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Spatial Attention Decorrelates Intrinsic Activity Fluctuations in Macaque Area V4

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SUMMARY

Attention typically amplifies neuronal responses evoked by task-relevant stimuli while attenuating responses to task-irrelevant distracters. In this context, visual distracters constitute an external source of noise that is diminished to improve attended signal quality. Activity that is internal to the cortex itself, stimulus-independent ongoing correlated fluctuations in firing, might also act as task-irrelevant noise. To examine this, we recorded from area V4 of macaques performing an attention-demanding task. The firing of neurons to identically repeated stimuli was highly variable. Much of this variability originates from ongoing low-frequency (<5 Hz) fluctuations in rate correlated across the neuronal population. When attention is directed to a stimulus inside a neuron's receptive field, these correlated fluctuations in rate are reduced. This attention-dependent reduction of ongoing cortical activity improves the signal-to-noise ratio of pooled neural signals substantially more than attention-dependent increases in firing rate.

INTRODUCTION

Attention has long been known to improve our ability to detect and discriminate the features of sensory stimuli (James, 1890). One factor that contributes to this improvement in sensory processing is an attention-dependent increase in the mean firing rates of neurons driven by an attended stimulus and associated reductions in the firing rates of neurons driven by task-irrelevant stimuli (for recent reviews, see Reynolds and Chelazzi, 2004; Knudsen, 2007). In addition to mean firing rate, a key factor determining the fidelity of neural signals is response variability. Even under the most controlled stimulus conditions, identically repeated sensory stimuli evoke neural responses that vary from trial to trial (Softky and Koch, 1993; Shadlen and Newsome, 1998). Response variability affects how reliably information is encoded by neuronal signals (Parker and Newsome, 1998; Zohary et al., 1994; Shadlen et al., 1996; Averbeck et al., 2006; Pillow et al., 2008). An attention-dependent reduction in response variability could, therefore, significantly enhance sensory processing of behaviorally relevant stimuli. Consistent with this, the variability of individual neurons is strongly reduced when spatial attention is directed toward the stimulus within the neuron's receptive field (Mitchell et al., 2007).

The potential benefits of attention-dependent reductions in response variability depend critically on the degree to which the sources of variability are correlated across the population. Uncorrelated sources of response variability can, in principle, be mitigated by pooling signals across a neural population, with noise approaching zero when signals are pooled over a sufficiently large number of neurons. Thus, if the response variability that is diminished by attention (Mitchell et al., 2007) were independent across neurons, attention-dependent reductions of this variability might yield only a modest improvement in signal quality. This is not the case with variability that is shared across neurons. Such correlated variability cannot be abolished simply by pooling over a large neural population (Britten et al., 1992; Zohary et al., 1994).

Uncorrelated noise, unique to each neuron's response, can arise from variability in synaptic transmission that is amplified by the threshold nonlinearity in spike generation (Calvin and Stevens, 1967; Carandini, 2004). Correlated activity results from shared inputs (Moore et al., 1970; Lytton and Sejnowski, 1991; Morita et al., 2008). Shared variability is evidenced by correlations in firing between pairs of simultaneously recorded neurons. Previous studies have found significant correlations between neurons in visual cortex (Zohary et al., 1994; Shadlen and Newsome, 1998; Bair et al., 2001; Kohn and Smith, 2005). Correlations are not limited to local populations but persist even between neurons separated as much as 10 mm in cortex (Smith and Kohn, 2008; Nauhaus et al., 2009). Thus, fluctuations may be shared over very large neuronal populations including many thousands of cells. Because they are shared among many neurons, correlated fluctuations quickly would dominate as the source of noise in pooled measures of neuronal activity (Chen et al., 2006) and, depending on how information is read-out from populations, could impose severe limits on the accuracy of information represented (Zohary et al., 1994). It is thus important to determine whether attention decorrelates response variability that is shared across the population.

RESULTS

We recorded the responses of neurons in area V4, an intermediate stage of visual processing that has previously been found to be modulated by attention, in two macaques as they performed the attention-demanding tracking task depicted in Figure 1. Using this task, we could direct attention toward or away from a stimulus that we positioned within the neurons'

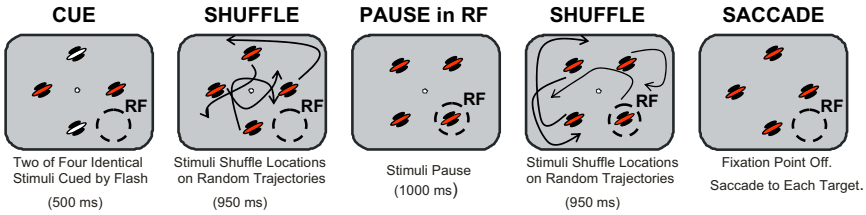

Figure 1. Attention Task

Each trial began with fixation of a central point. While fixation was maintained, one or two of four identical Gabor stimuli were cued with a brief luminance increase. All four stimuli then moved along independent randomized trajectories that brought one stimulus into the receptive field. 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.

receptive fields (Figure 1). We presented the same visual stimulus on all trials, providing a large number of identical stimulus repetitions from which to estimate variability in the neuronal response. On each trial, the stimulus paused and remained within the region of receptive field overlap for a period of 1000 ms, enabling us to estimate fluctuations in firing rate over a relatively long time period. Because the stimulus was constant during this period, the variability in firing reflects response fluctuations internal to cortex rather than stimulus-induced variability.

As previously reported (Mitchell et al., 2007), we find that the spiking response of individual neurons was highly variable to repeated stimuli and that attention reduces this variability. This is illustrated in Figure 2, which shows the responses of a single V4 neuron to 48 presentations of the identical stimulus. This neuron exhibited a robust response to the stimulus, which persisted through the pause period, until the stimulus left the receptive field. The raster plot at the top of the figure shows the neuron's response to this stimulus, on trials sorted according to whether attention was directed toward the stimulus in the receptive field ("Attended," top) or was instead directed away from the receptive field ("Ignored," middle). The left vertical yellow line indicates when the stimulus paused after entering the receptive field. The right yellow line shows the end of the 1000 ms pause period, when the stimulus initiated movement out of the receptive field.

We characterized neuronal response variability with reference to the variability expected of a Poisson process, in which each spike occurs with a fixed probability that is independent of the neuron's spiking history. For a homogenous Poisson process, the variance of the number of spikes within a fixed time interval is equal to the mean spike count in that interval. The Fano factor (F), the ratio of spike count variance to mean spike count, is therefore 1 for a Poisson process. We computed the Fano factor in each of the attention conditions, over 100 ms time windows. As shown in the lower panel, Fano factor tended to be >1 for unattended responses (shown in blue), indicating response variability greater than would be expected for a Poisson process. We focused our analysis on the last 800 ms of the sustained period, during which the firing rate was relatively stable and free of response transients due to the stimulus entering the receptive field. When attention was directed into the receptive field, the Fano factor was significantly reduced (permutation test, $p < 0.0001$). Across the 191 neurons, there was a significant median reduction of Fano factor of 8.8% (Wilcoxon sign rank test, $p < 0.0001$) with 42 units showing individually significant modulation ($p < 0.05$, permutation test), all of which were reductions (see population average in Figure 5A).

We examined whether this response variability reflected independent fluctuations in the responses of individual neurons or instead represents a source of correlated noise that is shared across the network. To assess this, we undertook two types of analyses. First, we computed the coherence between spikes from pairs of separate isolated units recorded simultaneously in the same session. The spike-to-spike coherence provides a frequency-resolved measure of the degree to which fluctuations in spiking in one unit are correlated with fluctuations in spiking of a second neuron. It is sensitive only to fluctuations in firing rate that occur within the duration of a single trial (<800 ms). The spike-to-spike coherence is shown in Figure 3A, for the same unit presented in Figure 2 paired with a simultaneously recorded neuron. The upper line, blue, shows the coherence (±1 SEM) when attention was directed away from the stimulus in the neuron's receptive field. The red line shows coherence with attention directed into the receptive field. In order to show the level of coherence that would be expected by chance, we randomly shuffled the trial-by-trial records of the second unit and computed coherence between the resulting random permutations of spiking responses (dashed lines). The attended and unattended coherence values both exceeded the level to be expected by chance across frequencies below 5 Hz, coinciding with the strong peak in the coherence. This indicates that attention reduced the degree to which low-frequency fluctuations in the neuron's spiking were correlated with fluctuations in the activity of the other neuron. We find that this attention-dependent reduction in low-frequency coherence was common across our recordings. We measured the percentage change in coherence at the peak below 5 Hz for each pair. Across 236 neuron pairs (69 recorded on a single electrode, 167 recorded on separate electrodes), there was a median percentage reduction of 22.6%, and overall values were significantly reduced (Wilcoxon signed rank test, $p < 0.0001$). Among the 18 pairs that showed individually significant changes in coherence over frequencies <5 Hz, all exhibited reductions.

A reduction in low-frequency correlated activity is also evident in the data shown in Figure 3B, which shows correlations in spike counts for the neuronal pair used to compute the coherence in 3A. Correlation coefficients were computed based on the spike counts of the two neurons across trials in simultaneous counting intervals. The upper line (blue) was derived from data recorded when attention was directed away from the receptive field, the lower line (red) from trials when attention was directed into the receptive field. Consistent with earlier studies, we find that response variability is correlated across neurons (Zohary et al.,

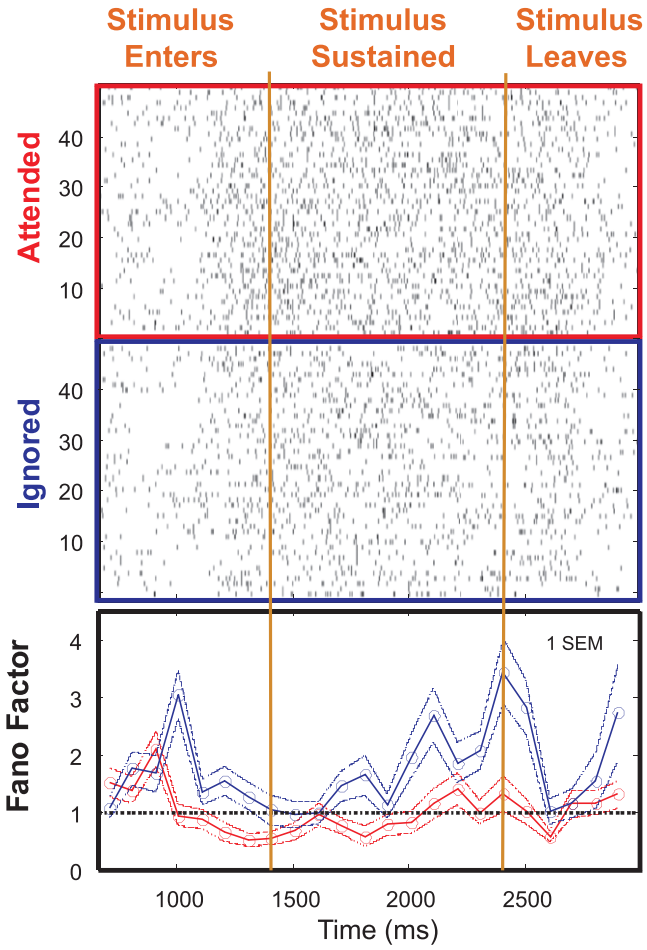

Figure 2. Example Neuron Showing an Attention-Dependent Reduction in Response Variability

Raster plots, in which tic marks indicate the times of spikes, are shown from 48 trials in which the stimulus placed inside the receptive field trials was attended (trials highlighted in red box) and 48 more trials in which the stimulus was ignored (trials highlighted in blue box). The leftmost yellow vertical line indicates the time in each trial when the stimulus paused in the receptive field, while the second yellow line marks the time at which it began to exit the receptive field. At the bottom, the Fano factor (variance spike counts across trials divided by the mean) is shown computed in 100 ms counting intervals spaced over the duration of the trial. The variability was significantly reduced when the stimulus was attended (red) compared to ignored (blue). Error bars ±1 SEM.

1994; Bair et al., 2001; Lampl et al., 1999; Kohn and Smith, 2005; Smith and Kohn, 2008; Jermakowicz et al., 2009; Huang and Lisberger, 2009), as indicated by values above zero (horizontal black line). To assess the time scale of correlations, we computed correlations using different sized counting windows (Bair et al., 2001; Smith and Kohn, 2008). Consistent with these studies, we find that the correlation coefficient grows larger with counting interval, indicating that correlations predominantly reflect low-frequency rate fluctuations. The correlations were reduced when attention was directed into the receptive field.

The average spike-to-spike coherence across all 236 neuron pairs (175 recorded from monkey M and 61 from monkey B) is shown in Figure 4A for attended (red) and unattended (blue) trials. Consistent with the individual neurons whose responses are shown in Figure 3, we find that the coherence in spiking is significantly reduced over frequencies below 20 Hz when attention is directed into the neuronal receptive field. Consistent with the pair of neurons shown in Figure 3, the strongest reductions were found below 5 Hz, for both monkeys (monkey M, 175 pairs: median reduction 26.5%, Wilcoxon sign rank test, $p < 0.0001$; monkey B, 61 pairs: median reduction 14.3%, Wilcoxon sign rank test, $p < 0.05$). Consistent with this low-frequency coherence, the average correlation in spiking between pairs increases with longer timescales, as seen in Figure 4B. We find that correlations in spiking averaged between counting windows from 30 to 300 ms are significantly reduced with attention directed into the receptive field in one monkey and marginally reduced in a second animal that had fewer pairs (monkey M, 175 pairs: median reduction 39.3%, Wilcoxon sign rank test, $p < 0.0001$; monkey B, 61 pairs: median reduction 49.9%, Wilcoxon sign rank test, $p = 0.062$). The distribution of correlations for attended and ignored conditions is shown for a single counting window of 100 ms in Figure 4C for the two animals (monkey M in green, monkey B in black).

Whereas coherence is computed within trials, correlation is computed from spike counts across different trials. Therefore, correlation is potentially sensitive not only to fluctuations occurring within a trial but also to fluctuations on much longer timescales that span multiple trial epochs. However, across our population, we find that correlation saturates near 100 ms (Figure 4B), and further, there is little effect when we factor out changes in rate that occur over intervals longer than 800 ms (see Experimental Procedures). This is consistent with earlier studies that have reported correlations between pairs of neurons that saturate at counting windows around 30–300 ms (Bair et al., 2001; Smith and Kohn, 2008). We analyzed separately the 69 neuron pairs that were recorded on a single electrode and the 167 pairs that were recorded on separate electrodes. Both sets showed significant reductions in correlation and coherence with attention (see Figure S1).

Previous studies have suggested that correlations in firing severely limit the quality of information represented by neuronal populations (Zohary et al., 1994; Shadlen and Newsome, 1998). We evaluated how these attention-dependent reductions in correlated firing might impact the signal-to-noise ratio (SNR) of pooled neuronal signals (Figure 4D). If neuronal fluctuations were uncorrelated, then their impact could be diminished to any desired extent by pooling over a sufficiently large population of neurons, resulting in an arbitrarily large SNR (black line). Correlations limit the benefit of pooling by imposing an upper asymptote on SNR as a function of the size of the neuronal pool. To quantify the potential limits imposed by the degree of correlations we observed in our unattended responses, we calculated SNR as a function of the number of neurons in the pool, assuming the mean level of correlation we observed in our unattended trials ($r = 0.068$ at a counting window of 100 ms). This leads to the level of saturation in the SNR shown in the blue line (see Zohary et al., 1994, Figure 3 for details). To measure the benefits of attention-dependent reductions in correlated firing, we repeated the calculation using the mean correlation we observed on attended trials ($r = 0.034$ at 100 ms windows).

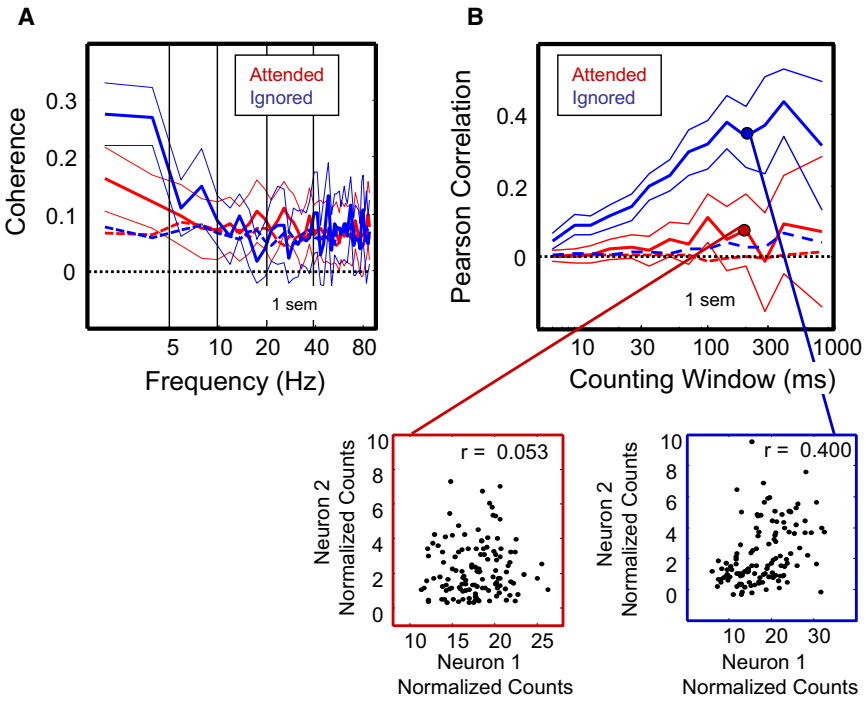

Figure 3. Single-Unit Examples Showing Attention-Dependent Reductions in Correlated Activity

(A) Spike-to-spike coherence between the unit depicted in Figure 2 (which showed individual reductions in variability) and another unit recorded simultaneously from a different electrode. This pair of units exhibited significant reductions in correlated firing at low frequencies (<5 Hz) for attended (red) compared to ignored (blue) trials. Dashed lines indicate the baseline coherence computed after shuffling trials.

(B) The Pearson correlation computed from the same pair of units using different sized counting windows. Correlations increased in magnitude with longer counting window, consistent with the coherent firing being at lower temporal frequencies. Correlations were significantly reduced for attended (red) compared to ignored (blue) trials. As expected, shuffling trials eliminated significant correlations (dashed lines). To compute correlations, spike counts were first normalized by subtracting out slow trends in firing rate for each unit using Gaussian smoothing on trial firing rates with a half-width of ten trials. Scatter plots of normalized spike counts used to compute the correlation are shown below for an attended and ignored case.

This resulted in a 39% improvement in the asymptotic SNR (red line).

We next compared this to the improvement attributable to attention-dependent increases in firing rate. In line with previous studies finding that attention increases responses (Reynolds and Chelazzi, 2004) we find that attention increased firing rate by an average of 20%. This increase in rate, with no corresponding change in correlations of firing, would cause only a 9.5% change in the SNR (orange line). Thus, given the simplest pooling strategy, the observed reductions in correlated firing would

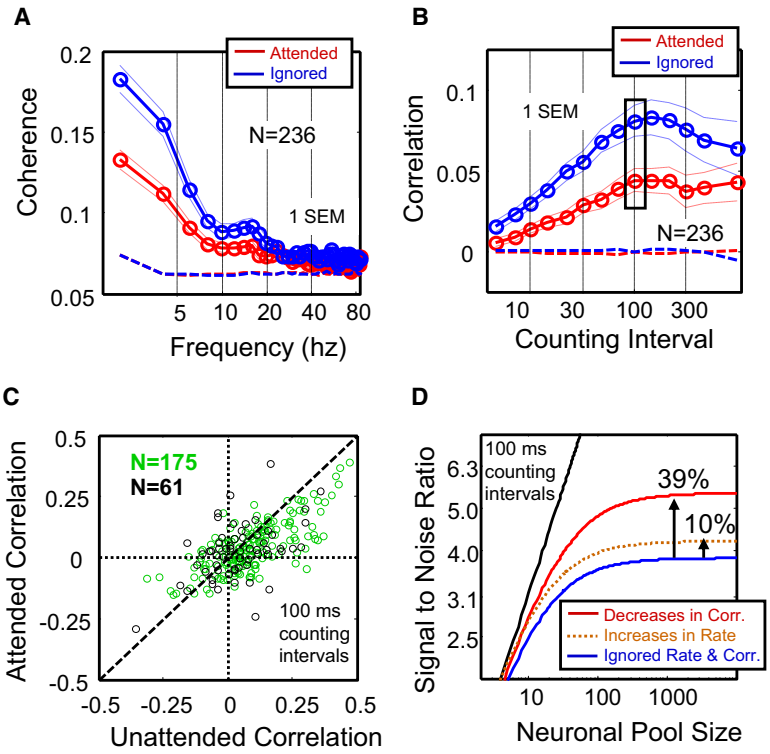

Figure 4. Timescales of Correlations in Noise across Population, for Attended and Unattended Stimuli

(A) The mean spike-to-spike coherence across 236 pairs for attended (red) and ignored (blue) stimulus trials. The coherence is strongest at low temporal frequencies (<5 Hz) and is significantly reduced by attention. Dashed lines indicate baseline coherence computed from shuffled trials.

(B) The Pearson correlation computed from the spike counts of 236 pairs as a function of counting window size. Correlations are strong on long timescales and are reduced for attended (red) compared to unattended (blue) stimuli.

(C) Scatter plot of attended and unattended correlations are shown split out by monkey subject (green and black) for the 100 ms counting window size (mean values highlighted by black box in panel B).

(D) Theoretical calculations for the signal-to-noise ratio as a function of neuronal pool size are shown (analysis methods identical to that of Zohary et al., 1994). For unattended trials (mean correlation of r = 0.068, rate = 10 Hz), the signal-to-noise ratio of 100 ms spike counts saturates at an SNR of 3.9 (blue line). A 20% increase in firing rate with attention would result in a 10% increase in the SNR (orange dashed line), whereas the observed reductions in correlation (r = 0.034) with no changes in rate results in a 39% increase.

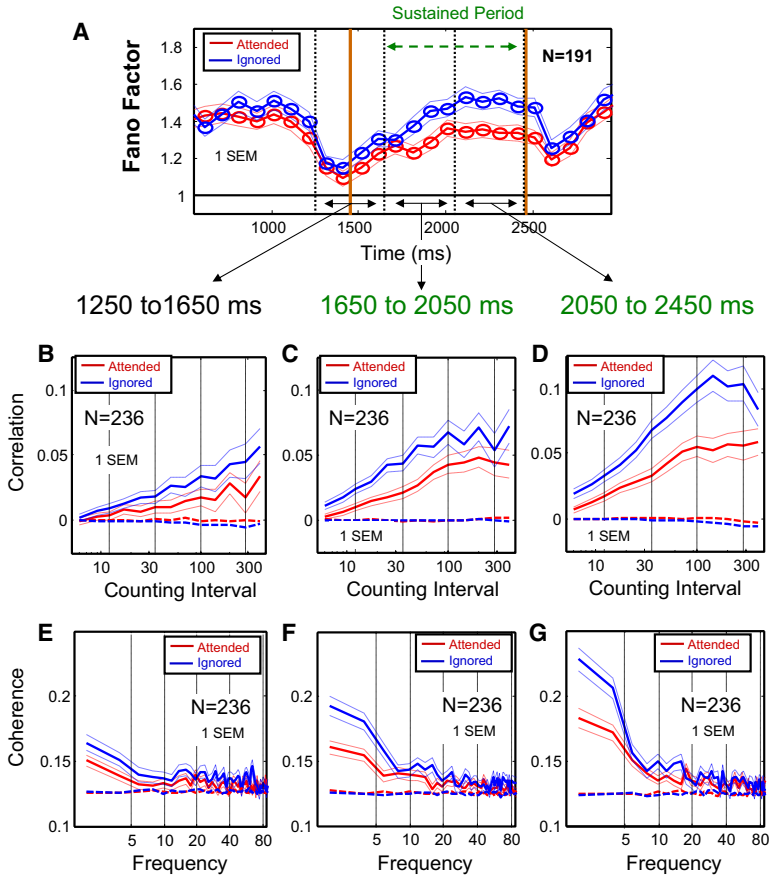

Figure 5. Time Course of Attentional Modulation

(A) Average Fano factors for attended (red line) and unattended (blue line) stimuli (±1 SEM indicated by dashed lines). Yellow vertical lines indicate beginning and end of pause period. The three 400 ms time periods over which we analyzed correlation and coherence are indicated by dashed vertical lines. The first period (1250–1650 ms after trial onset) began 200 ms before the stimulus paused, so it covered the transient response that occurred as the stimulus swept into the receptive field. The second (1650–2050 ms) and third (2050–2450 ms) windows covered the next two successive 400 ms periods, which together constitute the 800 ms sustained period that is the main focus of analyses in the manuscript.

(B–D) Correlations computed during each time window, for attended (red line) and unattended stimuli (blue line).

(E–G) Coherence computed during each time window, for attended (red line) and unattended stimuli (blue line).

improve signal quality by more than four times the improvement attributable to attention-dependent increases in firing rate.

Next, we quantified the time course of attention-dependent reductions in correlation and coherence. Figure 5 shows the results of this analysis. Figure 5A shows the Fano factor for attended stimuli (red line) and unattended stimuli (blue line), averaged over the population. The vertical yellow lines show the pause period. As reported earlier (Mitchell et al., 2007), attention significantly reduced individual neuron's response variability, as measured by the Fano factor during last 800 ms of the pause period. Panels (B)–(G) show correlations and coherence computed across successive 400 ms time windows centered on the early, middle, and late parts of the pause period. The first of these windows began 200 ms before the stimulus paused, so it covered the initial response that occurred as the stimulus swept into the receptive field. As noted earlier (Mitchell et al., 2007), the Fano factor in both attention conditions is reduced during this initial response period. This is consistent with a recent meta-analysis finding reductions in Fano factor in many brain areas during the transient response that follows stimulus onset (M. Churchland et al., 2009, Frontiers in Systems Neuroscience, conference abstract 92).

The second and third windows cover the next two successive 400 ms periods, which together constitute the 800 ms sustained period analyzed in Figures 3 and 4. These two windows each showed clear correlation that was significantly reduced by attention. Panels (B) and (E) show that correlations and coherence are reduced in this early period, as compared to the later sustained period (panels C and D, F and G). Even though the overall Fano factor, correlations, and coherence during the early period were reduced relative to the later sustained response that was the focus of our study, the correlation in the early period was still significantly reduced by attention. Thus, while it is stronger during the sustained response, the attention-dependent reduction in correlation holds throughout the stimulus-evoked response.

We next considered if small fixational eye movements present during task performance could contribute to the correlations in firing and corresponding attention-dependent reductions. Because eye movements displace the stimulus on the retina, they can act as an external source of stimulus-induced variability for visual neurons. Fixational eye movements have been shown to increase the variability of individual neuron's firing in primary visual cortex (Gur et al., 1997, 1999; Gur and Snodderly, 2006), and a previous study in visual area V4 also indicates that modulations in rate due to eye movements can be substantial (Leopold and Logothetis, 1998). Another study, however, found small eye movements could not account for the slow timescale correlations observed in extrastriate area MT in perceptual decision tasks (Bair and O'Keefe, 1998). Previously, we examined the data set reported here to determine if fixational eye movements contribute to the attention-dependent changes in individual neuronal response variability (Mitchell et al., 2007; Figure S7). We found that fixational eye movements produced a measurable modulation of firing rate, but that it was very small, giving less than a 5% modulation of rate during the 400 ms following movements. Removing the 400 ms periods following the detected eye movements from analysis had no appreciable effect on the Fano factor. We applied this same method to detect fixational eye movements in the current study and removed the 400 ms periods following eye movements in recalculating the spike-to-spike coherence and the spike count correlations between neuronal pairs. Similar to our previous report on the Fano factor, here we find that

fixational eye movements have no appreciable effect on either of our estimates of correlated activity (correlation or coherence) (see Figures S2A and S2B). We therefore conclude that the low-frequency variability we observed, and its reduction by attention, does not arise from fixational eye movements.

DISCUSSION

The present findings reveal that spatially selective attention acts to reduce task-irrelevant correlated noise. The source of noise originates from slow to intermediate timescale fluctuations in firing rate that are correlated across relatively large populations of neurons. The timescale and spatial spread of the correlations resembles that reported in earlier studies, where the variability in firing of single units was found to significantly influence behavioral variability (Zohary et al., 1994; Shadlen and Newsome, 1998; Bair et al., 2001). These earlier studies show that, depending on how information is decoded from populations, correlated noise can impose severe limits on the accuracy of information represented (Zohary et al., 1994). Similar theoretical analyses indicated that the attention-dependent reductions in correlated firing observed in the current study would produce much greater improvements in signal-to-noise ratio than the increases in firing rate associated with attention.

Relationship to Previous Studies of Response Variability

Slow correlated fluctuations in rate are common in cortical activity under a wide variety of stimulus and arousal conditions. Studies using voltage-sensitive dyes have imaged activity across large areas of cortex in anesthetized rats and cats. These studies find that in both spontaneous and stimulus evoked conditions there are stochastic waves of activity that propagate slowly across cortex (Arieli et al., 1996; Kenet et al., 2003; Han et al., 2008). This type of correlated firing produces correlations that are spatially and temporally extended. Recent studies using similar imaging techniques in awake macaques (Chen et al., 2006, 2008) and recording from large electrode arrays in the anesthetized macaques (Kohn and Smith, 2005; Smith and Kohn, 2008) find similar correlations in noise. The correlation values we observe are similar to those reported in earlier studies (Zohary et al., 1994; Shadlen and Newsome, 1998; Bair et al., 2001).

We have shown that for a simple model of response pooling the observed reductions in correlated firing would substantially improve the signal-to-noise ratio for attended signals. The exact degree of improvement will critically depend on the pooling strategy employed by cortex and could even favor using correlations to represent signals if they could be isolated from noise (Abbott and Dayan, 1999). For example, Chen and colleagues (2006, 2008) have shown that slow fluctuations in rate could be largely eliminated from subsequent stages of processing using a center-surround antagonism in space combined with temporal differencing in time, filtering parts of the signal that are more corrupted by noise (Chen et al., 2006, 2008). However, Chen and colleagues find that highly trained macaques do not achieve this theoretical performance, suggesting that the noise is either not fully eliminated or that there are as yet other unidentified sources of noise that corrupt perceptual decisions. Further studies will be critical in linking behavioral variability to sources of internal variability to determine the read-out strategy.

Recent research in primary visual cortex has analyzed the temporal and spatial structure of correlated firing. Smith and Kohn (2008) recorded simultaneously from an extended region of primary visual cortex using a Utah array. These arrays penetrate the superficial layers of cortex and therefore preferentially sample neuronal activity from layers II/III. They found that precise spike synchrony on the order of a few milliseconds is limited in spatial extent, suggesting that it results from common feedforward thalamocortical axons extending over short distances (<1 mm) within layer IV (Blasdel and Lund, 1983). In contrast, lower frequency rate fluctuations are correlated over at least 10 mm, possibly reflecting recurrent horizontal connections (which extend over distances of ~6 mm [Gilbert and Wiesel, 1983]) or feedback connections from extrastriate cortex which extend over >10 mm (Angelucci et al., 2002; Shmuel et al., 2005). Related experiments in cat and monkey V1 using the Utah array found additional evidence that low-frequency rate fluctuations result, at least in part, from activity propagated by long-range horizontal connections. Nauhaus et al. (2009) used spikes recorded on one electrode to compute spike-triggered local field potentials (LFPs) measured at different distances from the triggering spike. These became progressively delayed with distance, corresponding to a propagation of activity emanating from the spiking neuron at a velocity of ~0.3 m/s, which matches the propagation velocity of long-range horizontal connections in superficial layers (II-III) of cat primary visual cortex (Hirsch and Gilbert, 1991). The waves observed by Nauhaus et al. were most prominent among recording sites with neurons that shared orientation preference. Long-range layer II/III axons connect neurons with shared response preferences. This, coupled with the fact that the arrays record preferentially from superficial layers, suggests that the waves are conveyed by layer II/III neurons. During spontaneous activity, these waves of activity propagated over the entire extent of the 10 mm grid, consistent in spatial scale with the low-frequency rate fluctuations recorded by Smith and Kohn (2008). The spatial scale and magnitude of these waves were reduced when Nauhaus and colleagues presented a visual stimulus, and this reduction became more pronounced with elevation of stimulus contrast. Taken together, these findings suggest that a prominent source of low-frequency correlated response variability is the ongoing activity that is propagated within a cortical area by layer II/III long-range horizontal connections. Further, these fluctuations in activity are reduced in size and spatial extent by increases in stimulus drive.

Relationship to Previous Studies of Attention

Previous studies have reported that attention increases correlations among local populations of neurons (Fries et al., 2001; Gregoriou et al., 2009; for a recent review, see Womelsdorf and Fries, 2007). These studies have emphasized increases in gamma frequency synchronization, but they have also found reductions in low-frequency spike-field coherence (SFC). The present results suggest that this reduction in low-frequency SFC may reflect attention-dependent reductions in low-frequency correlated rate fluctuations.

Cohen and Newsome (2008) recently found another way in which noise correlations vary with attentional state. In their study, they recorded from pairs of MT neurons in monkeys performing a direction discrimination task. On some trials, one of the two motions to be distinguished was chosen to be preferred by both neurons and the other was nonpreferred. On other trials, the motion axis was rotated so that one of the two motions to be distinguished was preferred by one neuron and the other direction was preferred by the other neuron. Interneuronal correlations were significantly stronger when in the former condition, where the two neurons favored the same motion choice. They were able to reproduce their findings using a simple model in which feature-based attention sometimes alternated between the two directions being discriminated. According to this model, firing rates of both neurons were elevated when feature-based attention favored both neurons' preferred direction, and their rates were reduced when attention was directed to their nonpreferred direction, thereby increasing correlation. The present experiments are in no way incompatible with the findings of Cohen and Newsome. However, they suggest that a different mechanism is at work under our task and sensory conditions. First, the tasks were very different from one another. Cohen and Newsome held spatial attention constant while varying feature-based attention by requiring the animal to discriminate between motions that fell along one of two different motion axes. Our task did not vary feature-based attention. Monkeys simply attentively tracked target stimuli among distracters that were identical to targets except in spatial location, and the two conditions we compared differed only in whether spatial attention was directed into the receptive field or not. Second, the correlations observed by Cohen and Newsome depended on whether the features preferred by the two neurons under study fell along the axis of motion to be discriminated or across that axis. In our experiment, we used stimuli that were, to the extent possible, preferred by all neurons under study.

Possible Neural Mechanisms

We previously found that attention reduces individual neurons' variability (Mitchell et al., 2007). That finding could potentially have been explained using a model in which attention dampens response fluctuations that stem from processes internal to individual neurons. For example, many neurons exhibit burst spiking in which they fire doublets or triplets of action potentials. This represents a very fast type of rate fluctuation that is largely determined by the ionic channels involved in spike generation (Brumberg et al., 2000). The mechanisms governing burst generation can be altered by neuromodulators such as acetylcholine (Wang and McCormick, 1993) and would thus influence the variability of spiking of individual neurons. The present data show that the variation in firing rate that is reduced by attention is at least in part correlated across neurons, not simply dampened in individual neurons.

What neural mechanisms might account for this attention-dependent reduction in correlated response variability? One possible answer is suggested by models that have recently been developed to account for the spontaneous emergence of low-frequency correlated rate fluctuations (Yanagawa and Mogi, 2009; K. Rajan, L.F. Abbott, and H. Sompolinsky, personal communication). Of particular relevance, Rajan et al. (K. Rajan et al., personal communication) have shown that spontaneously generated fluctuations can be reduced by introduction of a stimulus input. In their model, the introduction of a stimulus results in a shift in the competition between stimulus-driven activity and the intrinsic response variability that emerges from the propagation of spontaneous activity within the cortical circuit. This is consistent with observations made in anesthetized animals (Lampl et al., 1999; Kohn and Smith, 2005; Smith and Kohn, 2008; Jermakowicz et al., 2009; Nauhaus et al., 2009). Several models of attention have proposed that attention either directly scales neuronal firing rates (McAdams and Maunsell, 1999) or scales the inputs to a normalization circuit (Reynolds et al., 1999; Reynolds and Chelazzi, 2004; Ghose and Maunsell, 2008; Reynolds and Heeger, 2009; Lee and Maunsell, 2009). These ideas can be combined to provide an explanation for the present observation that attention reduces correlated rate fluctuations. If attention increases stimulus drive, this could, like introducing a bottom-up stimulus, bias responses in favor of the stimulus drive, thereby suppressing intrinsic response variability. That is, attention-dependent reductions in response variability may be a simple consequence of attention-dependent increases in stimulus drive. In this view, when attention is directed to a stimulus, this diminishes the impact of spontaneously fluctuating network activity, reducing individual neurons' response variability and reducing low-frequency correlated rate fluctuations.

EXPERIMENTAL PROCEDURES

Stimulus Presentation and Electrophysiology

All procedures were approved by the Institutional Animal Care and Use Committee and conformed to NIH guidelines and have been described in more detail in a previous report (Mitchell et al., 2007). In brief, two to five tungsten electrodes (FHC, 1201 Main Street, Bowdoin, ME 04287) were advanced through the dura into macaque area V4 until the action potentials of a single neuron could be isolated based on distinct waveform shape. To begin each session, the receptive field was mapped using a subspace reverse correlation procedure that flashed colored oriented Gabor stimuli (one of eight orientations, one of six colors, at 80% luminance contrast, spatial frequency 1.2 cpd, Gabor Gaussian half-width 2°) at random spatial locations selected from a grid covering the display (3° spacing) at 60 Hz. Stimuli were presented on a computer monitor (Sony Trinitron Multiscan, TC, 640 × 480 pixel resolution, 120 Hz) placed 57 cm from the eye. Once the receptive field and preferred stimulus were determined, the neuron was recorded as a preferred stimulus (40% luminance contrast) was placed inside the receptive field during the performance of an attention-demanding task that is described shortly. When more than a single neuron could be isolated simultaneously, the stimulus was positioned within the region of receptive field overlap, and the orientation and color of the stimulus were selected to match the neuron with the most robust response. During mapping and the main task, eye position was continuously monitored with an infrared eye tracking system (240 Hz, ETL-400; ISCAN, Inc.). Stimulus presentation and reward delivery were handled by Cortex software (http://www.cortex.salk.edu/).

Behavioral Task

In each trial of the main task, either a tracked (attended) or distracter (unattended) stimulus was brought inside the receptive field and remained there for a sustained pause of 1000 ms. Two monkeys were trained to perform a multiple-object tracking task that has been used to study attention in human psychophysics (Pylyshyn and Storm, 1988; Sears and Pylyshyn, 2000; Cavanagh and Alvarez, 2005). Each trial began with the monkey fixating a central

point followed by the appearance of four identical Gabor stimuli, each of preferred color and orientation, and spaced equally on a ring of equal eccentricity. Then a subset of the stimuli (either one or two) was cued by a brief luminance flash and one of a set of eight different movie trajectories (generated random each day) repositioned the stimuli at a new set of equally eccentric locations. During this repositioning of stimuli, a single stimulus was brought inside the neuron's receptive field. The stimulus remained in the receptive field for a 1000 ms pause, and then all stimuli were repositioned again to another set of equally eccentric positions. The monkey maintained fixation on the central point throughout the trial and then at the end reported which stimuli were originally cued by making a saccade to their locations.

Stimulus trajectories were constrained to match sensory conditions between attended and unattended trials. No stimulus fell inside the neuron's receptive before the designated pause period. The set of trajectories were balanced so the starting and ending locations for any stimulus could not be predicted from its pause location. To ensure spatial symmetry in where attended stimuli were located during the pause, all subsets of stimuli were cued an equal number of times. Only correctly completed trials with two of four stimuli being tracked were included in analysis with each set of trajectories being included an equal number of times. This gives 40 trials on average per attention condition.

Inclusion Criteria and Data Analysis

The attention-dependent changes in neuronal spiking were examined only in those neurons that had a significant visually evoked response (N = 191). The visual response was considered significant if the mean visual response was greater than 5 Hz in the last 500 ms of the pause period and was significantly greater than the firing rate in the 500 ms directly after cueing when no stimulus was inside the receptive field (Mann-Whitney U test, $p < 0.05$). A minimum response of 5 Hz was needed in order to accurately characterize the variability in spiking. In the total population, 174 of 365 neurons were excluded due to low visually evoked responses. For paired responses of two neurons, we required that both neurons have significant evoked visual responses and that the square root of the product of their rates be at least 5 Hz. In the total population, 151 of 387 pairs were excluded due to low firing rates.

Trial-to-trial variability was estimated by the Fano factor, the ratio of the variance of the spike counts across trials divided by the mean of the spike counts. Analysis was restricted to the last 800 ms of the pause period when mean firing rate was relatively stable. We used a counting window of size 100 ms to compute spike counts in the Fano factor analysis. We computed the mean and variance for each 100 ms nonoverlapping window over the course of the trial. To assess the effect of attention we pooled the results to give a single value for the last 800 ms of the sustained period when firing rate was relatively stable. Statistical significance was assessed by permutation tests between the attended and unattended trials.

We examined the degree to which neuronal firing is correlated between pairs of units in two ways. First, we computed the coherence between two spiking signals using multitaper methods (Mitra and Pesaran, 1999; Jarvis and Mitra, 2001; Pesaran et al., 2002). The 800 ms sustained period was broken into several intervals of 400 ms, stepping 200 ms to cover the full period. The DC component of each spike train was removed, and tapered with a single Slepian taper, giving an effective smoothing of 2.5 Hz for the 400 ms data windows (NW = 1, K = 1). Confidence intervals were evaluated using the jack knife procedure by leaving out individual trials. To evaluate if time-locked trends in firing rate across the trial contributed to coherence estimates, we performed several random shuffles of the trial identities and recomputed the coherence. This provides a baseline for the coherence expected solely due to trends in firing time-locked to the trial. Coherence is computed from cross-correlations within trials, and then cross-correlations are pooled over trials and normalized by the power spectra of spike trains, also pooled over trials. Because the cross-correlations are computed within trials, coherence is only sensitive to fluctuations in firing rate captured within the relatively short interval of the trial (<800 ms).

We also examined the correlations in firing between pairs of units during the last 800 ms of the sustained period. Previous studies of correlated firing in cortex (Bair et al., 2001; Kohn and Smith, 2005; Smith and Kohn, 2008) have assessed the temporal scale of rate fluctuations by computing the correlation for several different counting windows. We computed the Pearson correlation for counting intervals that spanned the last 800 ms of the pause period (6, 9, 12, 17, 25, 35, 50, 71, 100, 141, 200, 283, 400, and 800 ms). When the correlation is computed in counting bins smaller than the sustained period of 800 ms, the total trial epoch is divided into bins (for example, there would be eight bins of 100 ms duration) and the mean in each bin for each neuron is subtracted out prior to computing correlations between different neurons. This eliminates any consistent changes in firing rate that are time locked to trial events, such as the response onset to the stimulus entering the receptive field.

Because the correlation is measured from spike counts across different trials, it is sensitive not only to fluctuations in rate that occur within trials, as is the case for the coherence measure, but also to trends in firing rate on much longer time scales that span trials. There are several reasons that firing rate might drift over long timescales in an experiment, including changes in alertness of the animal or even health of the tissue being recorded. If these trends were shared across neurons, they would contribute to the overall correlations measured. Previous studies have addressed these long time scale trends by subtracting out the mean firing rate smoothed over several trials prior to computing correlations on spike counts (Bair et al., 2001; Cohen and Newsome, 2008). Therefore, in our analysis of correlation we also subtracted out slow trends in firing rate for each unit. The mean firing rate during the pause period was averaged over adjacent trials using a Gaussian smoothing window with a width of $\sigma = 5$ trials. This smoothed firing rate was then subtracted from the spike counts of each trial to give normalized spike counts, which were used in computing correlation. Again, confidence intervals were evaluated using the jack knife procedure by leaving out individual trials.

We found that subtracting out the smoothed firing rate had very little effect on the overall correlations observed in the population. In Figure S3, the correlations are shown as square symbols when no smoothing is employed, superimposed over the correlations computed with smoothing (shown by lines). This indicates that fluctuations on very long timescales spanning trials did not contribute significantly to our results.

The magnitude of coherence estimates and estimates of correlation between spike counts critically depends on the number of spikes used to create the estimate (Zeitler et al., 2006; J. Curtis et al., 2009, Frontiers in Systems Neuroscience, conference abstract 138). See also Figures S4–S6. To control for differences in firing rate, we threw out randomly chosen sets of spikes from the attention condition with the higher firing rate for each individual unit in order to equate the total number of spikes in each condition. This procedure was repeated 20 times, each time throwing out a different random sample to equate the firing rates, and the results from the random samples were averaged both for coherence and correlation analyses. This reduces bias introduced by the rate-dependence in the correlation and coherence measures; however, our results remained qualitatively similar without any rate matching.

SUPPLEMENTAL DATA

Supplemental Data include supplemental analyses, associated discussion, and six figures and can be found with this article online at http://www.cell.com/neuron/supplemental/S0896-6273(09)00695-3.

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