

Temporal dynamics of neuronal modulation during exogenous and endogenous shifts of visual attention in macaque area MT

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Dynamically shifting attention between behaviorally relevant stimuli in the environment is a key condition for successful adaptive behavior. Here, we investigated how exogenous (reflexive) and endogenous (voluntary) shifts of visual spatial attention interact to modulate activity of single neurons in extrastriate area MT. We used a double-cueing paradigm, in which the first cue instructed two macaque monkeys to covertly attend to one of three moving random dot patterns until a second cue, whose unpredictable onset exogenously captured attention, either signaled to shift or maintain the current focus of attention. The neuronal activity revealed correlates of both exogenous and endogenous attention, which could be well distinguished by their characteristic temporal dynamics. The earliest effect was a transient interruption of the focus of endogenous attention by the onset of the second cue. The neuronal signature of this exogenous capture of attention was a short-latency decrease of responses to the stimulus attended so far. About 70 ms later, the influence of exogenous attention leveled off, which was reflected in two concurrent processes: responses to the newly cued stimulus continuously increased because of allocation of endogenous attention, while, surprisingly, there was also a gradual rebound of attentional enhancement of the previously relevant stimulus. Only after an additional 110 ms did endogenous disengagement of attention from this previously relevant stimulus become evident. These patterns of attentional modulation can be most parsimoniously explained by assuming two distinct attentional mechanisms drawing on the same capacity-limited system, with exogenous attention having a much faster time course than endogenous attention.

attentional time course | extrastriate cortex | middle temporal area | visual motion

Visual attention selectively modulates the sensory processing of information according to behavioral relevance (1–4). For instance, directing attention to a stimulus placed inside the receptive field (RF) of a visual neuron enhances the firing rate compared with when attention is focused somewhere else (5, 6). With only a few exceptions (7–9), most single-unit recordings in awake-behaving primates have investigated the effects of sustained attention on sensory responses, using paradigms in which the focus of attention constantly remained on a stimulus or a stream of stimuli for up to several seconds (6, 10–12). Although the ability to attend to a stimulus for a prolonged period is of great importance, many real-life situations crucially require flexible shifts of the focus of attention to direct the limited processing capacities to the currently most relevant information.

Behavioral experiments have documented two different modes of attentional orienting. Exogenous, or reflexive, shifting of attention is driven by salient stimuli and occurs largely involuntarily (13), whereas endogenous attention is goal-directed and under voluntary control (14). Although both modes of attentional orienting enhance behavioral performance and

neuronal responses, behavioral, neurophysiological, neuroimaging, and neuropsychological experiments have revealed important dissociations between them. According to behavioral studies, the effects of exogenous and endogenous attentional orienting have different temporal dynamics (15). Moreover, endogenous and exogenous attention differentially influence EEG gamma band activity recorded from scalp electrodes (16). Finally, the two modes of orienting are governed by partially segregated control networks (17) and are differentially affected in neuropsychological disorders such as autism spectrum disorder (18) or Alzheimer's disease (19).

These differences between the two modes of attentional orienting support the notion that they are distinct mechanisms that both affect the processing of sensory information. Here, we directly test whether exogenous and endogenous orienting differ in their modulation of single-neuron activity in extra-striate visual cortex.

Results

Two macaque monkeys were trained to fixate and to release a lever as soon as the target, a coherently moving random dot pattern (RDP) presented at a cued peripheral location, briefly changed its direction of motion. They also had to ignore changes in the direction of motion in two other RDPs that were presented simultaneously at other locations (distractors). Target and distractor changes occurred randomly in time. One of the three RDPs was always placed inside the classical RF of the neuron under study, the other two were outside, and each RDP moved either in the preferred or antipreferred direction of the neuron. The experiment consisted of three conditions: In simple cueing trials (Fig. 1*A*), the trial started with the presentation of the cue placed on a virtual line connecting the fixation point to the upcoming target. In shift cueing trials (Fig. 1*B*), a second cue appeared randomly during the trial, making one of the other two stimuli a target and thereby signaling the monkey to shift the spatial focus of attention. From the moment of shift cue onset, the monkey was only rewarded for responding to changes in the newly cued stimulus and had to ignore changes in the other two stimuli, including the previous target stimulus. Finally, in stay cueing trials (Fig. 1*C*) the second cue was presented at the same position as the first cue, instructing the monkey to continue attending to the already attended stimulus.

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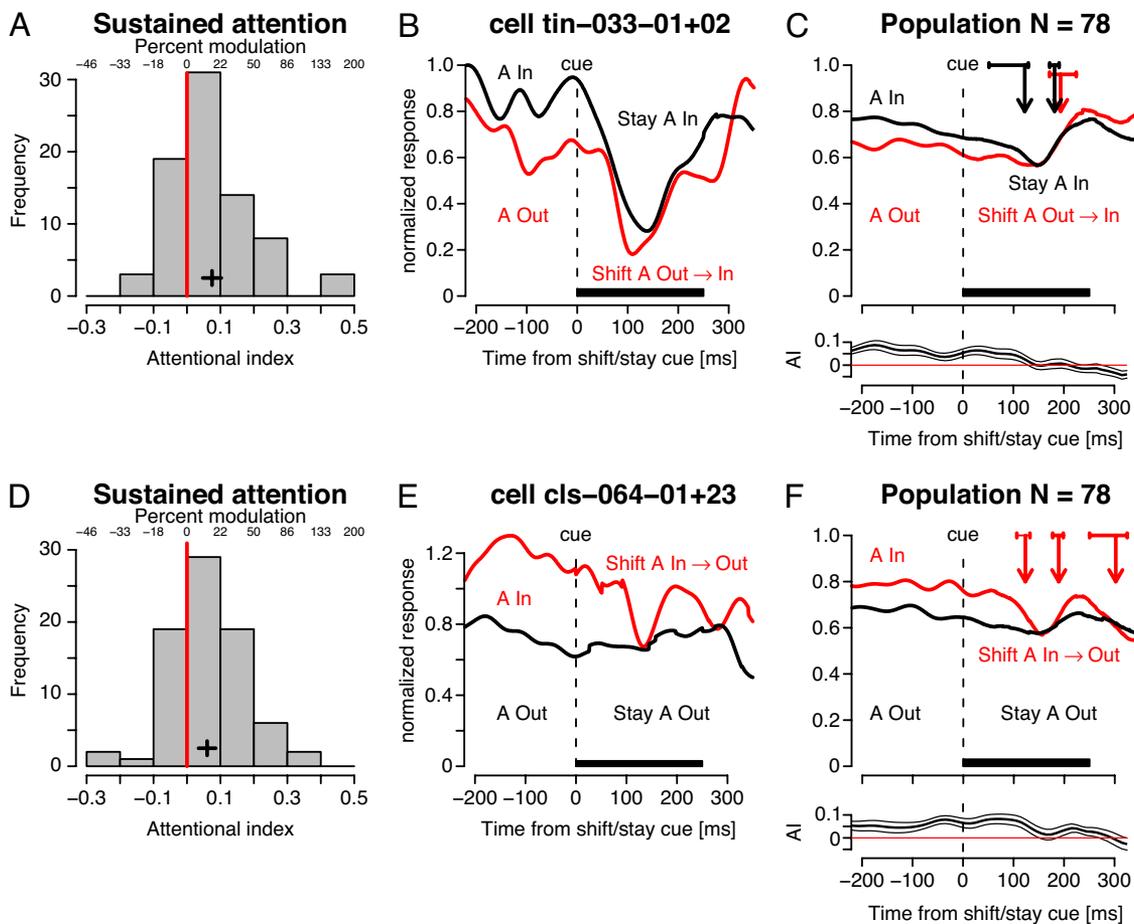


Fig. 3. Dynamics of attentional modulation, time-locked to the onset of the shift/stay cue (time 0). Before the onset of the shift or stay cue, neuronal activity is enhanced when attention is directed to the stimulus inside compared with outside the RF. (A and D) Distribution of spatial attention effects. The black crosses mark the average attentional modulation for each histogram, and horizontal arms span the 95% confidence interval of the means. (B and C) Single neuron data and population activity when attention is shifted from outside into the RF (red trace) or is cued to stay focused on the stimulus inside (black trace). (E and F) Illustration of conditions in which attention is shifted out of the RF (red trace) versus kept focused on the stimulus outside (black trace). The thick black horizontal bar marks the duration of the shift/stay cue; arrows indicate the average latency of the attentional modulation; adjacent horizontal lines cover the time interval corresponding to the 95% confidence interval for the mean. The time course of neuronal responses shows components of exogenous and endogenous attentional orienting. The initial, short-latency decrease of activity (≈ 120 ms; C, black trace; F, red trace) reflects the exogenous attraction of attention by the onset of the cue away from the RF because it even interrupts the endogenous focus of attention when the cue instructed the monkey to keep attending to the stimulus inside the RF. This effect of exogenous attention is only transient and levels off after ≈ 70 ms. Here, we observe both an increase of activity as attention is endogenously shifted into the RF (C, red trace, 190 ms) and a rebound of responses to the previously attended stimulus (F, red trace, 190 ms). Finally, endogenous disengagement of attention from the RF stimulus consists of a late decrease of responses (F, red trace, 300 ms). The time course of the attentional index (AI) is shown below C and F. See Fig. S3 for the same analyses performed on a selected sample of neurons.

average activity was higher when attention was directed to the stimulus inside versus outside the RF. We evaluated statistical significance of these effects by calculating, for each neuron separately, an attentional index (AI; see *Materials and Methods*) in a time window from 600 to 100 ms before cue onset. Fig. 3A and D shows the distribution of AIs for comparison 1 and comparison 2, respectively. Across the recorded population of 78 neurons, the distribution of AIs was centered on positive values in both comparisons. The average AI corresponded to a 15% increase in responses (Fig. 3A: 16.2%, t test, $P = 8.34 \times 10^{-7}$; Fig. 3D: 12.8%, t test, $P = 1.27 \times 10^{-5}$). These effects replicate previous studies of sustained spatial attention (6, 12). See supporting information (SI) Text and Figs. S1 and S2 for additional analyses.

Time Course of Attentional Modulation During Shifts of Attention. To analyze the dynamics of attentional modulation we computed the latency at which neuronal activity changed most strongly (see *Materials and Methods*). In Fig. 3, we depict the average latency

as an arrow with adjacent horizontal lines showing the time window that corresponds to the 95% confidence interval of the mean.

Fig. 3B (single neuron) and C (population) compares neuronal activity when attention shifts into the RF vs. is cued to stay focused inside. In Fig. 3C, after the onset of the shift cue (time 0, vertical dashed line), population activity in the Shift A Out \rightarrow In condition (red trace) increases with a latency of 193 ms (95% confidence interval: 170–222 ms) as attention is endogenously shifted into the RF. Across the recorded population, activity increased in 55 of 78 neurons at this latency, with the average slope of activity being significantly > 0 ($P = 5.6 \times 10^{-6}$, t test). In contrast, in the Stay A In condition (Fig. 3C, black trace), activity initially decreased with a latency of 122 ms after the onset of the stay cue (95% confidence interval: 51–129 ms). At this latency, a decrease of activity was evident in 54 of the 78 recorded neurons, and the average slope was significantly < 0 ($P = 0.002$, t test). This decrease of firing was followed by a response enhancement (maximal positive slope occurred at 181

(300–400 ms). These findings are in close agreement with our single-neuron results.

Recently, Khayat *et al.* (8) have provided a quantitative investigation of attentional modulations during endogenous shifts of attention using extracellular multiunit recordings in primary visual cortex (V1). Consistent with earlier findings in V4 by Motter (9), this study shows that enhancement of activity during allocation of attention precedes the decrease of activity caused by removal of attention. This temporal sequence of attentional modulations seems incompatible with a serial model postulating subsequent stages of disengagement, shifting, and engagement of attention (26), although the impact of this temporal asymmetry on overt behavior is still unclear. Our data on endogenous modulations are strikingly similar to the results reported by both studies, indicating that the same principle seems to hold for early and intermediate stages of visual processing in both ventral and dorsal pathways. A possible neuronal mechanism underlying this temporal asymmetry might be a shift of RFs toward the newly attended stimulus (27), with the leading edge of the RF shifting faster than the trailing edge. Such a distortion of RF shape has been reported in the context of predictive remapping during saccadic eye movements (28, 29). Here, RFs in LIP shift earlier toward the future saccade goal than away from the current fixation position (29), effectively increasing the RF size in the dimension toward the saccade target.

In conclusion, we show highly dynamic attentional modulations in extrastriate cortex that reflect changes in behavioral relevance on a very rapid time scale. Our data demonstrate the neural correlate of both exogenous and endogenous attentional orienting, which are controlled by two distinct, but interacting, mechanisms with a markedly different time course.

Materials and Methods

We recorded responses of 78 isolated direction-selective neurons in area MT of two macaque monkeys to moving RDPs in conditions of sustained attention and shifts of attention. Standard surgical techniques were used (30). Recordings were made by using a one-channel recording system (David Kopf Instruments) or a five-channel recording system (MiniMatrix; Thomas Recording); single units were isolated by using the Plexon Data Acquisition System. Cells were determined to be from MT by their physiological characteristics (directionality and RF position and size) and by the position of the electrode in the cortex. Only responses of neurons with a ratio of responses to preferred and antipreferred direction ≥ 3 were accepted for analyses. For a given neuron, we defined as the preferred direction the peak of a Gaussian fit to the responses to 12 different directions (sampled every 30°) in a condition when a single RDP was placed inside the RF while the animals detected a luminance change of the fixation point. The experiments in this study complied with the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by the Regierungspräsidentium Niedersachsen.

Stimuli. We used RDPs of small bright dots (density: 8 dots per degree², luminance 117 cd/m²) plotted within a stationary circular virtual aperture on a background of either 1 or 25 cd/m², in earlier and later recording sessions, respectively. The size of the aperture was chosen to match the boundaries of the classical RF of the neuron under study as determined by a hand-mapping procedure. Movement of the dots was created by an appropriate displacement of each dot at the monitor refresh rate of 76 Hz. In every trial, three RDPs of equal size were presented, one positioned inside the recorded cell's classical RF, the other two positioned at equal eccentricity outside of the cell's RF.

Behavioral Task. The monkeys were trained to attend to a moving RDP (the target) in the presence of two other moving RDPs (the distractors) while maintaining fixation on a stationary fixation point. A trial started as soon as the monkey's eye position was within a fixation window of 1° radius centered on a fixation square (size: 0.2 × 0.2°); 150 ms after the monkey touched a lever, a white square (0.35 × 0.35°), serving as the cue, appeared at an eccentricity of 1.5° on a virtual line connecting the upcoming target to the fixation point. The cue lasted for 250 ms. After a blank period of 500 ms three RDPs appeared at different, but iso-eccentric, positions on the screen. Three stimuli were used

to prevent the monkey from splitting attention and reduce the predictability of target assignments. These three RDPs coherently moved in either the preferred or antipreferred direction of the neuron under study for the remainder of the trial. All combinations of preferred or antipreferred directions in each stimulus were possible.

The experiment consisted of three conditions. In the simple cueing condition (33% of trials), the animals obtained a liquid reward for releasing the lever in response to a brief (130 ms) and subtle direction change in the target within a response time window of 60–700 ms after the change. The direction change occurred randomly between 13 and 3,700 ms after onset of coherent motion in the RDPs. The distractors could also change direction during the trial, but with a temporal separation of at least 500 ms. Trials in which both distractors, but not the target, changed their direction were rewarded after 4,250 ms, if the monkey did not release the lever. Trials in which the monkey broke fixation or responded outside of the reaction time window were considered errors and were aborted without reward. In the shift cueing condition (33% of trials), the cue appeared again (duration: 250 ms), randomly between 150 and 2,200 ms after onset of coherent motion, making one of the other two RDPs the target. The appearance of the second cue signaled the monkey to shift attention to the newly cued RDP and respond to direction changes in the new target. These direction changes could happen between 13 and 1,050 ms after the onset of the second cue. Again, in case of two distractor changes the monkey was rewarded to hold the lever until trial end. In the third condition, termed stay cueing (33% of trials), the timing of events was identical to the shift cueing trials with the exception that the second cue reappeared at the same position as the first cue, instructing the monkey to keep its attention focused on the target. The different conditions were randomly interleaved within the experiment.

Data Analysis. Data were analyzed offline by using Matlab (The MathWorks) and R. Average hit and false alarm rates were computed for each recording session in 10-ms bins (0–1,000 ms) after shift and stay cue onset, respectively, before being averaged across recording sessions. Average performance was fitted by using a local polynomial regression (loess) analysis, and bootstrap-estimated errors of the fit were obtained by resampling residuals.

For the analysis of neuronal data, only correctly completed trials were included. Response rates were determined by convolving the spike train in each trial with a Gaussian kernel ($\sigma = 30$). Only spikes that occurred before the first direction change (target or distractor event) after appearance of the second cue were considered. Responses were averaged across trials and normalized to the average response in the Stay A In condition (600–100 ms before cue onset), after subtraction of spontaneous firing rate. Population responses were computed by averaging across the normalized responses.

The effects of spatial attention were assessed in a time window of 600–1000 ms before onset of the second cue. For each recorded neuron, the AI was computed: $AI = (fr_{AIn} - fr_{AOut}) / (fr_{AIn} + fr_{AOut})$, where fr_{AIn} and fr_{AOut} are the mean responses if attention was directed to the stimulus inside and outside the RF, respectively. The AI is a conservative measure of the average attentional effect, which reduces the effect of outliers. Only trials in which the RDP inside and the attended RDP outside the RF moved in the preferred direction of the neuron were included in the analysis. The statistical significance of the AI was evaluated by using a one-sample *t* test.

To assess the time course of neuronal modulation we determined the slope of the average activity by fitting a linear regression line to each 50-ms interval, shifted by 1 ms (from cue onset to 350 ms after cue onset). We then determined the time points for which the slope was maximal and minimal, respectively. In case of the Shift A In → Out condition, in which two decreases of activity were evident, we first determined the point in time of maximal slope and then the minimal slopes before and after this temporal marker. We used a bootstrapping procedure to obtain confidence intervals for the latencies of modulation. A total of 1,000 bootstrap replications were simulated by randomly selecting individual neurons from the original recorded population with replacement. For each replication, the time points of maximal and minimal slopes were determined, using the procedure described above. The distribution of obtained latencies was used to construct 95% confidence intervals based on the BCa method (31). This slope-based method for latency estimates avoids the use of multiple statistical comparisons associated with a bin-based procedure in which the latency is often defined as the first of a number of bins that meet a significance criterion (32, 33). Furthermore, in comparison to procedures in which a theoretical function is fitted to the time course (8, 34), this procedure does not make assumptions about the shape of the time course of activity. Maximal and minimal slopes were compared against 0 by using *t* tests.

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Supporting Information

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SI Text

Effects of Sustained Attention Before Cue Onset. To demonstrate in more detail that the monkeys allocated spatial attention according to the task demands we performed additional analyses on the effects of sustained attention before shift or stay cue onset. First, instead of using an attentional index, we compared normalized firing rates for each neuron when attention was focused inside vs. outside the RF (time window 100–600 ms before cue onset; Fig. S1). In Fig. S1 filled circles depict neurons whose firing rates significantly differ across trials between the two conditions. In the Stay A In vs. Shift A Out \rightarrow In comparison (Fig. S1A) 28% of the cells (22 of 78) show an individually statistically significant difference between attentional conditions (2 are reduced, 20 enhanced by attention). In the Shift A In \rightarrow Out vs. Stay A Out condition (Fig. S1B) 17% of the cells (13 of 78) have an individually significant attentional modulation (all enhanced by attention). The number of neurons with individually significant differences expected by chance is 3.9. Comparing normalized firing rates across attentional conditions confirms that the population responds more strongly when attention is focused on the RF stimulus compared with elsewhere, because the majority of responses lie above the line of unity slope. This is also reflected in highly significant differences for both comparisons (Fig. S1A: $P = 2.38 \times 10^{-5}$; Fig. S1B: $P = 8.67 \times 10^{-6}$, Wilcoxon tests). This analysis confirms that attention to the stimulus inside vs. outside the RF enhanced neuronal responses.

To further document neuronal modulations by spatial attention, we used a signal-detection analysis to compute how well an ideal observer could predict the spatial focus of attention based on the firing rates of individual neurons. For each neuron separately, we computed the area under the ROC curve comparing the distribution of normalized average firing rates for trials with attention inside vs. outside the RF. If firing rates in these two conditions were indistinguishable, the area under the ROC curve would be 0.5. Across our sample of neurons, we found an average area of 0.587 for each of the two comparisons. This value is highly significantly different from 0.5 (Stay A In vs. Shift A Out \rightarrow In, $P = 5.32 \times 10^{-6}$; Shift A In \rightarrow Out vs. Stay A Out, $P = 2.13 \times 10^{-7}$).

To demonstrate that the attentional modulation of neuronal responses is related to behavioral performance, we compared the average modulation between correct and error trials. For each neuron, we computed the average attentional index in a time window of 300–800 ms after stimulus onset in the simple cueing condition, separately for correctly completed and error trials. We could only include 31 neurons in this analysis, because the number of error trials in the remaining recording sessions was too low. For correctly completed trials, the attentional index was 0.06, corresponding to a modulation of 13.2%. This value is similar to the effects of sustained spatial attention obtained before onset of the shift or stay cue (12.8% and 16.2%). Despite the small sample size, the index is significantly different from 0 ($P = 0.018$, t test). In contrast, for error trials, the average attentional index (0.027, corresponding to a modulation of only 5.6%) was not significantly different from 0 ($P = 0.32$, t test). These results indicate a correlation between neuronal modulation by attention and behavioral performance. However, one

should note that the number of error trials for most of the neurons is lower than the number of correctly completed trials, such that the computation of average firing rates for individual neurons tends to be more variable for the error trials.

Potential Sensory Influences of the Cue. It is important to point out that the dynamics of the response modulation cannot be attributed to sensory responses evoked by the cue. First, the cue was always presented within 1.5° from fixation, i.e., far from the classical RF of most recorded neurons. Second, there are no sensory differences in the attention conditions that were contrasted. In all comparisons, the stimulus in the RF always moves in the preferred direction of the neuron under study, an identical cue appears at the same position, and the stimulus outside the RF from which or to which attention is shifted is moving in the preferred direction. The only aspect that is different between conditions is the spatial focus of attention before cue onset, which determines the meaning of the cue. Thus, any potential sensory responses elicited by the cue should have equally affected activity in shift and stay conditions.

To analyze potential sensory activation caused by the onset of the cue, we used two conditions in which the animal directed attention to a luminance change of the fixation point. We compared activity in a condition with an irrelevant cue presented at the position pointing toward the RF against activity in the same time window when no cue was presented. For evaluation of potential responses to cue onset we used the time window 50–250 ms after cue onset, for evaluation of potential responses to cue offset we used the time window 50–250 ms after cue offset.

The recorded population does neither respond significantly to cue onset nor cue offset, as evaluated by a linear regression analysis [the intercept is not different from 0 for both cue onset ($P = 0.228$) and offset ($P = 0.67$)] (Fig. S2).

Furthermore, to ensure that the modulation we observed was not caused by the few neurons showing an individually significant response to the cue we reanalyzed the data presented in Fig. 3 with a selected data set. When removing all neurons with a significant on-response (15, of which 6 respond less after cue onset compared with a condition without cue) or off-response to the cue (10, of which 5 respond less after cue offset compared with a condition without cue) the responses of the population does not change qualitatively (Fig. S3; compare with Fig. 3). The modulation by sustained spatial attention before cue onset is 19.7% ($P = 3.79 \times 10^{-6}$) for the comparison Stay A In vs. Shift A Out \rightarrow In and 14.7% ($P = 1.53 \times 10^{-6}$) for the comparison Shift A In \rightarrow Out vs. Stay A Out. In the Shift A Out \rightarrow In condition, the average latency for the endogenous shifts of attention into the RF is 189 ms (full sample: 193 ms). In the Shift A In \rightarrow Out condition, the average latency for the exogenous pull of attention away from the RF is 126 ms, the average latency for the rebound effect is 192 ms, and the latency of the endogenous disengagement of attention is 262 ms (full sample: 123, 189, 302 ms). In the Stay A In condition, the average latency for the exogenous pull of attention away from the RF is 125 ms, the average latency for the reappearance of the endogenous effect is 180 ms (full sample: 122, 181 ms).

