Neuron
Article

Differential Attention-Dependent Response Modulation across Cell Classes in Macaque Visual Area V4

Jude F. Mitchell,[1,*] Kristy A. Sundberg,[1] and John H. Reynolds[1,*]
[1] Systems Neurobiology Lab, The Salk Institute, La Jolla, CA 92037-1099, USA
*Correspondence: jude@salk.edu (J.F.M.), reynolds@salk.edu (J.H.R.)
DOI 10.1016/j.neuron.2007.06.018

SUMMARY

The cortex contains multiple cell types, but studies of attention have not distinguished between them, limiting understanding of the local circuits that transform attentional feedback into improved visual processing. Parvalbumin-expressing inhibitory interneurons can be distinguished from pyramidal neurons based on their briefer action potential durations. We recorded neurons in area V4 as monkeys performed an attention-demanding task. We find that the distribution of action potential durations is strongly bimodal. Neurons with narrow action potentials have higher firing rates and larger attention-dependent increases in absolute firing rate than neurons with broad action potentials. The percentage increase in response is similar across the two classes. We also find evidence that attention increases the reliability of the neuronal response. This modulation is more than twofold stronger among putative interneurons. These findings lead to the surprising conclusion that the strongest attentional modulation occurs among local interneurons that do not transmit signals between areas.

INTRODUCTION

Cortical neurons differ from one another in important ways, including their neurochemical properties, patterns of connectivity, laminar distribution, gene expression patterns, and developmental origin (Markram et al., 2004; Wonders and Anderson, 2006). It is unknown whether different classes of neurons play distinct roles during performance of an attention-demanding task. This question must be answered if we are to understand the biological underpinnings of attention, but it has remained unresolved because many of the properties that distinguish neurons from one another are invisible to the extracellular recording electrodes that are used to record neuronal responses in behaving animals.

To determine whether attention modulates neuronal responses generically across visual cortical neurons or differs by class, we exploited observations made in anesthetized animals and cortical slices, where different types of neurons can be distinguished on the basis of morphology and protein expression. These intracellular recording studies have found that parvalbumin-expressing GABAergic interneurons with the morphology of basket cells and chandelier cells have short-duration action potentials, whereas excitatory pyramidal neurons have longer-duration action potentials (McCormick et al., 1985; Connors and Gutnick, 1990; Kawaguchi, 1993; Nowak et al., 2003). This difference is due, in part, to the expression of different classes of K^+ and Na^+ channels that differ from one another in their kinetics (Martina and Jonas, 1997; Martina et al., 1998; Erisir et al., 1999). The duration of the extracellular spike waveform is directly related to the duration of the intracellular waveform (Henze et al., 2000; Gold et al., 2006). This has made it possible to distinguish fast-spiking inhibitory interneurons from pyramidal neurons in extracellular recordings in the hippocampus (Fox and Ranck, 1981; Buzsaki and Eidelberg, 1982; Csicsvari et al., 1999; Frank et al., 2001). Narrow and broad action potentials have also been distinguished from one another in several neocortical areas, including prefrontal cortex (Wilson et al., 1994; Rao et al., 1999; Constantinidis and Goldman-Rakic, 2002; Gonzalez-Burgos et al., 2005; Hasenstaub et al., 2005), primary visual cortex (Gur et al., 1999), somatosensory cortex (Mountcastle et al., 1969; Simons, 1978; McCormick et al., 1985), and rat barrel cortex (Bruno and Simons, 2002; Swadlow, 2003). A recent study validated the utility of the classification in cortex by showing that known pyramidal neurons in macaque frontal eye fields (those which can be antidromically activated by stimulation of the superior colliculus) have broad spike waveforms (S.Y. Shin and M.A. Sommer, 2006, Soc. Neurosci., abstract). Two other studies, in prefrontal and somatosensory cortex of the rat (Bartho et al., 2004) and the inferior temporal cortex of the macaque (Tamura et al., 2004), have further confirmed that narrow-spiking neurons are inhibitory, as indicated by short-latency dips in the cross-correlation of action potential times recorded simultaneously from pairs of neurons. We therefore examined whether action potential widths in area V4 are distributed bimodally, and if so,

whether attention-dependent response modulation varies between narrow- and broad-spiking neurons.

RESULTS

Separating Narrow-Spiking from Broad-Spiking Neurons

Neurons were recorded from area V4 in two rhesus macaques performing an attention-demanding task, which is described in detail below. Including any multiunit activity in our analysis could have resulted in averaging waveforms, thus obscuring differences in the population. Therefore, our V4 sample included only units that had been clearly isolated from one another and from multiunit activity, based on clear clustering in the principle components of the waveforms on each electrode (Offline Sorter, Plexon, Inc.). In addition, we required that units exhibit a clear spike refractory period. In total, 218 single units were isolated (142 from Monkey A, 76 from Monkey B), of which 160 were significantly driven by the stimuli in the task (108 from Monkey A, 52 from Monkey B). We examined the distribution of spike waveforms in order to determine whether it was bimodal and could therefore be divided into narrow- and broad-spiking subpopulations. For each neuron, all recorded action potentials were aligned by their troughs and averaged. Figure 1A shows the mean waveforms (±1 standard deviation) for two neurons recorded simultaneously on the same electrode. Across our sample, waveforms had similar biphasic shapes but varied in duration, defined here as the time in μs between the waveform trough and peak (Bartho et al., 2004). Figure 1B shows the mean waveforms of all neurons. The height of the waveforms has been normalized to aid in comparing action potential widths. All but nine neurons, which appear separately in the inset, had waveforms with a downward voltage deflection followed by an upward voltage deflection with a clear peak. Except where noted, these nine neurons were excluded from further analysis. The distribution of waveform durations, shown in Figure 1C, was significantly bimodal according to Hartigan's dip test ($p = 0.0030$) (Hartigan and Hartigan, 1985; Mechler and Ringach, 2002). The distribution was still significantly bimodal when limited to recordings in which only one neuron was isolated per electrode (see the Supplemental Results in the Supplemental Data available with this article online and Figure S2).

Narrow- and broad-spiking neurons were separated on the basis of the two modes of the bimodal distribution, with narrow-spiking neurons defined as those ranging in duration from 100 to 200 μs and broad-spiking neurons defined as those ranging in duration from 201 to 500 μs. In Figures 1 and 2, those neurons that exhibited significant visually driven responses are indicated in red and blue, for narrow and broad waveforms respectively. Visually nonresponsive neurons are indicated in gray.

We validated this classification by confirming that other physiological properties of the cells differed systematically

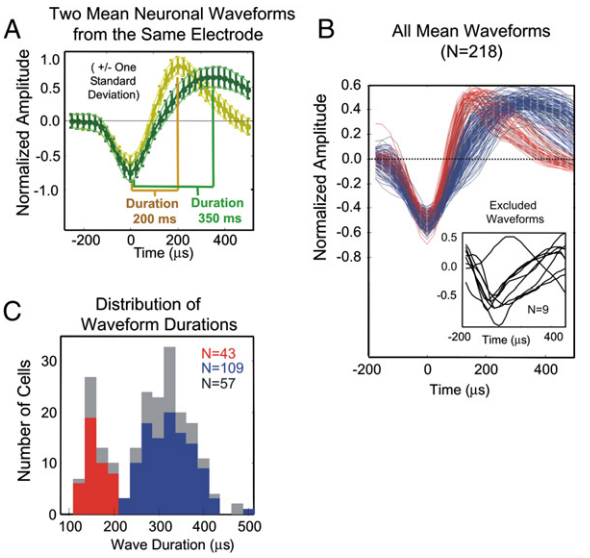

Figure 1. Classification of Broad- and Narrow-Spiking Neurons by Waveform Shape

(A) The mean waveforms (±1 standard deviation) of two neurons recorded from the same electrode. Waveform duration was defined as the time, in μs, from waveform trough to peak.

(B) Average waveforms of each of the 218 neurons in the total sample. Narrow and broad waveforms of visually responsive neurons are indicated in red and blue. Waveforms of non-visually responsive neurons are in gray. Nine waveforms that did not have a biphasic shape with a trough followed by a clearly defined peak were excluded from analysis.

(C) The distribution of waveform durations was significantly bimodal (Hartigan's dip test, $p = 0.0030$).

between groups. Intracellular studies have found that narrow-spiking inhibitory interneurons have higher firing rates than broad-spiking excitatory neurons when stimulated by current injection (McCormick et al., 1985; Connors and Gutnick, 1990; Foehring et al., 1991; Povysheva, et al., 2006) and visual stimuli (Contreras and Palmer, 2003). Consistent with these findings, our narrow-spiking neurons exhibited much stronger stimulus-evoked responses than did our broad-spiking neurons (median 28.6 Hz compared to 12.2 Hz, Mann-Whitney U test, $p < 0.001$). Narrow-spiking neurons also exhibited a higher level of spontaneous activity when no stimulus was present in the receptive field (RF) (median 9.4 Hz compared to 4.6 Hz, Mann-Whitney U test, $p < 0.001$). Intracellular studies also find that the repolarization of the membrane potential following a spike is slower among broad-spiking pyramidal neurons (McCormick et al., 1985; Nowak et al., 2003; Hasenstaub et al., 2005). In the extracellular signal, which resembles the negative derivative of the intracellular membrane potential, this gives both a broader and shallower peak following the initial trough (Henze et al., 2000). Consistent with this we find that broad-spiking neurons exhibit a shallower waveform peak relative to the trough (mean ratio 0.89 for broad-spiking neurons compared to 1.11 for narrow-spiking neurons, Mann-Whitney U test,

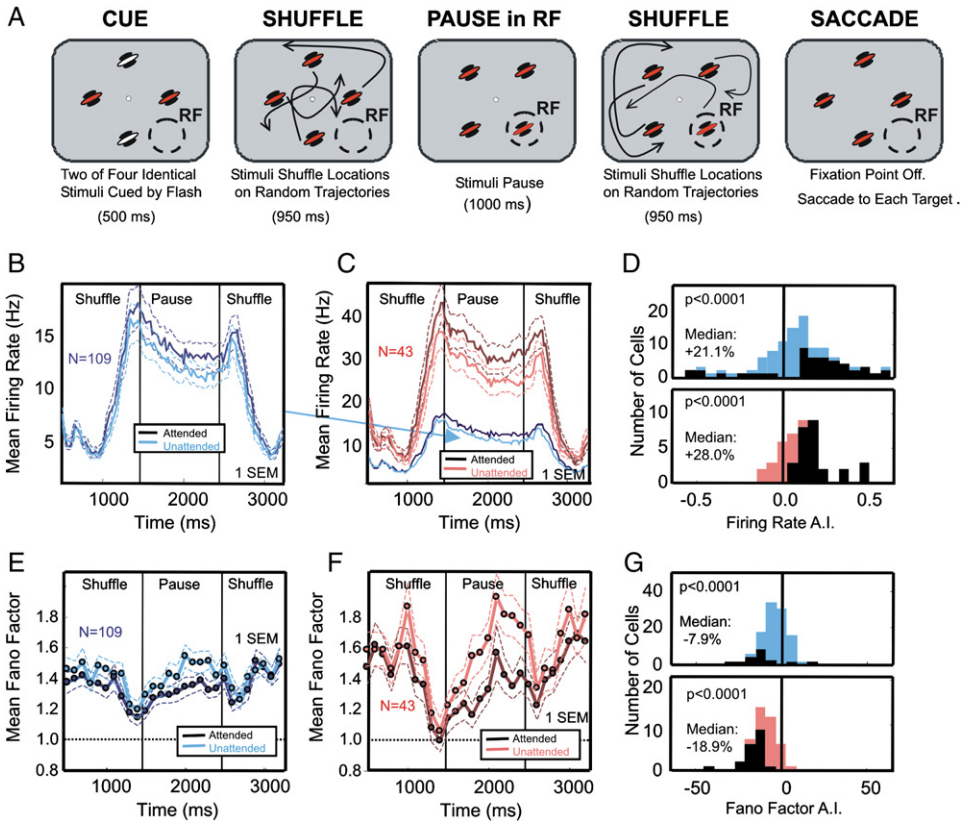

Figure 2. Comparison of Attention-Dependent Modulation of Rate and Fano Factor in Broad- and Narrow-Spiking Neurons

(A) Behavioral task. Each trial began with fixation of a central point. While fixation was maintained, two of four Gabor stimuli were cued with a brief luminance increase. All four stimuli then moved along independent randomized trajectories that brought one stimulus into the RF. All stimuli then paused for 1000 ms. Stimulus locations were then shuffled a second time and motion terminated. The fixation point then disappeared. Reward was delivered if a saccade was made to each target and no distracters.

(B and C) Average firing rate of broad-spiking (blue) and narrow-spiking (red) neurons for attended (dark red, dark blue) and unattended (light red, light blue) conditions (±1 SEM indicated by dashed lines).

(D) Distribution of firing rate attention indices for both classes. Individual units showing significant modulation are indicated in black.

(E and F) Average Fano factors of broad-spiking (blue) and narrow-spiking (red) neurons for attended (dark red, dark blue) and unattended (light red, light blue) stimuli (±1 SEM indicated by dashed lines).

(G) Distributions of Fano factor attention indices, for both classes.

$p < 0.001$). Finally, intracellular studies have estimated that roughly 70%–80% of cortical neurons are broad-spiking pyramidals (Connors and Gutnick, 1990; Markram et al., 2004). We found that 152 of 209 neurons (72.7%) had broad spike waveforms in our V4 sample.

Attention-Dependent Firing Rate Modulation for Narrow- and Broad-Spiking Neurons

The monkeys performed an attention-demanding multiple-object tracking task adapted from a paradigm used in humans (Pylyshyn and Storm, 1988; Sears and Pylyshyn, 2000; Cavanagh and Alvarez, 2005). The behavioral paradigm is depicted in Figure 2A. Monkeys maintained fixation on a central point while mentally tracking two of four identical Gabor stimuli, as all the stimuli moved along independent randomized trajectories. After an initial period of 950 ms of motion, all stimuli paused for 1000 ms before continuing along their trajectories. During this pause, one of the stimuli was positioned within the RF of the neuron under study. Sensory conditions were matched to ensure that the set of paths followed by the stimulus that entered the RF were identical across attention conditions (see Experimental Procedures). Therefore, any difference in response across cueing conditions can be attributed to the attentional cue.

The most well-established form of attention-dependent response modulation is an increase in firing rate when attention is directed to a stimulus within a neuron's RF (for reviews, see Treue, 2003; Reynolds and Chelazzi, 2004). Consistent with these earlier findings, the average firing rate during the 1000 ms pause period was increased by 22.9% for attended stimuli compared to identical unattended stimuli, averaged across the population of all 160 visually responsive neurons, including eight visually

responsive neurons of the nine with nonbiphasic waveforms (see Supplemental Results and Figure S1). The magnitude of this attention-dependent increase in firing rate is consistent with earlier studies that have used Gabor stimuli (McAdams and Maunsell, 1999a).

We examined whether this attention-dependent response increase differed between classes. Figure 2B shows the average response of the 109 visually responsive broad-spiking neurons for attended (dark blue) and unattended (light blue) stimuli. The response begins when the stimulus enters the RF, about 400 ms prior to the pause period, and also continues about 400 ms after the pause as the stimulus leaves the RF. There was a modest but significant increase in the firing rate with attention (mean attended = 13.9 Hz, unattended = 12.2 Hz, Wilcoxon signed rank test, $p < 0.001$). Figure 2C shows the average firing rate of the 43 visually responsive narrow-spiking neurons for attended (dark red line) and unattended (light red line) stimuli. The most noticeable difference between the two classes is the much higher firing rate of the narrow-spiking neurons. The lower response of the broad-spiking neurons, in blue, is included for comparison. The increase in absolute firing rate, in spikes/s, among narrow-spiking neurons (mean attended 34.6 Hz, unattended 28.6 Hz, Wilcoxon signed rank test, $p < 0.001$) was significantly larger than that of the broad-spiking neurons (Mann-Whitney U test, $p < 0.001$). However, the percentage increase did not differ significantly across the two populations, with a median increase of 21.1% among broad-spiking neurons compared to 28.0% among narrow-spiking neurons (Mann-Whitney U test, $p = 0.578$).

To visualize the distribution of effects in the two populations, we computed a rate normalized attention index for each unit, defined as $(A - U)/(A + U)$, where A and U are, respectively, the firing rate above baseline for an attended and unattended stimulus averaged over the 1000 ms pause period. The distribution of AI indices is summarized in Figure 2D for broad (blue)- and narrow (red)-spiking neurons. Scatter plots of the AI indices versus waveform duration are provided in Figure S3. In Figure 2D, those neurons with individually significant modulations are indicated in black. Both distributions were significantly shifted to the right of zero, indicating that attention tended to increase firing rate in both populations (Wilcoxon signed rank test, $p < 0.001$ for broad-spiking, $p < 0.001$ for narrow-spiking). However, the effect of attention on broad-spiking neurons was variable, with some neurons showing significant attention-dependent increases in firing rate and others showing significant decreases. Attention had a more consistent effect on the firing rates of narrow-spiking neurons. All 27 narrow-spiking neurons whose firing rate was significantly modulated showed an attention-dependent increase in response. Thirty-eight of the 47 significantly modulated broad-spiking neurons showed increases. This difference in the proportion of significant positive and negative attentional modulation was significant according to a bootstrap test ($p = 0.021$).

Attention-Dependent Changes in Response Variability

Response variability affects how reliably information is encoded by neuronal signals. An attention-dependent reduction in response variability could, therefore, enhance sensory processing of behaviorally relevant stimuli. To quantify response variability, we computed the Fano factor, the ratio of spike count variance to mean spike count. Figure 2E shows the average Fano factors of broad-spiking neurons for attended (dark blue) and unattended (light blue) stimuli. The Fano factor showed a modest, but significant, reduction with attention (mean attended = 1.31, unattended = 1.43, Wilcoxon signed rank test, $p < 0.001$). Figure 2F shows the average Fano factors of narrow-spiking neurons for attended (dark red) and unattended (light red) stimuli. The reduction among narrow-spiking neurons (mean attended = 1.31, unattended = 1.60, Wilcoxon signed rank test, $p < 0.001$) was significantly stronger than that of broad-spiking neurons (Mann-Whitney U test, $p < 0.001$). The percentage decrease was also significantly stronger among narrow-spiking neurons, with a median decrease of 18.9% as compared to 7.9% among broad-spiking neurons (Mann-Whitney U test, $p < 0.001$). The distribution of AIs for Fano factor is shown in Figure 2G for broad (blue)- and narrow (red)-spiking neurons. Each population separately showed a significant reduction in AI indices (Wilcoxon signed rank tests, $p < 0.001$).

We considered whether the stronger reduction in Fano factor for narrow-spiking cells might be a consequence of the fact that they exhibit much stronger stimulus-evoked responses than broad-spiking neurons. This explanation is plausible, as previous studies in early visual areas have shown that the Fano factor is smaller among neurons with higher firing rates (Kara et al., 2000). At higher firing rates, intervals between spikes become short, ultimately approaching the lower limit imposed by the spike refractory period, resulting in less variable spike timing. This relationship between spiking variance and rate for a model neuron is illustrated in Figure 3A. For a purely Poisson process, the variance in spiking would increase in exact proportion with the mean rate, resulting in a mean-variance relationship that falls along the line of unity (dashed line), but when we incorporate a relative refractory period, the variance in spiking begins to saturate at high firing rates (solid line). A substantial reduction in Fano factor occurs at high rates for a given percentage increase (dark red versus light red point) compared to an identical increase at lower rates (dark blue versus light blue point). Thus, an increase in firing rate with attention could plausibly produce a large reduction in Fano factor if it occurred in the saturating region of this curve.

To test this, we examined the relationship between spiking variability and rate for broad- and narrow-spiking neurons (Figures 3B and 3C). For each neuron we computed ten paired samples of the mean spike count and spike count variance (one sample for each of the 100 ms periods during the pause) for both the attended and the

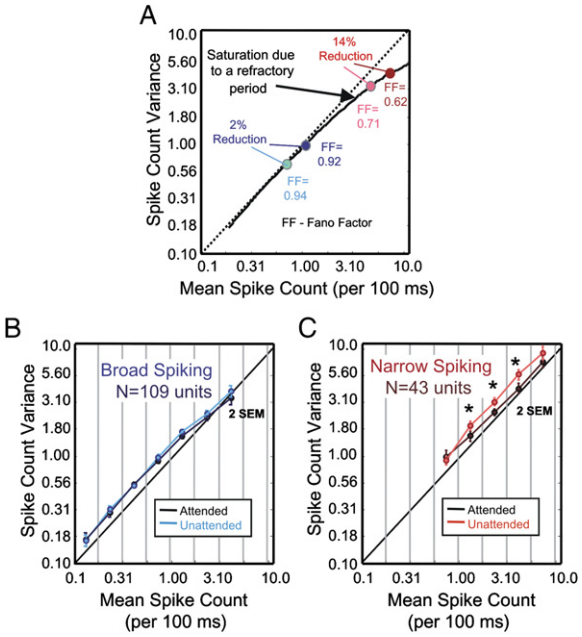

Figure 3. Comparison of Attention-Dependent Modulation of Spiking Variability at Different Firing Rates for Broad- and Narrow-Spiking Neurons

(A) Spike count variance versus spike count mean for a pure Poisson process (dashed line) and for a model neuron that includes a relative refractory period and saturates in variance at higher rates. An identical percentage increase in rate results in a larger reduction in Fano factor at higher firing rates (2% reduction at low rates, light and dark blue points; 14% reduction at high rates, light and dark red points).

(B) Measured mean spike count variance (±2 SEM) for broad-spiking neurons, sorted according to mean spike count (rate intervals marked by gray vertical lines). Measures of spike count mean and variance are derived from the ten 100 ms bins during the pause period and averaged across all 109 broad-spiking neurons for attended (black) and unattended (blue) trials.

(C) Same conventions as in (B), but averaged across 43 narrow-spiking neurons for attended (black) and unattended (red) trials. Asterisks indicate a significant reduction in variability within a bin (Mann-Whitney U test, $p < 0.05$).

unattended conditions. We divided these data into the eight firing rate intervals indicated by vertical gray lines in Figure 3B and 3C. We then computed the mean spike count variance within each interval. For broad-spiking neurons there was a modest saturation in variance with increasing rate (Figure 3B), consistent with the model neuron (Figure 3A). Variance decreased only slightly with attention (dark blue attended, light blue unattended) suggesting that the modest reduction in Fano factor found in this class of neurons could, as suggested by the model, be a consequence of the saturation in variance with increasing rate. In contrast, narrow-spiking neurons did not exhibit saturation in spike count variance with increasing rate (Figure 3C). The lack of saturation among these neurons is consistent with observations from intracellular studies showing that fast-spiking cells have shorter refractory periods (Nowak et al., 2003). Further, narrow-spiking neurons showed significant reductions in spike count variance with attention at matched firing rates (dark red, attended; light red, unattended; asterisks indicate a significant reduction in variance within a given firing rate range, Mann-Whitney U test, $p < 0.05$). Since firing rates were matched, this attention-dependent difference in response variance cannot be attributed to differences in firing rate. As described in the Supplemental Results, we also tested whether reductions in Fano factor were significant when firing rate was equated within individual neurons. Consistent with the above analyses, attention-dependent reductions in Fano factor remained significant among narrow-spiking neurons and were significantly stronger for narrow- than broad-spiking neurons (see Figure S4). Thus, the difference between classes in attention-dependent reduction in Fano factor cannot be attributed to differences in firing rate.

Eye Position and Eye Movement Analysis

To determine whether differences in eye position contributed to the differences in the neuronal responses evoked by attended and unattended stimuli, we examined whether eye position varied depending on whether or not the monkey was cued to attend to the stimulus in the RF. On average, both monkeys exhibited a small but significant deviation in eye position (0.03° in Monkey A and 0.08° in Monkey B) away from the RF location when attending to the stimulus in the RF. This deviation in the eye position is very small relative to the size of RFs, all of which were at least 3° in diameter at half height. Small deviations in eye position are thus unlikely to have caused appreciable changes in response. To examine this directly, we analyzed the correlation between firing rate and eye position. Shifts in eye position caused a negligible change in rate. Two tenths of one percent of the cue-dependent increase in firing rate was attributable to shifts in eye position for Monkey A, and 0.51% of the cue-dependent increase in firing rate could be attributed to shifts in eye position in Monkey B (see Supplemental Results and Figure S5). Analysis of the drift of the eyes, during the pause period, as indicated by the eye velocity, likewise revealed that it was a negligible factor that could not account for the observed attention-dependent changes in response (see Supplemental Results and Figure S6).

It is also possible that fixational eye movements may have contributed to the observed reduction in Fano factor when attention was directed toward the RF location. Studies have shown that a substantial portion of response variability in primary visual cortex is due to fixational eye movements (Gur et al., 1997; Gur and Snodderly, 2006), and although RFs are much larger in extrastriate areas, small eye movements can modulate the responses in extrastriate areas such as MT and V4 (Leopold and Logothetis, 1998; Bair and O'Keefe, 1998). It is unlikely that fixational eye movements would vary across trials in our

task because the monkeys were required to attend to two of the four stimuli on every trial. However, to test this possibility directly, we analyzed fixational movements during the 1000 ms pause period to determine whether they differed when the stimulus in the RF was attended and if they influenced the neuronal response. The precision of our infrared eye tracking system was sufficient to reliably detect fixational movements in one of the two monkeys studied (see Supplemental Results; Figure S7). Analysis in this monkey confirmed that fixational movements do produce a small transient dip (median 11.7% reduction) in the firing rate 50–150 ms interval after movement onset, which is followed by a small peak (median 9.7% increase) 150–300 ms after movement onset (see Supplemental Results; Figure S7). However, there were no systematic differences in the number, amplitude, or direction of the fixational eye movements between attention conditions. Furthermore, when all intervals following within 400 ms of a fixational eye movement were excluded from analysis, there was no significant reduction in the overall firing variability across the population. The median unattended Fano factor after removal was 1.53 compared to 1.52 before removal (Wilcoxon signed rank test, $p = 0.98$). Moreover, the attention-dependent reductions in variability observed between narrow- and broad-spiking categories were not significantly altered by the removal of these intervals, and remained significantly different across the two classes. Thus the reduction in Fano factor reflects a genuine attention-dependent modulation of firing reliability, which is significantly stronger among narrow-spiking neurons.

DISCUSSION

The present results show that neurons in macaque area V4 fall into two classes as defined by their extracellular action potential widths, and that these classes differ from one another in their firing rates (both baseline and stimulus-evoked) and in two different measures of attention-dependent response modulation. Narrow-spiking neurons exhibited firing rates that were two-fold higher than those of broad-spiking neurons, both in response to a stimulus and during spontaneous firing when no stimulus was within the RF. We find direct evidence that attention modulates the reliability of neuronal responses. When attention was directed toward the stimulus in the RF, this resulted in a statistically significant reduction in response variability, as measured by the Fano factor. The reduction in Fano factor was much more pronounced for narrow-spiking neurons (median 18.9%) than for broad-spiking neurons (median 7.9%). Narrow-spiking neurons also showed a significantly larger attention-dependent increase in absolute firing rate (5.9 Hz median increase compared to 1.7 Hz). However, the percentage increase in firing rate with attention was not significantly different between the two classes (a 28.0% increase for narrow-spiking compared to 21.1% for broad-spiking).

Relationship between Action Potential Duration and Cell Type

The differences in responsiveness and attentional modulation that were observed across the two classes of neurons support the conclusion that they correspond to functionally distinct cell types. However, neurons can be divided into many subcategories on the basis of the binding proteins, neuropeptides, and ionic channels that they express; their neurotransmitters; morphology; patterns of connectivity; laminar distribution; and developmental origin. Given the diversity of cell types that have been identified in the cortex, it is likely that these two classes are composed of multiple subclasses of neurons.

Although many factors that distinguish among neuronal classes are invisible to extracellular electrodes, some reasonable inferences can be made about the likely identities of narrow- and broad-spiking cells. Neuronal recording studies in anesthetized animals and in the slice, where morphology and protein expression patterns can be used to distinguish among types, have measured action potential shapes for different neuronal types. These experiments have been performed in a wide range of species, including rat, cat, monkey, guinea pig, and human, and across multiple brain areas, including hippocampus, prefrontal cortex, visual cortex, and sensorimotor cortex (McCormick et al., 1985; Foehring et al., 1991; Tasker et al., 1996; Henze et al., 2000; Nowak et al., 2003; Gonzalez-Burgos et al., 2004; Povysheva et al., 2006). They have found that most pyramidal neurons, which make up 70%–80% of cortical neurons, have broad action potentials, as do another 10%–15% of neurons, which are interneurons (Connors and Gutnick, 1990; Cauli et al., 1997; Kawaguchi, 1995; Kawaguchi and Kubota, 1997). The remaining 10%–15% of the neuronal population are fast-spiking interneurons with the morphology of basket cells and chandelier cells. This class of GABAergic interneuron is unique in expressing the calcium-binding protein parvalbumin. Its narrow action potentials are due, in part, to high levels of expression of two classes of potassium channels (the Kv3.1 and Kv3.2 channels), which have very fast kinetics (Martina and Jonas, 1997).

Related experiments, which have combined intra- and extracellular recordings, have established that the narrow and broad action potentials observed in intracellular recordings can also be distinguished on the basis of extracellular recordings. This has been established in several species and cortical areas, including the hippocampus of the rat (Henze et al., 2000; Gold et al., 2006), the neocortex of the ferret (Hasenstaub et al., 2005), and the neocortex of the monkey (Gonzalez-Burgos et al., 2005). Many studies have found differences in the extracellular waveform duration and used it as a means of distinguishing neurons in several species, including monkey, rabbit, ferret, and rat, and in several brain areas, including hippocampus, prefrontal cortex, visual cortex, somatosensory cortex, and motor cortex (Mountcastle et al., 1969; Simons, 1978; Fox and Ranck, 1981; Buzsaki and Eidelberg, 1982; Wilson et al., 1994; Rao et al., 1999; Csicsvari et al.,

1999; Gur et al., 1999; Frank et al., 2001; Constantinidis and Goldman-Rakic, 2002; Bruno and Simons, 2002; Swadlow, 2003; Hasenstaub et al., 2005). Other studies have independently verified that neurons with narrow action potentials correspond to fast-spiking interneurons on the basis of morphology (Nowak et al., 2003; Gonzalez-Burgos et al., 2005) and cross-correlation analysis (Tamura et al., 2004; Bartho et al., 2004). Further, antidromic stimulation in the superior colliculus has been used to verify that pyramidal neurons in the frontal eye fields are broad spiking (S.Y. Shin and M.A. Sommer, 2006, Soc. Neurosci., abstract). In each of these cases, the two modes of action potential width were effective in distinguishing fast-spiking interneurons from pyramidal neurons.

A second line of evidence that supports our classification is that narrow-spiking neurons exhibit higher levels of spontaneous and stimulus-driven activity. This is consistent with the high firing rates that are typically observed among fast-spiking interneurons (Connors and Gutnick, 1990). The narrow-spiking neurons in our sample also showed a significantly higher waveform peak-to-trough ratio than did broad-spiking neurons. This is consistent with previous work showing a slower repolarization of the membrane potential of broad-spiking neurons (Hasenstaub et al., 2005).

Thus, we conclude that the majority of the broad-spiking neurons in our sample are pyramidal neurons, possibly intermixed with a small number of broad-spiking interneurons, and that our sample of narrow-spiking action potentials largely corresponds to fast-spiking inhibitory interneurons with the morphology of basket cells and chandelier cells. It is important to note that a second class of fast-spiking neurons has been observed in layers 2/3 of the ferret and cat cortex, though these neurons have not been reported in the primate (Brumberg et al., 2000; Nowak et al., 2003). These neurons are a pyramidal class called chattering cells and can be distinguished from the fast-spiking interneurons based on their spiking statistics. Unlike the fast-spiking neurons, they tend to fire action potentials in rapid bursts. In our sample of 43 narrow-spiking neurons, we find eight that showed strong indications of burst firing (see Supplemental Results and Figure S8). This small subset had lower firing rates that were more compatible with that of broad-spiking neurons (mean 4.5 Hz spontaneous rate and 10.6 Hz stimulus-evoked rate). Further, they exhibited weak attention-dependent changes in firing rate (median increase, 2.9%) and weak reductions in Fano factor (median decrease, 8.9%), unlike the other neurons in our narrow-spiking population. Excluding them from analysis did not substantially alter our findings. They may constitute a separate category corresponding to chattering cells. However, because we observed only a small number of these neurons, we have not analyzed them separately here.

Although some studies find bimodal distributions of waveform duration as found in our sample (McCormick et al., 1985; Constantinidis and Goldman-Rakic, 2002; Bartho et al., 2004; Frank et al., 2001; Tamura et al., 2004), other studies find waveform duration to be insufficient to segregate neuronal types (i.e., Krimer et al., 2005; Swadlow, 2003; Gonzalez-Burgos et al., 2005). There are a number of possible reasons for this discrepancy, including the type of filtering used and the exact measure of waveform duration. At least one study reported a bimodal distribution for waveform duration when width was defined to be the difference in time between the trough to the peak (the measure we used in the current study), but this bimodality disappeared when the more common measure of duration, width at the half height of the action potential, was used (Frank et al., 2001). It is also worth noting that, for extracellular recordings, a bimodal distribution may not be observed if the distribution includes units that were not well isolated. Averaging together waveforms from narrow- and broad-spiking neurons will result in intermediate waveforms that fill the gap between the two modes of the distribution.

Relationship to Earlier Studies of Attention and Fano Factor

The current findings demonstrate that attention can enhance the quality of neuronal responses not only by increasing response strength, but also by reducing response variability. This finding, which held in both classes of neurons, was unexpected because a previous study of attention in area V4 found only a modest (less than 5%) decrease in Fano factor that was not statistically significant (McAdams and Maunsell, 1999b). When we combine all neurons into a single population for comparison with that study, we find a significant but relatively modest decrease in Fano factor (median decrease, 10.1%, Wilcoxon signed rank test, $p < 0.001$). There are a number of differences in experimental design that could account for the different findings. The tasks differed, with attentive tracking of targets in the current study and a match-to-sample task in the previous study. The stimuli also differed, with a fixed Gabor in the RF for 1000 ms in the current study, and a counterphase grating in the RF for 500 ms in the earlier study. In particular, the difference in stimulus duration may account for the differences in our results, as the reduction in Fano factor that we observed was larger late in the neuronal response period.

Implications for Models of Selective Attention

The observation that attention-dependent modulation is stronger among narrow-spiking neurons is surprising because these neurons do not project to other cortical areas. It is often assumed that attention-dependent increases in firing rate serve to boost the strength of signals transmitted from one cortical area to another. Pyramidal neurons, which carry these signals, might therefore have been expected to show the most pronounced and consistent changes in rate and Fano factor. Furthermore, because inhibitory interneurons suppress their local pyramidal targets, one might even have expected their firing rate to

be reduced with attention, releasing their pyramidal targets from inhibition.

Several models of spatial attention have been advanced that point to a class of local circuit interactions that would be expected to rely on attention-dependent modulation of inhibitory interneurons (Koch and Ullman, 1985; Desimone and Duncan, 1995; Reynolds et al., 1999; Itti and Koch, 2000). These models incorporate competitive interactions between local populations of neurons that respond to attended and unattended stimuli. Consistent with these models, several single-unit studies have found that attentional modulation of firing rate is often larger in the presence of competing stimuli than when a single stimulus appears alone within the RF (Moran and Desimone, 1985; Motter, 1993; Treue and Maunsell, 1996; Luck et al., 1997). However, these studies did not distinguish inhibitory from excitatory neurons, so they only provided indirect evidence for attentional modulation of inhibition. The present study provides direct evidence that attention modulates inhibitory interneurons.

These models offer a possible explanation for the surprising finding that attentional modulation was larger among inhibitory neurons. If inhibitory interneurons do serve to suppress neuronal responses evoked by distracter stimuli, the increase in activity among inhibitory neurons may cause a more pronounced modulation of pyramidal neuron responses under more naturalistic conditions, where task-irrelevant distracters surround targets. Alternatively, the observation that fast-spiking neurons are strongly modulated by attention raises the possibility that they may play a role in modulating response synchronization. This proposal would be consistent with evidence that attention modulates high-frequency synchronization in macaque area V4 (Fries et al., 2001) and with recent experiments showing that fast-spiking interneurons mediate high-frequency response synchronization in the frontal cortex of the ferret (Hasenstaub et al., 2005). It is now feasible to test these and related hypotheses about the different functions served by narrow- and broad-spiking neurons in the attentive primate.

EXPERIMENTAL PROCEDURES

Electrophysiology

Neurons were recorded in area V4 in two rhesus macaques. Experimental and surgical procedures have been described previously (Reynolds et al., 1999). All procedures were approved by the Institutional Animal Care and Use Committee and conformed to NIH guidelines. A recording chamber was placed over the prelunate gyrus, on the basis of preoperative MRI imaging. 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 three times each week (Spinks et al., 2003).

In each recording 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). Neuronal signals were recorded extracellularly, filtered, and stored using the Multichannel Acquisition Processor system (Plexon, Inc). The raw field potential was filtered from 400 Hz to 8.8 kHz. To isolate spikes a threshold was set manually based on the amplitude of the noise. The timestamp and waveform of each threshold-crossing event were saved. We set the threshold low enough to ensure some fraction of noise events were saved so we could later distinguish to what extent isolated units were separated from the noise distribution. Waveforms were sampled at 40 kHz (25 μs/sample), and an 800 μs trace of each waveform was stored that extended from 200 μs before to 600 μs after the crossing of a negative threshold. For each neuron, all recorded action potentials were aligned by their troughs and averaged. We used the trough to align waveforms because it was generally the sharpest feature of the waveform and was thus less sensitive to low-amplitude noise than the peak of the waveform. The average waveform then was interpolated by a spline to give a precision of 2.5 μs.

The action potentials of pyramidal neurons differ from fast-spiking interneurons in their slower membrane repolarization after the initial rising and falling phase (McCormick et al., 1985; Nowak et al., 2003; Hasenstaub et al., 2005). This is reflected in the extracellular waveform by a longer and shallower peak following the initial trough (Henze et al., 2000). Earlier extracellular recording studies have taken advantage of this to separate classes according to waveform duration. Several different metrics of waveform duration have been used, including the timing of the peak (Wilson et al., 1994; Frank et al., 2001; Gonzalez-Burgos et al., 2004; Bartho et al., 2004), the return to baseline after the peak (Rao et al., 1999; Gonzalez-Burgos et al., 2004), and the difference in time between the initial trough and the trough after the peak (Constantinidis and Goldman-Rakic, 2002). We defined waveform duration to be the time from the trough to the peak of the average waveform. We selected this metric on the basis of studies showing that this measure best distinguishes pyramidal neurons from fast-spiking interneurons. One study reported that the width of the trough also distinguishes classes (Bruno and Simons, 2002), but two other studies found it less reliable than other measures using the peak (Frank et al., 2001; Bartho et al., 2004). Bartho and colleagues (2004) examined several different extracellular waveform features (peak-trough duration, trough width, spike asymmetry, and the amplitude ratio of positive and negative peaks) and determined how well each of these distinguished between cells that were determined to be excitatory and inhibitory using cross-correlation analysis. They concluded that the peak-to-trough measure provided the most reliable separation of the two classes. This measure is also suitable when waveform traces are stored in short windows that may not capture the full decay after the peak, as was the case in our recordings (800 μs windows).

Single units were isolated in the Plexon Offline Sorter based on waveform shape and were included only if they formed an identifiable cluster, separate from noise and other units, when projected into the principal components of waveforms recorded on that electrode. To further ensure that no multiunit recordings were included, we estimated the interspike interval distribution of each neuron and fit a Gaussian recovery function (Berry and Meister, 1998) to confirm that each had a well-defined refractory period. The median refractory period was 2.2 ms, with a spread from the 5th to 95th percentile of 1.5 to 10.1 ms.

Stimulus Presentation and Eye Movement Monitoring

Stimuli were presented on a computer monitor (Sony Trinitron Multiscan, TC, 640 × 480 pixel resolution, 120 Hz) placed 57 cm from the eye. 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/).

RF Mapping

At the beginning of each recording session, neuronal RFs were mapped to determine a single stimulus that would elicit a visual response among the neurons recorded. Monkeys fixated a central point while

tracking one target moving among three distracters in the hemifield opposite to the RFs of the V4 neurons under study. During this task each neuron's RF was mapped using subspace reverse correlation in which Gabor stimuli appeared at 60 Hz. Each stimulus appeared at a random location selected from an 8 × 10 grid with 3° spacing. The color and orientation of each stimulus were randomly selected (one of eight orientations, one of six colors, at 80% luminance contrast, spatial frequency 1.2 cpd, Gabor Gaussian half-width 2°). This resulted in an estimate of the spatial RF, orientation, and color preference of each neuron. Recordings were often made from multiple electrodes, and the preferences of units on separate channels did not always match. A color, orientation, and RF location were selected that would excite the best isolated units. The stimulus during the tracking task was identical to those used in mapping but was normally presented at 40% luminance contrast instead of the 80% contrast used during mapping, except in a few preliminary recording sessions, which contributed 21 of the total population of 218 neurons. We used high-contrast stimuli in our reverse correlation mapping because they evoke stronger responses, providing a better estimate of neuronal feature preferences. We used intermediate contrast stimuli in the main experiment to maximize the magnitude of attentional modulation. Attention-dependent modulation in firing rate has been found to be larger for intermediate contrasts than for saturating contrasts (Reynolds et al., 2000; see, however, Williford and Maunsell, 2006).

Task and Stimuli

After stimulus parameters were set on the basis of the RF mapping procedure, neuronal responses were recorded as the monkey performed an attention-demanding multiple-object tracking task adapted from a paradigm used in humans (Pylyshyn and Storm, 1988; Sears and Pylyshyn, 2000; Cavanagh and Alvarez, 2005). The monkey began each trial by fixating a central point for 200 ms and then maintained fixation through the trial. Four identical Gabor stimuli appeared at equally eccentric positions separated by 90°, as illustrated in the upper left panel of Figure 2A. The four stimuli were placed so that they fell outside each neuron's RF. Two stimuli were then briefly elevated in luminance, identifying them as targets. All stimuli then moved along independent trajectories at approximately 10°/s for 950 ms, placing them at a new set of equally spaced locations, one of which was within the RF. The stimuli paused for 1000 ms before moving to another set of locations and stopping. The fixation point then disappeared, and the monkey made a saccade to each target. Reward was delivered if the monkey identified both targets, in either order, without first foveating either nontarget. Despite the difficulty of the task, both monkeys performed it accurately, responding correctly on 82.3% (monkey A) and 70.9% (monkey B) of trials.

Analyses were performed only on correctly completed trials to ensure that the monkey was attending to the cued items. When unequal numbers of correct trials were completed between cueing conditions for a particular tracking movie, excess trials were excluded at random to equate the number of times a particular movie appeared in each cueing condition. This ensured that the particular paths taken by stimuli to enter and to leave the RF were identically balanced across cueing conditions, thereby equating sensory conditions (median 40 repeats per attention condition).

Stimulus Trajectories Used in the Main Experiment

Eight novel sets of stimulus trajectories were generated for each session. Across these sets, trajectories were balanced to ensure that, from each starting location, it was equally likely that the target would travel to any of the pause locations, and subsequently to any of the final locations. Within each set, the individual trajectories were constrained to ensure that only one item entered the RF during the trial, no collisions occurred between items, no items approached within 3° of fixation, and trajectories were smooth. Each set was identically repeated for all possible cueing permutations.

Inclusion Criteria and Data Analysis

All well-isolated neurons were included in the waveform analysis so as to provide the least biased sample of the underlying population (n = 218). Attention-dependent changes in firing rate and Fano factor were examined for the subset of neurons with significant visually evoked responses (n = 160). The visual response was considered significant if the mean firing rate in the last 500 ms of the pause period was significantly greater than the baseline firing rate (Mann-Whitney U test, $p < 0.05$). Baseline firing rate was computed from the 500 ms following the cueing period, when no stimulus was present in the RF.

The Fano factor was computed in nonoverlapping 100 ms bins. The spike count was computed in each bin for each trial. Then, for each bin, the Fano factor was computed as the ratio of variance in spike counts across trials to spike count mean. All attention-dependent changes in firing rate and Fano factor were analyzed in the interval corresponding to the 1000 ms pause period, as this was the period when the stimulus was stationary within the RF. The significance of rate modulation in individual units was assessed by a Mann-Whitney U test ($p < 0.05$) for a difference in median rate for attended compared to unattended trials. To assess the significance of Fano factor modulation in individual units, we computed the null distribution of its AI index by Monte-Carlo sampling, randomly shuffling attended and unattended trial identities, and computing the AI index 1000 times. If the actual index occurred in the tails of the null distribution ($p < 0.05$, two-sided), the neuron was considered to have exhibited significant modulation of Fano factor. Figures 2B and 2C, which depict the mean rate over the trial, were smoothed with a Gaussian kernel ($\sigma = 12.5$ ms).

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/55/1/131/DC1/.

ACKNOWLEDGMENTS

We thank C. Williams and J. Reyes for help with animals and technical support. This work was supported by a grant from the National Eye Institute (EY016161, J.F.M. and J.H.R.), a National Institutes of Health Training Fellowship (J.F.M.), and a National Science Foundation Graduate Research Fellowship (K.A.S.).

Received: April 6, 2007
Revised: June 4, 2007
Accepted: June 13, 2007
Published: July 5, 2007

REFERENCES

Bair, W., and O'Keefe, L.P. (1998). The influence of fixational eye movements on the response of neurons in area MT of the macaque. Vis. Neurosci. *15*, 779–786.

Bartho, P., Hirase, M., Monoconduit, L., Zugaro, M., Harris, K.D., and Buzsaki, G. (2004). Characterization of neocortical principle cells and interneurons by network interactions and extracellular features. J. Neurophysiol. *92*, 600–608.

Berry, M.J., II, and Meister, M. (1998). Refractoriness and neural precision. J. Neurosci. *18*, 2200–2211.

Brumberg, J.C., Nowak, L.G., and McCormick, D.A. (2000). Ionic mechanisms underlying repetitive high-frequency burst firing in supragranular cortical neurons. J. Neurosci. *20*, 4829–4843.

Bruno, R.M., and Simons, D.J. (2002). Feedforward mechanisms of excitatory and inhibitory cortical receptive fields. J. Neurosci. *22*, 10966–10975.

Buzsaki, G., and Eidelberg, E. (1982). Direct afferent excitation and long-term potentiation of hippocampal interneurons. J. Neurophysiol. *48*, 597–607.

Cavanagh, P., and Alvarez, G.A. (2005). Tracking multiple targets with multifocal attention. Trends Cogn. Sci. *9*, 349–354.

Cauli, B., Audinat, E., Lambolez, B., Angulo, M.C., Ropert, N., Tsuzuki, K., Hestrin, S., and Rossier, J. (1997). Molecular and physiological diversity of cortical nonpyramidal cells. J. Neurosci. *17*, 3894–3906.

Connors, B.W., and Gutnick, M.J. (1990). Intrinsic firing patterns of diverse neocortical neurons. Trends Neurosci. *13*, 99–104.

Constantinidis, C., and Goldman-Rakic, P.S. (2002). Correlated discharges among putative pyramidal neurons and interneurons in the primate prefrontal cortex. J. Neurophysiol. *88*, 3487–3497.

Contreras, D., and Palmer, L. (2003). Response to contrast of electrophysiologically defined cell classes in primary visual cortex. J. Neurosci. *23*, 6936–6945.

Csicsvari, J., Hirase, H., Czurko, A., Mamiya, A., and Buzsaki, G. (1999). Oscillatory coupling of hippocampal pyramidal cells and interneurons in the behaving rat. J. Neurosci. *19*, 274–287.

Desimone, R., and Duncan, J. (1995). Neural mechanisms of selective visual attention. Annu. Rev. Neurosci. *18*, 193–222.

Erisir, A., Lau, D., Rudy, B., and Leonard, C.S. (1999). Function of specific K(+) channels in sustained high-frequency firing of fast-spiking neocortical interneurons. J. Neurophysiol. *82*, 2476–2489.

Foehring, R.C., Lorenzon, N.M., Herron, P., and Wilson, C.J. (1991). Correlation of physiologically and morphologically identified neuronal types in human association cortex in vitro. J. Neurophysiol. *66*, 1825–1837.

Fox, S.E., and Ranck, J.B. (1981). Electrophysiological characteristics of hippocampal complex-spike cells and theta cells. Exp. Brain Res. *41*, 399–410.

Frank, L.M., Brown, E.N., and Wilson, M.A. (2001). A comparison of the firing properties of putative excitatory and inhibitory neurons from CA1 and the entorhinal cortex. J. Neurophysiol. *86*, 2029–2040.

Fries, P., Reynolds, J.H., Rorie, A.E., and Desimone, R. (2001). Attention modulates oscillatory neuronal synchronization in macaque area V4. Science *291*, 1560–1563.

Gold, C., Henze, D.A., Koch, C., and Buzsaki, G. (2006). On the origin of the extracellular action potential waveform: A modeling study. J. Neurophysiol. *95*, 3113–3128.

Gonzalez-Burgos, G., Krimer, L.S., Urban, N.N., Barrionuevo, G., and Lewis, D.A. (2004). Synaptic efficacy during repetitive activation of excitatory inputs in primate dorsolateral prefrontal cortex. Cereb. Cortex *14*, 530–542.

Gonzalez-Burgos, G., Krimer, L.S., Povysheva, N.V., Barrionuevo, G., and Lewis, D.A. (2005). Functional properties of fast spiking interneurons and their synaptic connections with pyramidal cells in primate dorsolateral prefrontal cortex. J. Neurophysiol. *93*, 942–953.

Gur, M., Beylin, A., and Snodderly, D.M. (1997). Response variability of neurons in primary visual cortex (V1) of alert monkeys. J. Neurosci. *17*, 2914–2920.

Gur, M., Beylin, A., and Snodderly, D.M. (1999). Physiological properties of macaque V1 neurons are correlated with extracellular spike amplitude, duration, and polarity. J. Neurophysiol. *82*, 1451–1464.

Gur, M., and Snodderly, D.M. (2006). High response reliability of neurons in primary visual cortex (V1) of alert, trained monkeys. Cereb. Cortex *16*, 888–895.

Hartigan, J.A., and Hartigan, P.M. (1985). The dip test of unimodality. Annals of Statistics. *13*, 70–84.

Hasenstaub, A., Shu, Y., Haider, B., Kraushaar, U., Duque, A., and McCormick, D. (2005). Inhibitory postsynaptic potentials carry synchronized frequency information in active cortical networks. Neuron *47*, 423–435.

Henze, D.A., Borhegyi, Z., Csicsvari, J., Mamiya, A., Harris, K.D., and Buzsaki, G. (2000). Intracellular features predicted by extracellular recordings in the hippocampus in vivo. J. Neurophysiol. *84*, 390–400.

Itti, L., and Koch, C. (2000). A saliency-based search mechanism for overt and covert shifts of visual attention. Vision Res. *40*, 1489–1506.

Kara, P., Reinagel, P., and Reid, R.C. (2000). Low response variability in simultaneously recorded retinal, thalamic, and cortical neurons. Neuron *27*, 635–646.

Kawaguchi, Y. (1993). Groupings of nonpyramidal and pyramidal cells with specific physiological and morphological characteristics in rat frontal cortex. J. Neurophysiol. *69*, 416–431.

Kawaguchi, Y. (1995). Physiological subgroups of nonpyramidal cells with specific morphological characteristics in layer II/III of rat frontal cortex. J. Neurosci. *15*, 2638–2655.

Kawaguchi, Y., and Kubota, Y. (1997). GABAergic cell subtypes and their synaptic connections in rat frontal cortex. Cereb. Cortex *7*, 476–486.

Koch, C., and Ullman, S. (1985). Shifts in selective visual attention: Towards the underlying neural circuitry. Hum. Neurobiol. *4*, 219–227.

Krimer, L.S., Zaitsev, A.V., Czanner, G., Kroner, S., Gonzalez-Burgos, G., Povysheva, N.V., Iyengar, S., Barrionuevo, G., and Lewis, D.A. (2005). Cluster analysis-based physiological classification and morphological properties of inhibitory neurons in layers 2–3 of monkey dorsolateral prefrontal cortex. J. Neurophysiol. *94*, 3009–3022.

Leopold, D.A., and Logothetis, N.K. (1998). Microsaccades differentially modulate neural activity in the striate and extrastriate visual cortex. Exp. Brain Res. *123*, 341–345.

Luck, S.J., Chelazzi, L., Hillyard, S.A., and Desimone, R. (1997). Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. J. Neurophysiol. *77*, 24–42.

Markram, H., Toledo-Rodriguez, M., Wang, Y., Gupta, A., Silberberg, G., and Wu, C. (2004). Interneurons of the neocortical inhibitory system. Nat. Rev. Neurosci. *5*, 793–807.

Martina, M., and Jonas, P. (1997). Functional differences in Na+ channel gating between fast-spiking interneurones and principal neurones of rat hippocampus. J. Physiol. *505*, 593–603.

Martina, M., Schultz, J.H., Ehmke, H., Monyer, H., and Jonas, P. (1998). Functional and molecular differences between voltage-gated K+ channels of fast-spiking interneurons and pyramidal neurons of rat hippocampus. J. Neurosci. *18*, 8111–8125.

McAdams, C.J., and Maunsell, J.H. (1999a). Effects of attention on orientation tuning functions of single neurons in macaque cortical area V4. J. Neurosci. *19*, 431–441.

McAdams, C.J., and Maunsell, J.H. (1999b). Effects of attention on the reliability of individual neurons in monkey visual cortex. Neuron *23*, 765–773.

McCormick, D.A., Connors, B.W., Lighthall, J.W., and Prince, D.A. (1985). Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex. J. Neurophysiol. *54*, 782–806.

Mechler, F., and Ringach, D.L. (2002). On the classification of simple and complex cells. Vision Res. *42*, 1017–1033.

Moran, J., and Desimone, R. (1985). Selective attention gates visual processing in the extrastriate cortex. Science *229*, 782–784.

Motter, B.C. (1993). Focal attention produces spatially selective processing in visual cortical areas V1, V2, and V4 in the presence of competing stimuli. J. Neurophysiol. *70*, 909–919.

Mountcastle, V.B., Talbot, W.H., Sakata, H., and Hyvarinen, J. (1969). Cortical neuronal mechanisms in flutter-vibration studied in unanesthetized monkeys. Neuronal periodicity and frequency discrimination. J. Neurophysiol. *32*, 452–484.

Nowak, L.G., Azouz, R., Sanchez-Vives, M.V., Gray, C.M., and McCormick, D.A. (2003). Electrophysiological classes of cat primary visual

cortical neurons in vivo as revealed by quantitative analyses. J. Neurophysiol. *89*, 1541–1566.

Povysheva, N.V., Gonzalez-Burgos, G., Zaitsev, A.V., Kroner, S., Barrionuevo, G., Lewis, D.A., and Krimer, L.S. (2006). Properiteis of excitatory synaptic responses in fast-spiking interneurons and pyramidal cells from monkey and rat prefrontal cortex. Cereb. Cortex *16*, 541–552.

Pylyshyn, Z.W., and Storm, R.W. (1988). Tracking multiple independent targets: Evidence for a parallel tracking mechanism. Spat. Vis. *3*, 179–197.

Rao, S.G., Williams, G.V., and Goldman-Rakic, P.S. (1999). Isodirectional tuning of adjacent interneurons and pyramidal cells during working memory: Evidence for microcolumnar organization in PFC. J. Neurophysiol. *81*, 1903–1916.

Reynolds, J.H., Chelazzi, L., and Desimone, R. (1999). Competitive mechanisms subserve attention in macaque areas V2 and V4. J. Neurosci. *19*, 1736–1753.

Reynolds, J.H., Pasternak, T., and Desimone, R. (2000). Attention increases sensitivity of V4 neurons. Neuron *26*, 703–714.

Reynolds, J.H., and Chelazzi, L. (2004). Attentional modulation of visual processing. Annu. Rev. Neurosci. *27*, 611–647.

Sears, C.R., and Pylyshyn, Z.W. (2000). Multiple object tracking and attention processing. Can. J. Exp. Psychol. *54*, 1–14.

Simons, D.J. (1978). Response properties of vibrissa units in rat SI somatosensory neocortex. J. Neurophysiol. *41*, 798–820.

Spinks, R.L., Baker, S.N., Jackson, A., Khaw, P.T., and Lemon, R.N. (2003). Problem of dural scarring in recording from awake, behaving monkeys: A solution using 5-fluorouracil. J. Neurophysiol. *90*, 1324–1332.

Swadlow, H.A. (2003). Fast-spike interneurons and cerebral feedforward inhibition in awake sensory neocortex. Cereb. Cortex *13*, 25–32.

Tamura, H., Kaneko, H., Kawasaki, K., and Fujita, I. (2004). Presumed inhibitory neurons in the macaque inferior temporal cortex: Visual response properties and functional interactions with adjacent neurons. J. Neurophysiol. *91*, 2782–2796.

Tasker, J.G., Hoffman, N.W., Kim, Y.I., Fisher, R.S., Peacock, W.J., and Dudek, F.E. (1996). Electrical properties of neocortical neurons in slices from children with intractable epilepsy. J. Neurophysiol. *75*, 931–939.

Treue, S. (2003). Visual attention: The where, what, how and why of saliency. Curr. Opin. Neurobiol. *13*, 428–432.

Treue, S., and Maunsell, J.H. (1996). Attentional modulation of visual motion processing in cortical areas MT and MST. Nature *382*, 539–541.

Williford, T., and Maunsell, J.H. (2006). Effects of spatial attention on contrast response functions in macaque area V4. J. Neurophysiol. *96*, 40–54.

Wilson, F.A., O'Scalaidhe, S.P., and Goldman-Rakic, P.S. (1994). Functional synergism between putative gamma-aminobutyrate-containing neurons and pyramidal neurons in prefrontal cortex. Proc. Natl. Acad. Sci. USA *91*, 4009–4013.

Wonders, C.P., and Anderson, S.A. (2006). The origin and specification of cortical interneurons. Nat. Rev. Neurosci. *7*, 687–696.