zhou, & von Mitzlaff, 1991; Li et al., 1992) or LGN neurons (Li & He, 1987) are stimulated are most likely based on the so-called modulated periphery or shift-effect, that is, an increase of spike responses to the sudden movements of large, especially fast moving, contours well outside the circumscribed CRFs (cats: Levick, Oyster, & Davis, 1965; McIlwain, 1964; macaque monkeys: Krüger, 1977; Krüger, Fischer, & Barth, 1975). Since the periphery effect is especially pronounced in Y-type RGCs and LGN neurons (Barlow, Derrington, Harris, & Lennie, 1977; Derrington & Fuchs, 1979; Fischer & Krüger, 1974; Ikeda & Wright, 1972b; Krüger & Fischer, 1973a, 1973b) it is likely that the counter-suppression effects observed in the present study were especially pronounced in area 17 neurons that received direct or indirect excitatory inputs from Y-type LGN neurons.

Clearly, a substantial subcortical contribution to the surround effects observed in the present study is beyond doubt. However, the involvement of cortical circuitry, for example, long-range intrinsic horizontal associational connections (Crook, Engelmann, & Löwel, 2002) as well as feedback projections from ‘higher-order’ visual cortical areas (Bardy, Huang, FitzGibbon, & Dreher, 2005; Hupé et al., 1998; cf. also Ichida, Schwabe, Bressloff, & Angelucci, 2007; Smith, Bair, & Movshon, 2006) in center–surround interactions in area 17 has been also clearly demonstrated. In particular, an increased extent of spatial summation in the RF of cortical neurons at low contrast may also be attributable to the strengthening of lateral coupling among excitatory cortico-cortical synapses (cf. Sceniak et al., 1999) and/or the inactivation of high-threshold local inhibitory interneurons (cf. Ichida et al., 2007).

Contrast dependence of suppression and counter-suppression

The contrast-dependence of suppression and counter-suppression (or facilitation) observed in the present study appear to be fundamentally different from the modulatory effects of surround stimulation reported by a number of other groups (Polat et al., 1998; Sengpiel et al., 1997; Toth et al., 1996). In particular, in these studies the modulatory
effects were dependent on the contrast difference between the CRF and surround stimulation. High contrast surround stimulation suppressed the responses to the CRF stimulation when the contrast of the CRF-confined stimuli was also high and facilitated the CRF responses when the contrast of the CRF-confined stimuli was low. Such contrast-dependent spatial interactions were thought to be ideally suited for mediating detection of perceptual pop-out (Toth et al., 1996). It remains possible that there is no single mechanism underlying the perceptual phenomena of pop-out or figure-ground segregation (Lamme, 1995; Toth et al., 1996; Zipser, Lamme, & Schiller, 1996). 

It has been suggested that neurons in cat LGN are capable of extracting visual information from local contrast (luminance borders) as well as luminance gradients across an extended visual space (Li et al., 1991). A large disinhibitory regions in the peripheral part of the receptive field surround could be beneficial for integrating other attributes of an object in visual environments, such as area brightness and image gray scales (Li et al., 1991). It is also important to note in this context that in the cat at least, the mean firing rates of some X-type and most Y-type RGCs change significantly when 10–20% (or higher) contrast gratings were presented in the distant parts of their extraclassical RFs (Passaglia, Enroth-Cugell, & Troy, 2001). Furthermore, the direction of change in the mean firing rates (increase vs. decrease) depends on the spatial and temporal frequencies of remote gratings. Thus, the presentation of low spatial and high temporal frequency remote gratings results in substantial increases while the presentation of high spatial and low temporal frequency remote gratings results in substantial decreases in the mean firing rates of RGCs (Passaglia et al., 2001).

We have shown that suppression and counter-suppression of area 17 neurons are contrast-dependent. At high contrast, a usually strong near surround suppression (accompanied in some cells by a relatively weak counter-suppression) may be primarily used by the visual system for focal feature extraction. At lower contrast, the spike responses to stimuli of the same spatial dimension are weaker. However, a decrease in magnitude of surround suppression and an increase in magnitude of counter-suppression could allow cortical neurons to extract much more visual information (e.g. average luminance and gradient) from the surround area to improve the chance of detection and/or object recognition. Thus, the contrast-dependent property described here may contribute to maximizing the performance of the visual system under various stimulus conditions.

Implication of stimulus contrast on center and surround mechanism

Spatial summation of cortical neurons can be described well by the DoG model (cf. Sceniak et al., 1999, 2001; the present study). In the present study, which implemented a third Gaussian distribution, we have demonstrated the existence of an extensive excitatory space or counter-suppressive region usually more than 10° in diameter, extending to the far surround. This space is apparently weaker in strength than that of the center (excitatory) and surround (suppressive). The 3G-model applied in the present study fitted well to the envelop of spatial summation for cortical cells exhibiting counter-suppression responses (Figures 1C–1F).

The excitatory summation space usually expands as stimulus contrast decreases (cf. Cavanaugh et al., 2002; Ichida et al., 2007; Sadakane et al., 2006; Sceniak et al., 1999, 2001). We also found a systematic increase of suppressive space at low contrast. The rate of expansion of suppressive space was substantially lower than that of center excitatory space. Thus, at low contrast excitatory and suppressive spaces appear to overlap more extensively and a relatively larger part of suppression is masked. This could weaken the apparent suppression of the center response at low contrast when stimuli extend beyond the CRF. However, the lack of a close correlation between the change in the extent of the overlap of excitatory and suppressive spaces and the reduction of the strength of suppression, suggests that contrast-dependent effects on surround suppression may involve more than a single mechanism. Although the strength of suppression, $K_s$, was reduced markedly at low contrast the reduction was significantly smaller than the reduction in the strength of excitation, $K_c$. It is unlikely that changes in surround contrast gain alone result in the observed contrast-dependent effect on surround suppression. Nor is it likely to be responsible for the expansion of summation area at low contrast as predicted by the model of Cavanaugh et al. (2002). Consistent with the findings by Sceniak et al. (1999) we also found that the suppression estimate, $SI_e$, defined by the ratio of suppressive area, $K_s \cdot w_s$, to excitatory area, $K_c \cdot w_c$, was unaffected by stimulus contrast. Whatever the underlying mechanisms, a decrease in the stimulus contrast triggers a clear trend for the expansion of excitatory space and a decrease in the strength of surround suppression.

We also found that the counter-suppressive space is larger but its strength weaker than those of the excitatory center and suppressive surround. At low contrast the reductions in both counter-suppression strength, $K_{cs}$, and area, $K_{cs} \cdot w_{cs}$, are similar to those of center and surround. None of these changes alone were closely correlated with the contrast effect on counter-suppression. Thus, it remains an open question as to what extent the widely adopted Gaussian model can be used to single out the mechanisms underlying empirical phenomena in general and, more specifically, the contrast-dependent effects on suppression and counter-suppression observed here.

Conclusions

Stimulation of the silent surround usually reduces the magnitude of the responses of area 17 neurons to visual
stimuli presented to their CRFs. However, a substantial proportion of neurons exhibited a counter-suppressive effect when the distal part of the silent surround was stimulated concurrently with their CRFs. Surround suppression and counter-suppression appear to be contrast-dependent. Thus, a reduction in stimulus contrast results in opposite effects; suppression becoming weaker and counter-suppression becoming stronger. The analysis of model estimates suggests that the enlargement of excitatory summation area accompanied by the decrease in the strength of suppression at low contrast may be attributable partly to an increased extent of spatial overlap between center excitatory space and suppressive space. An increase in counter-suppression at low contrast might be due to a change in the balance between the strength of counter-suppression and the strength of center excitation and surround suppression.

Abbreviations

CRF, classical receptive field; CSI, counter-suppression index; CSIe, counter-suppression estimate; DoG or 2G, Difference of Gaussians; Kc, center excitation strength; Ks, suppression strength; Kcs, counter-suppression strength; LGN, lateral geniculate nucleus; Rcs, maximum counter-suppression; RF, receptive field; RGC, retinal ganglion cell; RIR, relative integrated response; Rmax, maximum response; Rmin, minimum response; SI, suppression index; SIe, suppression estimate; 3G, Supplementary DoG; V1, primary visual cortex; wc, center excitatory space constant; wcbs, counter-suppressive space constant; ws, suppressive space constant.

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