Spatial Attention Modulates Center-Surround Interactions in Macaque Visual Area V4

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DOI 10.1016/j.neuron.2009.02.023

SUMMARY

In natural viewing, a visual stimulus that is the target of attention is generally surrounded by many irrelevant distracters. Stimuli falling in the receptive field surround can influence the neuronal response evoked by a stimulus appearing within the classical receptive field. Such modulation by task-irrelevant distracters may degrade the target-related neuronal signal. We therefore examined whether directing attention to a target stimulus can reduce the influence of task-irrelevant distracters on neuronal response. We find that in area V4 attention to a stimulus within a neuron's receptive field filters out a large fraction of the suppression induced by distracters appearing in the surround. When attention is instead directed to the surround stimulus, suppression is increased, thereby filtering out part of the neuronal response to the irrelevant distracter positioned within the receptive field. These findings demonstrate that attention modulates the neural mechanisms that give rise to center-surround interactions.

INTRODUCTION

Numerous studies of visual attention have found that when attention is directed to a stimulus, the neuronal response evoked by that stimulus is elevated (Mountcastle et al., 1987; Spitzer et al., 1988; Treue and Maunsell, 1996; McAdams and Maunsell, 1999; Treue and Martinez-Trujillo, 1999; Reynolds et al., 2000; Roelfsema et al., 1998; Williford and Maunsell, 2006). Several of these studies have found evidence that when a single stimulus falls within a neuron's classical receptive field (RF), this attentional increase in response can be characterized as multiplicative (McAdams and Maunsell, 1999; Treue and Martinez-Trujillo, 1999). For example, McAdams and Maunsell varied the orientation of a grating to derive a neuronal tuning curve and found that the response evoked by an attended stimulus could be obtained by multiplying the unattended response by a fixed gain factor. These studies probed the influence of attention with only a single stimulus in the neuron's RF. This is quite different from natural viewing conditions where the target of attention is embedded in complex scenes filled with task-irrelevant distracters.

Another class of experiments has measured the effect of directing attention to one of two stimuli in the classical RF (Moran and Desimone, 1985; Treue and Maunsell, 1996; Reynolds et al., 1999; Martinez-Trujillo and Treue, 2002; Recanzone and Wurtz, 2000; Ghose and Maunsell, 2008). In these studies, one stimulus was selected to evoke a strong response from the neuron, and the other stimulus was selected to evoke a much weaker response. When attention was directed away from the pair, the response to the pair typically fell between the responses evoked by the individual stimuli. When attention was directed to one of the stimuli, the response typically became more similar to the response evoked when that stimulus was presented alone. These findings are consistent with attention acting to filter out the influence of irrelevant stimuli via modulation of the circuitry that mediates response normalization (Reynolds et al., 1999; Reynolds and Chelazzi, 2004; Ghose and Maunsell, 2008; Reynolds and Heeger, 2009).

In the current study, we examined attentional modulation when two stimuli appear together, one within the classical RF and the other in the RF surround. Stimuli placed in the surround do not evoke a visual response but can modulate the response evoked by a stimulus appearing inside the classical RF (Desimone and Schein, 1987; Cavanaugh et al., 2002). This is important because the surrounds of visual neurons are typically large. Thus, under normal viewing conditions, many distracter stimuli fall at positions in the surround and modulate the response evoked by a stimulus appearing within the neuron's classical RF. Because stimuli in the surround fail to elicit a direct response, it is unclear whether attention to the stimulus in the classical RF will act simply to multiplicatively scale the response evoked by the center stimulus or will instead act to diminish the influence of the unattended surround stimulus.

We examined this by measuring the change in attentional modulation induced by the addition of a stimulus to the RF surround. Attentional modulation was stronger in the presence of the surround stimulus. One explanation for this is that attention might modulate the strength of surround suppression. Consistent with this explanation, surround suppression was stronger when attention was directed to the surround than to the center. This difference reflects both a decrease in surround suppression with attention to the center stimulus and an increase in surround suppression with attention to the surround stimulus. These results show that in addition to boosting responses evoked by an attended stimulus, attention modulates surround suppression so as to filter out the influence of task-irrelevant distracters.
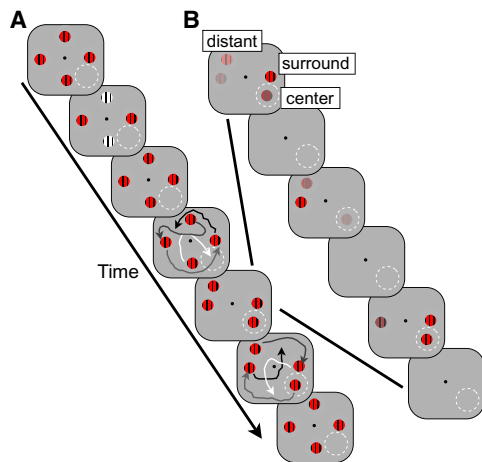
Figure 1. Task Design
(A) Schematic of the full trial.
(B) Expansion of the pause period. Eight stimulus repetitions are presented during the pause period of each trial (only three are illustrated here).

RESULTS

Behavioral Task

Neuronal recordings were made in area V4 of two adult male rhesus macaques as they performed an attention-demanding multiple-object-tracking task (Figure 1). This task was adapted from a behavioral paradigm used in human studies of attention (Sears and Pylyshyn, 2000; Cavanagh and Alvarez, 2005), and it has been shown to drive attentional modulation of V4 neurons (Mitchell et al., 2007). The monkey initiated the trial by foveating a fixation spot at the center of a computer monitor and maintained fixation throughout the trial. Four stimuli appeared, and attention was cued by a brief luminance increment of the stimulus that the animal was required to attentionally track during that trial. All stimuli then moved along independent trajectories to new positions and paused. During the pause, one stimulus was at a position within the classical RF of the neuron under study (center stimulus), one stimulus was outside, but near, the classical RF (surround stimulus), and the other two stimuli were contralateral to the RF (distant stimuli, see Figure 1). Depending on which stimulus was initially cued, identical stimulus trajectories resulted in attention being directed toward the center stimulus (attend-center), the surround stimulus (attend-surround), or the distant stimuli (attend-distant). All data were collected during this pause period. During the pause, all stimuli flashed eight times, increasing the number of stimulus presentations that could be used to characterize the neuronal response. Flash duration was 50 ms, followed by a 150 ms interstimulus interval. The contrast of each stimulus changed with each flash and was selected at random from a fixed set of contrasts. The goal of this was two-fold. First, one of the contrasts in the set was zero, enabling us to probe the response of the neuron to the center or surround stimulus presented alone. Second, this enabled us to examine surround suppression and attention as a function of luminance contrast. Following the pause, the stimuli moved

along trajectories that took each randomly to one of the four starting positions. The fixation point was then extinguished and the monkey earned a juice reward by making a saccade to the stimulus that had been cued at the beginning of the trial. With this task, the attentional cue and saccade goal were decoupled from both the location of attention during the pause and the RF location. In a subset of recordings made in monkey M, two stimuli were cued (see Experimental Procedures).

Experimental Results

We recorded responses of 240 well-isolated V4 neurons in two animals as they performed the task described above. From these neurons, we excluded cells that failed to respond significantly to the center stimulus alone or responded at less than 0.5 Hz in any condition. Neurons were also excluded if they responded significantly to the surround stimulus, indicating that we had inadvertently positioned the surround stimulus at a position inside the classical RF (see Experimental Procedures and Figure S1 available online). This yielded 150 neurons (78 from animal M, 72 from animal J) from 128 recording sites that are the focus of this study. Neurons were probed at multiple stimulus contrast values and often at two surround locations. In these cases, each center/surround stimulus pair was tested for inclusion independently. If multiple center/surround stimulus pairs from the same cell met these inclusion criteria, responses to the different stimulus pairs were averaged together. Therefore, each cell is included only once in each analysis. All main results remain significant if each center/surround stimulus pair is included for analysis independently. In Figures 2, 3, and 6, square icons indicate the stimulus configuration and location of attention of each condition plotted. The dot in the upper left corner of the icon depicts the fixation spot, the dotted circle the RF location, the arrow the attended location, and the gratings the stimuli. When the arrow is missing, attention was directed to the distant stimuli (which were positioned to the upper-left of the fixation point and do not appear in the figure).

We first determined whether the addition of a surround stimulus changed the magnitude of attentional modulation. If attention scaled neuronal response multiplicatively, as found in previous studies with single stimuli placed in the RF, then the attention-dependent percentage increase in firing rate would be similar regardless of whether the surround stimulus was present or absent. We therefore compared attentional modulation in the presence and absence of the surround stimulus. When attention was directed to the stimulus at the RF center, the neuronal response was elevated. This is illustrated in Figure 2A, which shows the mean normalized population average response ±1 SEM to the center stimulus appearing without the surround stimulus, when attention was directed either to the center stimulus (red) or to the surround stimulus location (gray). Attention to the center stimulus led to an 18.8% increase in the population average firing rate, which is consistent in magnitude with the findings of previous studies. In the presence of the surround stimulus, attention to the center stimulus led to a considerably larger 36.8% increase in the population average firing rate (Figure 2B). This suggests that the response modulation induced by attention is not simply multiplicative.
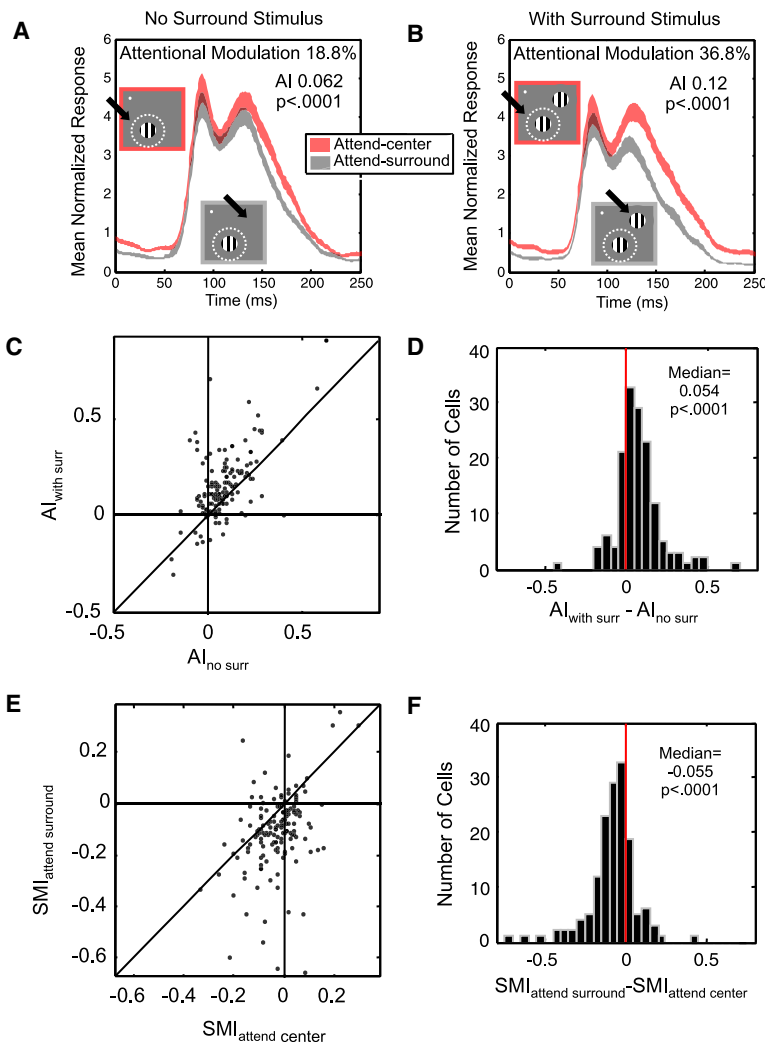
Figure 2. Surround Stimulus Presence Enhances Attentional Modulation

(A) Mean normalized population average response ±1 SEM to the center stimulus presented alone with attention directed to the center stimulus location (red) or to the surround stimulus location (gray).

(B) Mean normalized population average response ±1 SEM to the center and surround stimulus presented together with attention directed to the center stimulus location (red) or to the surround stimulus location (gray).

(C) Scatter plot of $AI_{no\ surr}$ versus $AI_{with\ surr}$.

(D) Population histogram of the difference in AIs between the no-surround and with-surround conditions. Positive values indicate cells exhibiting stronger attentional modulation in the presence than absence of the surround stimulus.

(E) Scatter plot of $SMI_{attend\ center}$ versus $SMI_{attend\ surround}$.

(F) Population histogram of the difference in SMIs between the attend-surround and attend-center conditions. Negative values indicate cells exhibiting stronger surround suppression in the attend-surround versus attend-center condition.

are summarized in the histogram in Figure 2D, which shows the distribution of the differences between the two indices. Positive values correspond to neurons that showed stronger attentional modulation in the presence of the surround stimulus. Attentional modulation was significantly stronger in the presence of the surround stimulus (median $AI_{no\ surr}$ = 0.062, p < 0.0001; median $AI_{with\ surr}$ = 0.12, p < 0.0001; median difference = 0.054; paired test p < 0.0001).

Consistent with earlier studies (Luck et al., 1997; Reynolds et al., 2000; Williford and Maunsell, 2006), attention to the center stimulus led to an elevation of the baseline firing rate and stimulus-evoked responses. This can be seen in Figures 2A and 2B during the period prior to the stimulus-evoked response. We therefore tested whether the presence of the surround stimulus induced larger attentional modulation even after subtracting the baseline response (see Experimental Procedures). When baseline response was subtracted, the overall attentional modulation was smaller in both the absence (9.6%, median $AI_{no\ surr}$ = 0.045, p = 0.0005) and presence (29.8%, median $AI_{with\ surr}$ = 0.132, p < 0.0001) of the surround stimulus (paired test p < 0.0001). The change in attentional modulation upon addition of the surround stimulus, however, was magnified (96% enhancement without subtracting baseline, 210% enhancement after subtracting baseline). To be conservative, we therefore use the non-baseline-subtracted responses for all further analyses.

Surround stimuli have been found to be suppressive in V4 (Desimone and Schein, 1987). This raises the possibility that the increase in the strength of attentional modulation in the presence of a surround stimulus may reflect attention-dependent modulation of surround suppression. We tested this by computing a surround modulation index for each cell, which provided a measure of surround modulation strength:

To examine the effect of adding the surround stimulus across the neural population, we computed two attentional modulation indices for each cell of the form:

$$A.I. = \frac{(attend\_center - attend\_surround)}{(attend\_center + attend\_surround)} \quad (1)$$

where attend-center and attend-surround are the responses of the neuron (without subtracting baseline response) computed over the interval from 40 to 240 ms after stimulus onset in the respective attentional conditions. This index was computed based on responses recorded with and without a surround stimulus, yielding two indices: $AI_{with\ surr}$ and $AI_{no\ surr}$, respectively. Figure 2C shows $AI_{with\ surr}$ plotted as a function of $AI_{no\ surr}$. If attention to the center stimulus elicited the same percentage attentional modulation regardless of the presence of the surround stimulus, points would fall along the line of unity. Instead, consistent with what was seen in the population average responses, most cells exhibited stronger attentional modulation in the presence than absence of the surround stimulus (points falling above the line of unity). These results

$$SMI = \frac{(center\_plus\_surround\_response - center\_alone\_response)}{center\_plus\_surround\_response + center\_alone\_response}$$

(2)

We computed this index with attention to the center ($SMI_{attend\ center}$) and with attention to the surround stimulus ($SMI_{attend\ surround}$). Consistent with the hypothesis that attention modulates surround suppression, suppression was stronger with attention to the surround stimulus than with attention to the center. This is illustrated in Figure 2E, which shows $SMI_{attend\ surround}$ plotted as a function of $SMI_{attend\ center}$. The majority of points fall below the line of unity, showing that the magnitude of surround suppression was larger with attention directed to the surround stimulus. Figure 2F shows a histogram of the difference between these two indices. Surround suppression was significantly stronger with attention to the surround (median $SMI_{attend\ surround} = -0.095$, p < 0.0001; median $SMI_{attend\ center} = -0.024$, p < 0.0001; median difference = −0.055; paired test p < 0.0001).

This could reflect a reduction of surround suppression when attention is directed to the center stimulus, an enhancement of surround suppression when attention is directed to the surround stimulus, or a combination of these two factors. To assess this, we measured surround suppression when attention was directed far from the RF (attend-distant condition) and quantified the change in suppression when attention was instead directed to the center or surround stimulus. Figure 3 illustrates the responses across time of three individual example neurons (3A-C) and the mean normalized population average response (3D) in these three conditions. Example neurons A and B are representative of the main effect seen across the population. In the attend-distant condition, the presence of the surround stimulus was suppressive (first column), leading to a 16.5% and a 17.4% reduction in response, respectively, for these two neurons. This suppression was stronger when the surround stimulus was attended (middle column), leading to larger reductions in response of 48.9% and 22% for these two neurons. In contrast, suppression was reduced by more than half when the center stimulus was attended (right column) with only 4.8% and 8.3% reductions in firing rate. Some neurons, exemplified by the neuron in Figure 3C, were not strongly modulated by the presence of the surround stimulus in the attend-distant condition. For this cell, the presence of the surround stimulus lead to only a 1.1% reduction of response in the attend-distant condition, and we observed a similar degree of suppression (1.7%) in the attend-center condition. This is typical of the neurons we recorded that showed no surround suppression. For this neuron, however, attending to the surround converted the surround stimulus from ineffective to effective leading to a 12.5% reduction of response.

These patterns are evident in the mean-normalized population responses, which appear in Figure 3D. Consistent with the individual example neurons, attending to the surround stimulus magnified surround suppression by 52.6% (attend-distant surround modulation = 11.6% suppression, attend-surround = 17.7% suppression). Attention to the center stimulus diminished the strength of surround suppression by 54.3% (attend-distant surround modulation = 11.6% suppression, attend-center = 5.3%

suppression). Thus, directing attention to the center stimulus reduced the influence of the task-irrelevant surround stimulus, and directing attention to the surround stimulus magnified surround suppression.

In order to quantify for each neuron the surround modulation in the attend-distant condition, we computed a surround modulation index, $SMI_{attend\ distant}$, using the same formula (Equation 2) that was used to compute surround modulation in the attend-center and attend-surround conditions. The effect of attention across the population is shown in Figure 4, which plots surround modulation with attention to the surround (4A) or center (4B) as a function of surround modulation in the attend-distant condition. Consistent with the single-neuron examples and the population average responses, attention to the surround stimulus tended to increase the magnitude of surround suppression (Figure 4A). Points tend to fall below the line of unity, indicating greater suppression in the attend-surround condition. Figure 4C shows the distribution of the differences between these surround modulation indices ($SMI_{attend\ surround} - SMI_{attend\ distant}$). Negative values correspond to neurons that showed stronger surround suppression in the attend-surround versus attend-distant condition. Surround suppression was significantly stronger with attention directed to the surround stimulus ($SMI_{attend\ distant} = -0.051$, p < 0.0001; $SMI_{attend\ surround} = -0.095$, p < 0.0001; median difference = −0.035; paired test p < 0.0001).

It is possible that in the center alone, attend-surround condition (Figure 3E, center column, red icon), which was used to calculate the $SMI_{attend\ surround}$, the animal's attention may have been erroneously drawn away from the blank surround stimulus location to the center stimulus. To confirm that attention to the surround stimulus increases surround suppression with a comparison not subject to this potential confound, we directly compared the response to the center-surround stimulus pair, when attention was directed either to the surround stimulus or to the distant location (Figure 3E, blue icons, center and left column, respectively). Directing attention to the surround stimulus caused a significant 4.9% reduction in firing rate, as compared to the attend-distant condition (paired test attend-surround versus attend-distant p < 0.0001). Thus, attention to the surround magnified the surround modulation that was observed in the attend-distant condition.

Also consistent with the example neurons and the population average response, attention to the center stimulus tended to reduce surround suppression. This is shown in Figure 4B, which plots the $SMI_{attend\ center}$ as a function of $SMI_{attend\ distant}$. Cells that exhibit surround suppression in the attend-distant condition (points to the left side of the plot) tend to fall above the line of unity, reflecting a diminishment of surround suppression. Figure 4D shows the distribution of the differences between these surround modulation indices ($SMI_{attend\ center} - SMI_{attend\ distant}$). Positive values correspond to neurons that showed a reduction of surround suppression in the attend-center versus attend-distant condition. Surround suppression was significantly weaker with attention directed to the center stimulus (median $SMI_{attend\ distant} = -0.051$, p < 0.0001; median $SMI_{attend\ center} = -0.024$, p < 0.0001; median difference = 0.019; paired test p = 0.0007).

The above results are consistent with the conclusion that directing attention to the center stimulus reduces the
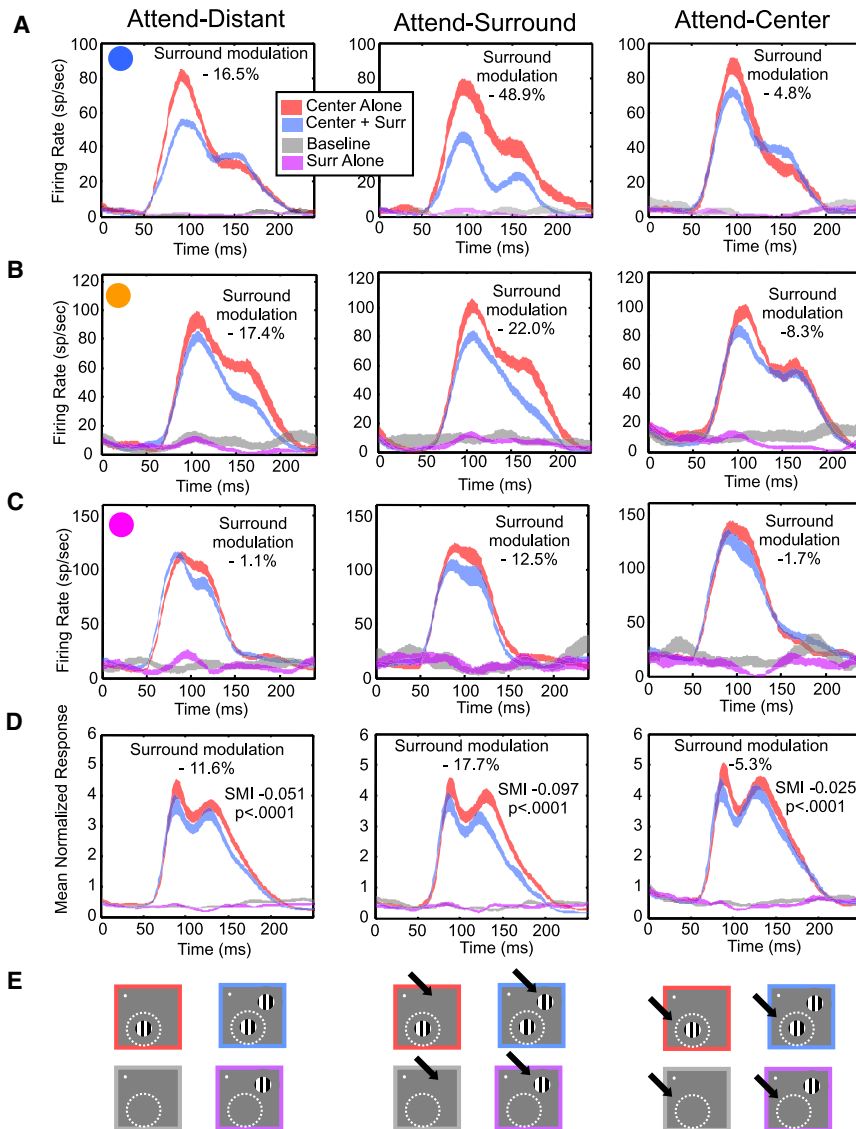
Figure 3. Single-Unit Examples and Population Results

In each row, the left column shows the response evoked by the center stimulus ±1 SEM in the absence (red) and presence (blue) of the surround stimulus when attention was directed to the distant stimulus. Gray and purple lines show the responses in the baseline (0% center and 0% surround stimulus) and surround alone conditions (0% center stimulus, 100% surround stimulus), respectively. Responses in the attend-surround and attend-center condition are plotted in the center and right columns, respectively. Colored circles in the upper left corner of the single-unit example panels (left column) denote the icon used to represent these individual example cells in Figure 4.

(A–C) Single-unit examples.

(D) Mean normalized population average response.

(E) Icons representing the stimulus configuration and location of attention in all conditions plotted in panels (A)–(D).

$SMI_{attend\ distant}$, p = 0.003). The most strongly suppressed neurons (n = 43, median $SMI_{attend\ distant}$ = −0.154, range −0.095 to −0.42) showed the strongest attention effect ($SMI_{attend\ center}$ = −0.043, which was significantly less than $SMI_{attend\ distant}$, p < 0.0001). The change in surround modulation (SMI) between the attend-center and attend-distant conditions was significantly larger for neurons in the strongly suppressed quantile than the intermediately suppressed quantile (p = 0.0006) and significantly larger for the intermediately suppressed quantile than the weakly modulated quantile (p = 0.002). Thus, the influence of attention to the center stim-

suppression caused by the surround stimulus. If so, the effects of attention would be expected to be greatest for those neurons that showed the strongest surround suppression. We find, consistent with an attention-dependent reduction in surround suppression, that the change in response with attention to the center stimulus depended on the magnitude of surround suppression observed when attention was directed away from the RF. We categorized neurons into quantiles based upon the strength of surround suppression in the attend-distant condition. Neurons showing the weakest surround modulation (n = 43, median $SMI_{attend\ distant}$ = −0.010, range −0.031 to 0.031) showed no significant change in SMI with attention (median $SMI_{attend\ center}$ = −0.012, not significantly different from $SMI_{attend\ distant}$, p = 0.37). Neurons showing intermediate levels of surround suppression (n = 43, median $SMI_{attend\ distant}$ = −0.064, range −0.032 to −0.094) showed significant reductions in surround modulation with attention to the center stimulus ($SMI_{attend\ center}$ = −0.024, which was significantly less than

ulus was not simply to increase firing rate by a constant gain factor, which would have resulted in significant changes in SMI in all quantiles. The effect of attention instead depended on the sensory interaction between the center and surround stimulus. Thus, we conclude that attention to the center and surround, respectively, diminish and magnify surround suppression.

Effects across Time

We next examined the evolution of the attention-dependent modulation of surround suppression across time. We computed the median SMI across the population, in each attention condition, in successive 40 ms bins. The results of this analysis appear in Figure 5. Cells were excluded from this analysis if they exhibited an undefined index value (due to zero response in both conditions used to calculate the index) in one or multiple time bins. This resulted in 112 cells being included for this analysis. Consistent with the earlier analyses, we find significant surround suppression in the attend-distant condition, which is diminished
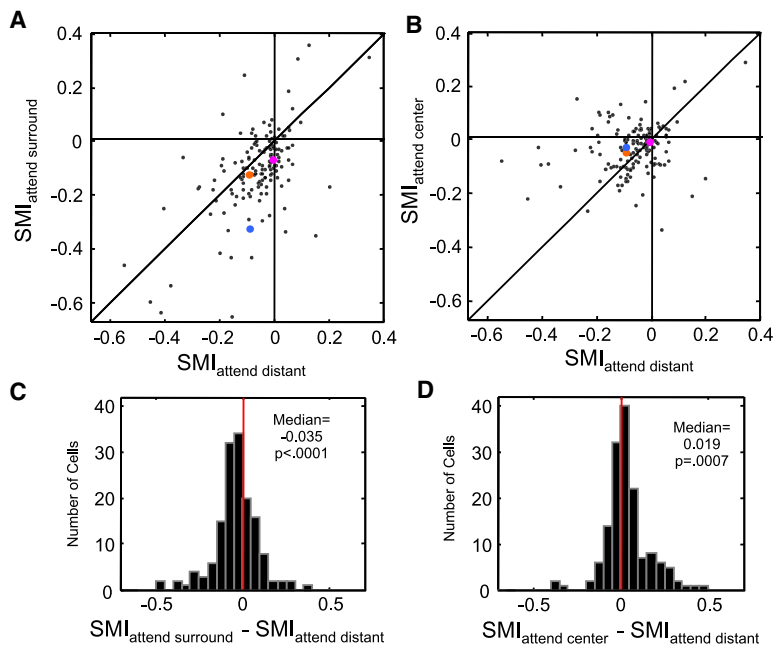
Figure 4. Attention to the Center and Surround Stimulus Modulates Surround Modulation

(A) Scatter plot of $SMI_{attend\ distant}$ versus $SMI_{attend\ surround}$.

(B) Scatter plot of $SMI_{attend\ distant}$ versus $SMI_{attend\ center}$.

(C) Population histogram of the difference in SMIs between the attend-distant and attend-surround conditions. Negative values indicate cells exhibiting stronger surround suppression in the attend-surround versus attend-distant condition.

(D) Population histogram of the difference in SMIs between the attend-distant and attend-center conditions. Positive values indicate cells exhibiting stronger surround suppression in the attend-distant versus attend-center condition.

and enhanced with attention to the center and surround, respectively. In the attend-distant condition, the surround stimulus induced significant surround suppression in the period 75–235 ms poststimulus onset (second to fifth time bins). In the attend-center condition, the surround stimulus was only significantly suppressive in the period 75–195 ms poststimulus onset (second to fourth time bin). Paired tests between the attend-distant and attend-center conditions revealed that attention to the center stimulus significantly reduced surround suppression in the period 115–195 ms after stimulus onset (third and fourth bins). Thus, the early stimulus-driven response represented in the second bin (75–115 ms poststimulus onset) exhibits significant surround suppression that is not measurably reduced by directing attention to the center stimulus. This delay is also apparent in the population average illustrated in the right column of Figure 3D. In the attend-surround condition, the surround stimulus was significantly suppressive over the same time period as the attend-distant condition, 75–235 ms poststimulus onset (second to fifth time bins). Attention to the surround stimulus significantly increased surround suppression in the period 115–235 ms after stimulus onset (third through fifth bins). Therefore, the effect of attention to both the center and surround stimulus is weak during the early part of the stimulus-evoked response and grows in strength over time.

Effects across Contrast

One hundred twenty-two cells were tested at multiple center stimulus contrast levels, allowing us to examine the interaction between attention condition and center stimulus contrast. Figures 6A–6E show the mean normalized population average responses across time in the three attentional conditions, as in Figure 3D, but with the responses at different center stimulus contrasts separated. In the attend-distant condition, surround suppression is weakest for the highest contrast center stimulus (top row) and becomes stronger as center stimulus contrast is

reduced. The influence of attention was consistent across contrasts and with what we observed in the pooled data. Attention to the center stimulus reduced surround suppression (right column), and attention to the surround stimulus increased surround suppression at all contrast values (middle column). These results are summarized by contrast response functions in Figure 6F.

Although not the focus of the current study, we also examined the influence of attention directed to the center stimulus presented alone as a function of contrast. Reynolds et al. (2000) varied contrast and found that attentional modulation was stronger at intermediate rather than high contrast. A related study by Williford and Maunsell (2006), however, found significant attentional modulation for high-contrast stimuli. In the present study, neuronal responses were often not saturated at the highest contrast tested, limiting our ability to compare attentional modulation at saturating contrast, but our results show similarities to both previous studies. Consistent with the findings of Reynolds et al. (2000) and Martinez-Trujillo and Treue (2002), attentional modulation was considerably (more than 2-fold) stronger at lower contrasts (45.3% and 49% attentional modulation at 11% and 6.5% contrast, respectively) than high contrast (18.8% at 99% contrast). However, the attention-dependent increase in firing rate at high contrast was stronger than was found in these earlier two studies, in line with the findings of Williford and Maunsell (2006). The differences between the present findings and each of the earlier studies are likely attributable to differences in stimulus size, stimulus type, and the attentional task employed. These factors remain to be examined systematically.

Eye Movements

To determine whether differences in eye position contributed to the differences in neural response evoked by attended and unattended stimuli, we compared the eye positions of the animals in the attend-away and attend-center conditions. On average, both monkeys exhibited a small deviation in eye position (0.06° in monkey J, p = 0.001, 0.04° in monkey M, p < 0.001, signed rank test) away from the RF when attending to the stimulus in the RF. This deviation in the eye position is very small relative to the size of stimuli (2° in diameter) and the size of the neuronal RFs (range of RF diameters = 4°–11°). It is therefore unlikely that deviations in eye position contributed significantly to cue-dependent changes in firing rate.
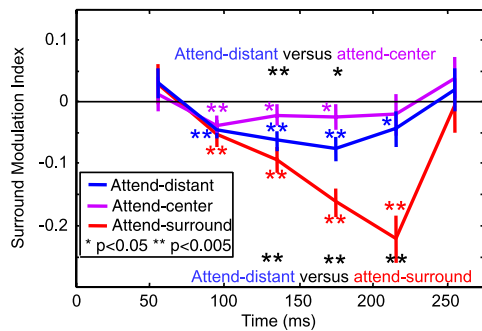
Figure 5. Time Course of Attention-Dependent Modulation of Surround Suppression

Attend-distant (blue), attend-center (purple), and attend-surround (red) SMIs plotted in nonoverlapping 40 ms time bins. Index values plotted at the center of each time bin. Colored asterisks denote index values significantly different from zero. Black asterisks denote significant differences between attend-distant and attend-center (top row) or attend-distant and attend-surround (bottom row). Error bars represent ±1 SEM.

DISCUSSION

The present experiments provide evidence that attention modulates center-surround interactions. Attentional modulation of the population average response was approximately doubled by addition of a surround stimulus, and surround suppression was stronger when attention was directed to the surround rather than center stimulus. This did not reflect a general increase in firing rate with attention to the center because the magnitude of the attention effect depended on the magnitude of the surround suppression observed when attention was directed far from the RF. Attention filtered out the influence of irrelevant distracter stimuli on the response of the neuron both by decreasing surround suppression when attention was directed to the center stimulus and by boosting surround suppression when attention was directed to the surround stimulus. Attention thus modulates center-surround mechanisms to boost the responses of attended stimuli and to filter out the influence of nearby distracter stimuli.

Modeling Implications

Reynolds et al. (1999) proposed a normalization model of attention in which attention multiplicatively scaled the excitatory and inhibitory responses within a normalization circuit. The model predicted that in the absence of attentional modulation the response to a pair of high-contrast stimuli within the classical RF should fall between the responses evoked by the two individual stimuli. That is, the response to the more preferred stimulus should be diminished by the addition of a nonpreferred stimulus within the classical RF. The model also predicted that directing attention to the preferred or nonpreferred stimulus should diminish or magnify the suppressive effect of the nonpreferred stimulus. These model predictions were tested by Reynolds et al. (1999) and were supported by the data.
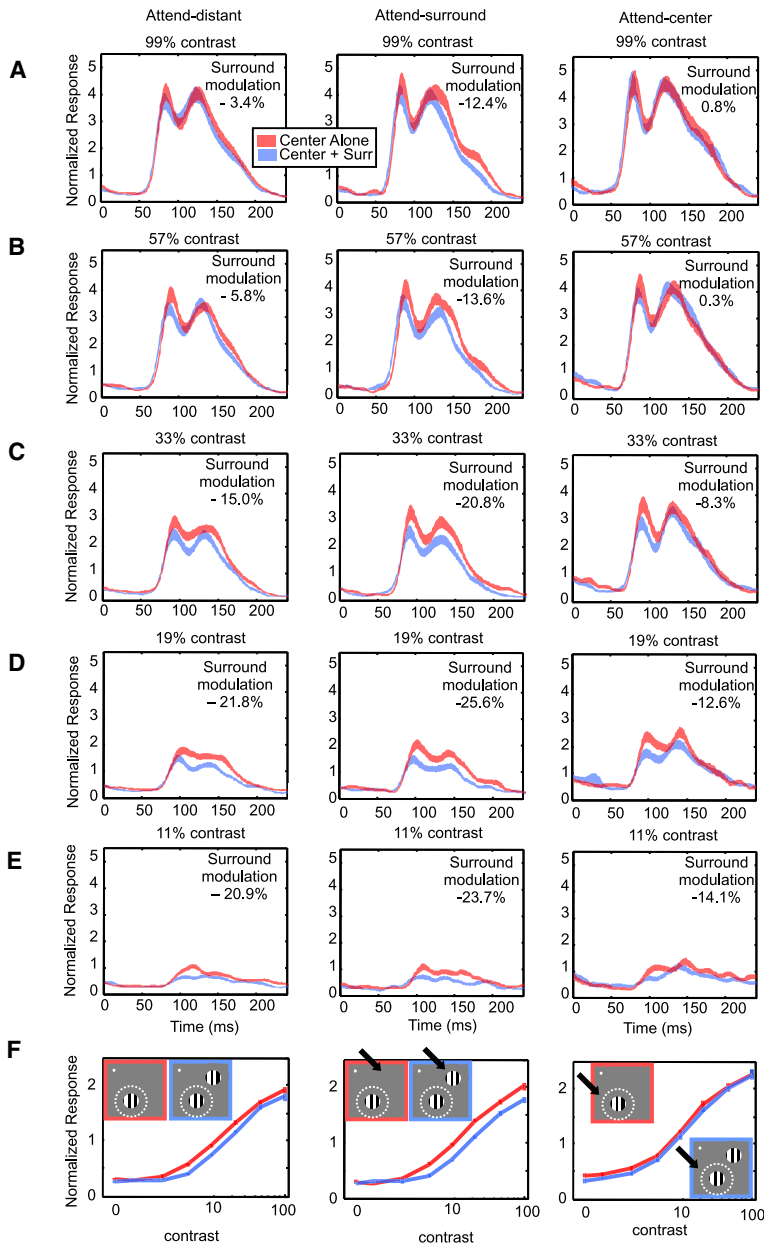
The present findings show that surround suppression is reduced by directing attention to the center stimulus and magnified by directing attention to the surround stimulus. Thus, atten-

tional feedback modulates the neural mechanisms that give rise to surround suppression. A leading class of models of surround suppression depends on divisive normalization (Cavanaugh et al., 2002), which extended earlier normalization models (Sperling and Sondhi, 1968; Albrecht and Geisler, 1991; Heeger, 1992; Carandini and Heeger, 1994; Simoncelli and Heeger, 1998) to include a broad divisive surround component. Following the lead of Cavanaugh et al. (2002), Reynolds and Chelazzi (2004) and Reynolds and Heeger (2009) proposed that the normalization model of attention be extended to include a broad divisive surround. This proposal leads to several predictions that are supported by the present results. The first is that when attention is directed to a suppressive stimulus in the RF surround, the strength of inhibitory inputs driven by the surround stimulus should increase, thereby reducing the response evoked by a stimulus appearing within the classical RF. This is consistent with our finding of a 52.6% increase in suppression when attention is directed to the surround stimulus. Second, when attention is directed to the stimulus in the RF center, the strength of the inputs from the center stimulus should increase, thereby diminishing the suppressive effect of the surround stimulus. This is consistent with our finding that directing attention to the center caused surround suppression to diminish by 54.3%. Finally, the influence of attention should have little effect when the sensory interactions between the center and surround stimulus are weak or absent. This is supported by the lack of a significant change in surround modulation with attention to the center stimulus among cells showing weak surround effects in the attend-distant condition. Thus, the present results support a generalized normalization model of attention that incorporates a broad divisive surround.

Influence of Feature Attention

As discussed in the preceding section, previous studies characterizing the influence of attention on the response of neurons to pairs of stimuli positioned within the RF are consistent with a normalization model of attention. It has, however, been suggested that these findings are also consistent with a gain model that incorporates feature attention (Treue and Martinez-Trujillo,1999; Martinez-Trujillo and Treue, 2004). The feature gain similarity model posits that the attentional gain factor depends upon the relationship between the features of the attended stimulus and the feature preferences of the neuron. When attention is directed to a stimulus composed of features near the peak of the neuron's feature tuning curve (preferred stimulus), the attentional gain factor is assumed to increase, leading to an increase in firing rate. When attention is instead directed to a nonpreferred stimulus, the attentional gain factor is assumed to decrease, leading to a reduction of response. Therefore, both the attention-dependent increase in firing rate with attention to the preferred stimulus and the attention-dependent reduction in firing rate with attention to the nonpreferred stimulus can be explained by both the feature-similarity gain model and spatial attention in the normalization model of attention.

The present experiment differs from the earlier experiments in that all stimuli in our experiment were identical in their features, thereby equating feature attention. Further, the critical comparison held spatial attention constant and varied only in the

Figure 6. Results Are Similar across Contrast

(A–E) Left column plots the mean normalized population response ±1 SEM to the center stimulus in the absence (red) and presence (blue) of the surround stimulus when attention is directed to the distant stimulus. The responses in the attend-surround and attend-center condition are plotted in the center and right columns, respectively. (A) Center stimulus contrast 99%. (B) 57%. (C) 33%. (D) 19%. (E) 11%.
(F) Contrast response functions illustrating the mean response as a function of center stimulus contrast in the absence (red) and presence (blue) of the surround stimulus.

this study. It may have, but it was held constant across conditions. The interactions between feature attention, spatial attention, and center-surround interactions remain to be examined systematically.

Influence of Attentional Effort and Exogenous Cuing

Our main finding is that attentional modulation is stronger in the presence than in the absence of a task-irrelevant distracter placed within the neuron's RF surround. It is important to consider whether this effect could be explained as resulting from increased attentional effort. It is not unreasonable to suppose that the animals had to exert greater effort to maintain attention on a target when a distracter appeared nearby. Previous studies have shown that increased effort can cause elevations in firing rate (Spitzer et al., 1988; Boudreau et al., 2006). An elevation of firing rate with effort might explain the larger increase in response with attention to the center stimulus that we observed when the surround stimulus was added. However, this would not explain why the change in response depended specifically on the magnitude of surround suppression for the individual neuron we happened to be recording from in a given experiment. Neurons that exhibited weak or no surround suppression in the attend-distant condition did not exhibit a significant change in SMI with attention to the center stimulus. In contrast, neurons exhibiting moderate and strong suppression in the attend-distant condition showed significant changes in SMI (reduced surround suppression) with attention directed to the center stimulus. Thus, since the mere presence of a nearby stimulus did not cause an increase in firing rate, the present findings cannot be explained by differences in effort.

A related concern is that the stimulus flashes during the pause period may have acted as exogenous cues drawing attention away from the cued stimulus. It is unlikely that this had a substantial influence on our findings. First, the task required a saccade to the cued stimulus at the end of each trial. If attention had been pulled away from the cued stimulus by onsets during the pause period, this would have resulted in a high error rate, which was not observed. Second, as with the effort confound, this

presence or absence of the surround stimulus. This comparison showed that directing attention to the center stimulus resulted in a modest increase in response in the absence of a surround stimulus but that the identical attentional change had a much stronger effect in the presence of a surround stimulus. Furthermore, the size of this effect depended upon the strength of surround suppression measured when attention was directed far from the RF. These results cannot be explained as resulting from feature-based attention, as this would predict a fixed attentional gain factor in the presence and absence of the surround stimulus. The results are consistent with the normalization model of attention. Although the present results cannot be explained as resulting from feature-based attention, they do not rule out that feature attention may influence the responses of neurons in

exogenous cueing confound cannot account for our finding that the influence of attention depended upon the strength of surround suppression in the attend-distant condition. Third, our main findings, significant increases in surround suppression with attention to the surround stimulus and significant decreases in surround suppression with attention to the center stimulus, held under conditions in which exogenous cueing could only lead us to underestimate the magnitude of our results. When attention is directed to the center stimulus, exogenous cueing would lead to attention being drawn away to the nearby surround stimulus. This hypothetical diversion of attention with a nearby surround stimulus present would reduce the response elevation induced by attention to the center stimulus. This, therefore, could have only caused us to underestimate the increased attentional modulation we observed in the presence of a surround stimulus. When we compare surround suppression with attention to the surround stimulus versus a distant stimulus, we find a reduction in response (increase in surround suppression) with attention to the surround stimulus. Exogenous cueing would cause attention to be drawn from the cued surround stimulus to the center stimulus, causing an increase in response. This, therefore, could only cause us to underestimate the increased surround suppression (decrease in response) we observe when attention is directed to the surround stimulus.

Relationship to Previous Experiments with Surround Stimuli

Moran and Desimone (1985) were the first to test the influence of spatial attention on a target in the presence of a nearby distracter. They found that when a preferred and a nonpreferred stimulus were placed within the RF of a neuron, its responses were larger when the animal attended to the preferred rather than the nonpreferred stimulus. In a key comparison, they found that these effects disappeared when one of the two stimuli was moved to a location just outside the classical RF. This comparison was the basis for their proposal that RFs shrink around the attended location. They argued that with two stimuli in the RF, this shrinking excluded the unattended stimulus from the RF, but when one of the stimuli was already physically positioned outside the RF, attention had no influence. The view that follows from this is that the large attention effects that are observed with two stimuli emerge at stages of processing where RFs are large enough to encompass both stimuli.

The present results instead show very large attentional modulation with one stimulus inside the RF and the other in the near surround. This is important from a modeling standpoint. First, our findings suggest that attention effects observed with two stimuli in the RF likely emerge at earlier stages of processing with smaller RFs, where one stimulus falls within a neuron's classical RF and the other falls within the surround. Second, because these effects result specifically from modulation of center-surround interactions, our findings strongly support models in which attention modulates the neural mechanisms that give rise to surround suppression.

The striking difference in findings between the Moran and Desimone study and the current study is likely due to differences in stimuli. In the present study, we did not find a significant effect of attention to the center stimulus when the surround was not effective at inducing surround suppression. In the Moran and Desimone study, the stimulus placed outside the RF was a nonpreferred stimulus, which are generally less effective than preferred stimuli at inducing surround modulation in area V4 (Schein and Desimone, 1990). The results in the two studies are therefore consistent under the assumption that the nonpreferred surround stimuli in the earlier study were not effective at inducing surround suppression.

Motter (1993) found that although some neurons in V4 were modulated by attention when a single stimulus was presented within their RF, many neurons were only modulated in the presence of one or more stimuli located outside the classical RF. He found that attention caused response increases in some cells and decreases in others, but did not examine why certain cells showed one or the other pattern. The innovation of the current experiment was to directly measure the influence of the surround stimulus on the neuron's center stimulus response when attention was directed away. This condition allowed us to determine that the influence of attending to the center stimulus in the presence of the surround stimulus depended critically on whether the presence of the surround stimulus was suppressive. These results therefore extend Motter's original finding and allowed us to test the predictions of the normalization model of attention.

Surround stimuli generally have suppressive influences on neuronal responses in area V4 and other visual areas. Consistent with this, the surround stimuli used in the present experiment predominately had a suppressive effect on neuronal response. It has been shown, however, that collinear and low-contrast center and surround stimuli can often lead to surround facilitation instead of suppression (Pack et al., 2005; Polat et al., 1998; Sceniak et al., 1999). Ito and Gilbert (1999) have shown that attention can modulate contextual influences in primary visual cortex. In this experiment, attention to the stimulus in the RF did not significantly modulate the neuron's response in the absence of the collinear flanking bars, but did in their presence. Large differences between this and the present experiment make a comparison of results difficult. In particular, the effect of attention in Ito and Gilbert's study depended crucially on the behavioral training state of the animal. Another V1 study (Roberts et al., 2007) found that attention can modify the spatial integration (measured by length tuning) of neurons in a manner that varied with eccentricity. Although not directly comparable to our V4 results, both V1 studies highlight that attention can modulate the way neurons integrate information from stimuli positioned outside their classical RF. Additional research will be needed to explore the influence of attention on surround facilitation, length tuning, and the interactions between attention, collinearity, and contrast.

Previous work has also examined changes in neural response when attention is directed to locations outside the classical RF. Connor et al. (1996) found that directing attention to different stimuli positioned outside the classical RF of V4 neurons modulates neuronal responses evoked by an unattended probe stimulus appearing at various positions within the classical RF. They found that the specific location of attention strongly influenced the response to the probe and interpreted their effect as a combination of attention-dependent RF shifts and a signal encoding the relative location of attentional focus to the neuron's RF. An experiment in MT has also found evidence for RF shifts toward

the focus of attention and suggests that such shifts may be the results of multiplicative attentional modulation at earlier stages of visual processing (Womelsdorf et al., 2006). Unlike these previous studies, we did not test multiple locations within the RF, but our results are broadly consistent with the earlier findings, as we find that directing attention to a stimulus outside the RF modulates neuronal response.

EXPERIMENTAL PROCEDURES

Subjects and Surgery

Preoperative magnetic resonance imaging (MRI) was used to identify the stereotaxic coordinates of V4 in two adult male monkeys (Macaca mulatta). Experimental and surgical procedures have been described previously (Reynolds et al., 1999). A recording chamber was placed over the prelunate gyrus. At the beginning of the study, several recordings were made at different positions in each recording chamber to ensure that the electrode was in area V4, on the basis of RF sizes, topographic organization, and feature preferences. To inhibit granulation tissue growth in the chamber, the antimitotic 5 fluorouracil (5FU) was applied to the tissue in the chamber three times each week (Spinks et al., 2003). Experimental and surgical procedures were approved by the Salk Institute Institutional Animal Care and Use Committee and conformed to NIH guidelines for the care and use of laboratory animals.

Electrophysiology and Stimulus Presentation

In each experimental session, two to four tungsten electrodes (FHC) were advanced into cortex using a multielectrode drive (NAN 4-tower drive, Plexon Inc., or 3NRM-3A microdrive, Crist Instruments). Electrodes were passed through guide tubes that touched but did not penetrate the dura. Guide tubes were positioned using a grid with 1 mm spacing between adjacent locations. Neuronal signals were recorded extracellularly, filtered, and stored using the Multichannel Acquisition Processor system (Plexon, Inc.). To record spiking activity, the signal was filtered from 400 Hz to 8.8 KHz and digitized at 40 KHz. Single units were isolated online with Rasputin software (Plexon, Inc.). Spike sorting was then repeated offline using the Plexon Offline Sorter to ensure that all action potentials were well isolated throughout the recording session. Single units recorded on a given electrode were isolated by waveform shape and included for analysis only if the waveforms formed an identifiable cluster when projected into the space defined by the principal components derived from all waveforms recorded on that electrode. Forty of 150 neurons included for analysis were recorded simultaneously with one or two other neurons on the same electrode.

Stimuli were presented on a computer monitor (Sony Trinitron Multiscan, TC, 640 × 480 pixel resolution, 120 Hz) placed 57 cm from the eye. Lookup tables were linearized using a PR-650 or PR-701S spectroradiometer (Photo-Research, Inc.). Eye position was continuously monitored with an infrared eye tracking system (240 Hz, ETL-400; ISCAN, Inc.). Experimental control was handled by NIMH Cortex software (http://www.cortex.salk.edu/).

Behavioral Task

Neuronal responses were recorded as the monkey performed an attention-demanding multiple-object tracking task (Mitchell et al., 2007). The monkey began each trial by fixating a central point for 200 ms and then maintained fixation through the trial. Four identical circular-apertured square-wave gratings (2° diameter, 2 cpd) appeared at equally eccentric positions separated by 90°, as illustrated in Figure 1A. The four stimuli were placed so that they fell outside each neuron's classical RF. One or two stimuli were then briefly elevated in luminance, identifying them as targets. All stimuli then moved along independent trajectories at ~10°/s for 950 ms, placing them at a new set of equally eccentric locations. The center and surround stimulus locations were separated from one another by an angle of 67.5°. The other two stimuli were at point-symmetric positions in the contralateral field (distant stimuli). All stimuli paused for 1600 ms in this configuration, with the cueing of stimuli at the beginning of the trial determining the animal's attentional state. In one-target tracking, the attend-distant condition was when the cued item paused at

one of the two distant locations, the attend-center condition was when the cued item paused at the position within the RF, and the attend-surround condition was when the cued item paused at the position just outside the RF. In two-target tracking, the attend-distant condition was when the two cued items paused at the two distant locations, and the attend-center and attend-surround conditions were when one cued item paused in a distant location and the other paused in either the center or surround stimulus location. Following the pause period, stimuli moved to another set of locations, the fixation point disappeared, and the monkey made a saccade to each target. Reward was delivered if the monkey saccaded to all targets, without first saccading to a nontarget.

During the movement and pause phases of the trial, stimuli were flashed for 50 ms with a 150 ms blank between flashes. Eight flashes occurred during the pause period. Each time the stimuli flashed, they were presented at a different contrast value. This improved the probability of identifying sensory conditions that would, for the individual neuron under study, yield significant surround modulation and also allowed us to examine the consistency of our effect across contrast. For most experiments, eight contrasts were used (99%, 57%, 33%, 19%, 11%, 6.5%, 3.5%, and 0%). During the movement phases, the contrasts of the four stimuli were independently chosen from the top four contrast values. During the pause, the contrast of the center stimulus was chosen from all eight contrast values and the surround stimulus was chosen from the top three contrasts plus 0% contrast. When a 0% contrast flash occurred at the center or surround stimulus location, we could measure the neuronal response to the surround or center stimulus presented alone. In order to complete the task accurately, the animals had to attend to and track the cued objects despite their temporary disappearances. The contrasts of the distant stimuli were randomly chosen from the pool of contrasts being sampled by the point symmetric stimulus. In a small subset of experiments, only 99% and 0% contrast were used during the pause period, but the contrast of stimuli during the movement phase remained unchanged. In some experiments, both possible surround locations (clockwise and counterclockwise from the center stimulus) were probed on interleaved trials. Some neurons were tested with multiple surround stimulus contrasts, but data from only the highest-contrast surround stimuli were included for analysis. This was done because the surround stimulus more strongly modulated neuronal responses at high contrast. Analyses were performed only on correctly completed trials to ensure that the monkey was attending to the cued items. Incorrect trials were repeated later in the experimental session. Both monkeys performed this task above 70% correct, well above chance levels of 25% for experiments with one-target tracking and 16.5% for two-target tracking experiments. All cells in monkey J and roughly half (39 of 76) of cells in monkey M were recorded in the one-target tracking paradigm. Results were similar between one- and two-target tracking, so results were combined across these behavioral conditions.

Data Analysis

All statistical comparisons were made with nonparametric tests to avoid making potentially unwarranted assumptions about underlying distributions, using Matlab (signrank and ranksum functions, Mathworks, Inc.). Paired comparisons and one-sample tests were computed using the Wilcoxon signed rank test, and unpaired comparisons were computed using the Wilcoxon rank sum test. Signed rank tests were used in any case where the statistical test was not otherwise noted. Significance levels were set at 0.05, and the Bonferonni correction for multiple comparisons was used when noted. Single-unit example response histograms were smoothed with a 20 ms standard deviation Gaussian kernel, and population average response histograms were smoothed with a 10 ms standard deviation Gaussian kernel. Error bars on response histograms were calculated from the smoothed data. Unless otherwise noted, responses are averaged across the time window from 40 to 240 ms poststimulus onset. Percentage modulations were always calculated on the mean responses across trials for the single-unit examples and the mean responses across cells for the population average histograms. Index values were always calculated on the mean responses across trials for each cell with the median index value across cells reported for the population average.

Baseline response was estimated by computing the average response when a 0% contrast stimulus was presented at both the center and surround

location. The attention condition matched baseline rate was then subtracted from the stimulus-evoked response on a cell-by-cell basis. Nine cells were excluded from this analysis because the stimulus-evoked response in at least one condition was less than the baseline response (generally due to the surround stimulus suppressing the response of the neuron below baseline).

Inclusion Criteria

Cells were excluded from analysis if the surround stimulus gave a response significantly above baseline (rank sum test, corrected for multiple comparisons). When the surround was probed at different contrast values, all contrast surround stimuli were tested to increase our sensitivity in excluding cells where the surround stimulus was inadvertently positioned within the RF. When two surround positions were probed, they were tested independently to determine if either surround stimulus elicited a response. In the case that one but not the other surround stimulus location elicited responses significantly above baseline, the location eliciting a response was excluded from analysis and the other included. Units were then tested to determine if the center stimulus was correctly positioned within the RF. Cells were included for analysis if they responded significantly above baseline to the presentation of any contrast center stimulus (rank sum test, corrected for multiple comparisons). When center stimuli of multiple contrast values were used, only those center stimulus contrasts that elicited a response significantly above baseline were included in the main analysis. When multiple center/surround stimulus pairs for an individual cell met the above inclusion criteria, the responses to all stimulus pairs were averaged before the data were combined for population analysis. Responses from all attention conditions were combined when testing neurons against these inclusion criteria. This prevents regression to the mean from biasing our results when we compare responses across attention conditions. These criteria resulted in the inclusion of 152 of the 240 neurons recorded (64 excluded for failing to respond to the center stimulus and 24 excluded for giving significant responses to the surround stimulus). An additional two neurons were excluded from analysis because the average response in at least one condition was less than 0.5 Hz.

For the examination of response across contrast (Figure 6), the response of the neuron at all center stimulus contrasts were included for analysis if the response to any center stimulus was significantly greater than baseline.

The population average surround stimulus alone response was not elevated over the baseline firing rate, indicating that our selection criteria effectively removed neurons where the surround stimulus was inadvertently placed within the classical RF (see Figure S1).

SUPPLEMENTAL DATA

The Supplemental Data include one figure and can be found with this article online at http://www.neuron.org/supplemental/S0896-6273(09)00169-X.

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