Chapter 7: Dynamics of attention shifts in frontal eye fields and primary visual cortex as revealed by simultaneous recordings

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Summary

Models of attention are based on the notion that top-down signals from frontal cortex influence the processing of information in early visual areas (Desimone and Duncan, 1995). The manner, through which such a putative interaction occurs, however, is not clear. We recorded the neuronal activity in the frontal eye fields (area FEF) and the primary visual cortex (area V1) while monkeys were performing a curve tracing task, which requires shifts of attention. In order to monitor neuronal interactions under different attentional demands we manipulated the task difficulty. We characterized the effects of attention by measuring the strength and the latency of attentional modulation in these areas. An increase in task difficulty resulted in reduction of strength and increased latencies of the attentional modulation in each area. We found that attentional modulation in area FEF was stronger than in area V1. The latency of modulation was, however, not significantly different between these two areas, which suggests they jointly participate in the attentional selection process during curve tracing. We also measured the correlation between the strengths of responses of neurons within area V1 and between V1 and area FEF. This so-called rate-covariation was stronger between pairs of recording sites within area V1 than across the two areas. The interareal rate-covariation between area FEF and V1 was stronger if the same curve fell in neurons’ receptive fields compared to when different curves fell on the receptive fields. Moreover, the rate-covariation between neurons in different areas that coded the same curve was significantly affected by attention and task difficulty, being strongest when an easy stimulus that was attended stimulated the receptive fields. The pattern of rate-covariation points to an intricate communication network between FEF and V1 that is flexibly modulated by behavioural context.

Introduction

Even the simplest image, say the picture of a coffee mug, contains many details that are not always relevant for our behaviour. For example, at times we may be interested in details of the shape of the mug while at other times we may only wish to know whether it contains coffee or not. This example illustrates the important task that our visual system has to perform, namely selection of the most relevant items of an object based on our current behavioural goals. A minimal addition to this picture, say putting another coffee mug next to the first one, results in a substantial increase in the processing effort that our visual system faces. Again in this example, the behavioural context can help the visual system to select the
relevant item, for example by a simple check of which of the two mugs contains coffee irrespective of other differences in their appearance. The selection of one object for detailed processing over other objects is the function of selective attention (Desimone and Duncan, 1995; Luck and Ford, 1998; Posner and Driver, 1992; Theeuwes, 1993; Treisman, 1969; Desimone and Duncan, 1995). As is obvious in above examples, the behavioural context determines the object that needs to be selected by the visual system. In other words, the desire to perform a certain action should bias the processing towards a specific subset of image elements present in a scene. This notion, typically referred to as the top-down control of attentive selection, forms the tenet of biased competition theory of attention (Desimone and Duncan, 1995; Kastner and Ungerleider, 2001). Since top-down mechanisms are tightly linked to actions, it is expected that the underlying neuronal processes are found in cortical areas that are related to action planning. Frontal Eye Fields (FEF) is one such area that is directly linked to the control of eye movements (Schall, 1991; Marrocco, 1978; Schiller and Sandell, 1983; Schiller and Chou, 1998; Tehovnik et al., 2000). A closer look at the anatomy and physiology of FEF reveals that this area is also at the prime position to take part in top-down control of attention. Firstly, FEF is a site where the ventral and dorsal streams of visual processing (the so-called “what” and “where” system respectively) converge (Felleman and Van Essen, 1991; Schall, 1995). This means the FEF has access to the information about both the identity and the location of an object, features that are both important determinants of action selection. Secondly, in many instances allocation of attention is associated with eye-movement planning (a so-called overt shift of attention) and it is conceivable that the neuronal processing for covert attention shifts takes place in same areas of the cortex, as has been shown for FEF in a number of previous studies (Goldberg and Segraves, 1987; Schall and Bichot, 1998; Schall, 1995; Goldberg and Bruce, 1985). Thirdly, in addition to overt orienting of attention, there has been converging evidence that FEF is involved in covert allocation of attention, namely attending to a location in space without moving the eyes (Thompson et al., 2005b; Wardak et al., 2006; Murthy et al., 2001; Juan et al., 2004; Thompson et al., 1997). It is therefore now widely accepted that FEF rather than being solely involved in planning of eye movements is also actively engaged in visual processing and selection of visual stimuli (Thompson et al., 1996; Schall, 2002; Schall et al., 1995). In fact distinct neuronal populations have been identified within FEF that are predominantly active during visual processing, motor planning or both (visual, movement and visuo-movement cells, respectively (Schall et al., 1995; Bruce and Goldberg, 1985).
Although ample evidence exists that top-down signals including those originating from frontal eye fields guide the allocation of attention, the exact underlying processes are only partially understood. One possible scenario is proposed by the biased competition theory that suggested that top-down signals act to bias the processing of information in early visual areas in favour of the attended object (Desimone and Duncan, 1995). The most direct evidence supporting this view has been provided by an important recent study (Moore and Armstrong, 2003). Subthreshold microstimulation was applied to area FEF while the responses of V4 neurons were simultaneously recorded. Visual responses of area V4 were enhanced at the locations that retinotopically corresponded with the receptive field of the stimulated FEF neuron. Importantly, this enhancement only occurred if a visual stimulus was presented at the location of V4 receptive field and was maximal if this stimulus matched the neuron’s feature preference. Since the effects elicited by microstimulation of FEF were similar to the way that attention modulates the responses of area V4 (Reynolds et al., 1999) and other early visual areas (Treue and Maunsell, 1996; Motter, 1993; Luck et al., 1997; Roelfsema et al., 1998), the authors suggested that FEF is part of a network that guides the allocation of attention through controlling the gain of visually driven signals (also see Armstrong and Moore, 2007; Schafer and Moore, 2007; Armstrong et al., 2006; Moore and Fallah, 2004). Similar findings have recently been reported when microstimulation pulses were applied to FEF and activity of multiple early visual areas was monitored by using fMRI (Ekstrom et al., 2008).

Here we set out to study how under physiological conditions (without any stimulation pulse) the signals from a putative orienting network (with FEF as a member) interact with signals from early visual areas (for example V4 and V1). It should be noted that several possibilities exist for such an interaction. Firstly, it is possible that signals from fronto-parietal cortex select the relevant object and then feed a guiding signal back to the early visual areas (Serences and Yantis, 2007; Corbetta and Shulman, 2002). In this view, early visual areas are initially only involved in sensory processing while higher visual areas have a decisive selection role. Alternatively, it is possible that both early visual areas and fronto-parietal cortices jointly take part in selection of the object or location of interest. In this latter view early visual areas are not passive recipients of an orienting signal from frontal or parietal cortices but actively take part in selection process. We have recently provided evidence in support of the latter view (Khayat et al., 2009). We found that the timing of attentional modulation in FEF is similar to that in area V1, which suggests that they may jointly participate in attentional selection of a target. However, these recordings were not performed
under optimal conditions, since FEF and V1 recordings were done at different times and in different animals. Simultaneous recording of activity in FEF and early visual areas such as V1 provides the possibility to directly monitor the interaction between these areas. In the present study we undertook this approach by recording the activity of FEF and area V1 neurons at the same time and while the monkey was performing a curve tracing task. We manipulated the difficulty of the curve tracing task by varying the luminance contrast of a small segment at the start of the target curve. This manipulation allowed us to investigate the interaction between FEF and area V1 neurons under different task difficulties that could possibly influence the interplay between the neuronal populations of these two areas. Having these tools in hand we asked two major questions: firstly, do areas FEF and V1 also exhibit correlates of visual attention at the same time if the curve tracing task becomes more difficult? This is an important question since an easy task may engage these areas equally and simultaneously while making the task more difficult may push this balance towards one of these areas. Our second aim is to measure coupling between the firing rates (rate-covariation) between FEF and V1 neurons across trials (Shadlen et al., 1996) and to investigate the effect of task difficulty on the coupling.

**Methods**

All experimental procedures complied with the NIH Guide for Care and Use of Laboratory Animals, and were approved by the institutional animal care and use committee of the Royal Netherlands Academy of Arts and Sciences. One male macaque monkey participated in our experiments (monkey G). Three operations were performed under aseptic conditions and general anaesthesia. The anaesthesia was induced with ketamine (15 mg/kg i.m.), and maintained after intubation by ventilating with a mixture of 70% N2O and 30% O2, supplemented with 0.8% isoflurane, fentanyl (0.005 mg/kg i.v.), and midazolam (0.5 mg/kg·h i.v.). The animal recovered for at least 21 days before training was resumed and during recovery antibiotics and analgesics were administered as needed.

During the first operation a head-holder was implanted which allowed painless immobilization of the animal during the experimental recordings. The head-holder was securely attached to the monkey’s skull using titanium orthopaedic bone screws embedded in dental cement. During this first operation a gold ring was inserted under the conjunctiva of one eye to allow eye movement recordings. In a second operation, arrays of 4x5 or 5x5 electrodes (Cyberkinetics Neurotechnology Systems Inc.) were chronically implanted in area
V1 (in right hemisphere). Details of the surgical procedures and the postoperative care have been described elsewhere (Roelfsema et al., 1998; Roelfsema et al., 2007). During the third operation we implanted a recording chamber above frontal eye fields as described previously (Khayat et al., 2009). Area FEF was localized prior to the surgery by using a MRI scan. During the surgery we first made a trepanation over area FEF. A recording chamber (Cilux, Crist instruments) was placed above the right arcuate sulcus and was embedded in cement and supported by titanium bone screws.

**Behavioural task**

The monkey sat in a primate chair with the head restrained, at a distance of 0.75m from a screen. The stimuli were back-projected onto the screen (70° of visual angle; 1024 × 768 pixels resolution) by a video projector in combination with a TIGA graphics board running at a frame rate of 72 Hz. A trial started as soon as the monkey’s eye position was within a 1-1.5° square window centred on a 0.2° fixation point (FP). After 300 ms, the stimuli appeared (Figure 1A), but the monkey had to maintain steady fixation. The stimuli consisted of two white curves and two red circles at the end of each curve. One of the curves was connected to the FP and served as a target curve (T in Figure 1A), while the other, unconnected curve served as a distractor curve (D). We manipulated the task difficulty by varying the luminance contrast of the contour element that connected the target curve to the fixation point. The contrast of this segment could take three different values: a maximum level equal to the contrast of the rest of the curve (90% Michelson Contrast), an intermediate level lower than the maximum (16%) and a minimum lower than the other two (8%). These values were tailored to the performance of the animal so that the monkey almost always made correct choices in easy trials but made errors in a fraction of the more difficult trials. The stimuli were displayed for 500 ms after which time the FP was extinguished to cue the monkey to make a saccade to the circle located at the end of the target curve. Correct responses were rewarded by a drop of apple juice. If the monkeys broke fixation any time before FP offset the trial was terminated immediately. The monkey was trained for 2-3 weeks on this task before the electrophysiological recording sessions started.

**Physiological Recordings and the data analysis**

During the recording sessions the monkey’s eye position was monitored by a double magnetic induction technique (Bour et al., 1984) (sampling rate of 1 kHz). We simultaneously recorded extracellular activity of neurons in area V1 and FEF. In area V1, the extracellular responses were recorded from the chronically implanted multi-electrode arrays (Cyberkinetics
Neurotechnology Systems Inc.) with TDT (Tucker-Davis-Technologies) multi-channel recording equipment. The recording procedures are described in detail elsewhere (Super and Roelfsema, 2005). In brief, we obtained multiunit activity (MUA) of neurons after amplification, band-pass filtering, full-wave rectification and a final low-pass filtering of the signal that was recorded from microelectrode arrays with a sampling rate of 760 Hz. This MUA signal provides an instantaneous measure of the number and the size of action potentials of neurons in the vicinity of the electrode tip (Super and Roelfsema, 2005). As a first step after the post-operative recovery of the animal, we measured the dimensions of the receptive fields by determining the onset and offset of the visual response to a slowly moving light bar, for each of the eight movement directions (Super and Roelfsema, 2005). The receptive fields were located at the lower right visual quadrant. The median area of the receptive fields was 0.8 deg² (range 0.12 deg² to 3.9 deg²). Receptive field eccentricity ranged from 0.9° to 4.4° with an average of 2.5°.

The responses of single neurons in area FEF were recorded with standard techniques (Bruce and Goldberg, 1985). We recorded single neurons in FEF with tungsten electrodes (FHC, impedance ~2 MΩ). These electrodes were lowered through the dura with a hydraulic microdrive (Narashige). Spikes were detected if they crossed a threshold that was determined by the experimenter based on the amplitude of the single unit spike using a window discriminator (implemented in the TDT software). Upon isolation of a neuron, we first mapped its response field (RF) quantitatively by presenting a single saccade target at various directions and eccentricities. The details of this mapping procedure have been described elsewhere (Khayat et al., 2009). The RFs shown in figures 2 and 5 correspond to the estimated region of the visual field where the neuron’s response was within 75% of the maximal response. We used a memory-guided saccade task to classify the FEF neuron as a visual, visuomovement or movement cell (Bruce and Goldberg, 1985; Khayat et al., 2009). The curve tracing task was recorded while one of the saccade circles was positioned in the centre of the FEF neuron’s response field. The other circle, as well as the curve connected to it, was positioned outside the RF, at an angle of approximately 90°. One of the curves fell in the receptive fields of the V1 neurons. In some recording sessions it was possible to construct a single curve that fell in the receptive field of the FEF neuron and also in the receptive field of the V1 recording site (figure 3A, upper panel). Otherwise, we placed one of the curves into the FEF receptive field and the other curve into the V1 receptive fields (figure 3A, lower panel). At the end of the recording session, we usually confirmed that the electrode penetration was made in FEF with intracortical microstimulation (biphasic current pulses, 100
ms train duration, 200 Hz). The penetration was considered to be in FEF if a saccade could be triggered using currents that were <100 µA (generally <50 µA) (Bruce et al., 1985).

Computation of peristimulus time histograms (PSTHs)
We recorded the responses of 22 FEF single neurons (in monkey G). PSTHs of single cell responses were computed by counting the number of spikes in time bins of 200 ms length and averaging the spike counts across trials. The population responses were computed by averaging across PSTHs of individual FEF cells. We only included the visual and visuomovement cells in our analyses since they are more directly related to allocation of attention rather than motor planning (also see Khayat et al., 2009).

The multiunit responses were recorded from 48 V1 sites. The PSTHs at these MUA recording sites were normalized by subtracting the spontaneous activity (in a window from 300 ms to 0 before stimulus onset) and dividing by the maximum response (in a window from 50 to 150 ms after the stimulus onset). We only included recording sites in our analyses that were sufficiently responsive to the visual stimuli. To this aim, we computed the ratio between the evoked response (50-150 ms after stimulus onset) and the standard deviation of the spontaneous activity. We only included recording sites with a ratio larger than 1.5. With this criterion, 22 V1 sites in monkey G were included in our analyses. We used a Mann-Whitney U-test to determine whether the single-trial responses in a window 200-500 ms after stimulus onset differed significantly between the two attention conditions (target or distracter in RF).

Measurement of the magnitude of attentional response modulation
The strength of the attentional response modulation was measured by computing the modulation index (MI), similar to our previous study (Khayat et al., 2009). MI was defined as the difference in response strength normalized to the average response: \((R_T - R_D)/(R_T + R_D)/2\), where \(R_T\) and \(R_D\) are responses to the target and distractor curve, respectively.

Measurement of the latency of attentional response modulation
We estimated response latencies by fitting a function \(f(t)\) to the neuronal responses with the following form:

\[
\begin{align*}
  f(t) &= a(1 - \exp(-b(t - t_0))) & t \geq t_0 \\
  f(t) &= 0 & t < t_0
\end{align*}
\]

Here \(t_0\) defines the time when the function \(f(t)\) starts to rise from zero and can be used to measure the onset of the attentional modulation. To be able to compare our results with those
of Khayat et al. (2009) we also computed the \( \text{lat}_{33} \), i.e. the time when the function reaches 33% of its maximum value.

We computed a 95% confidence interval for the latency of the visual response and of the response modulation with a bootstrapping procedure (Press et al., 1986). If there are \( N \) recording sites, we randomly selected \( N \) sites with replacement, and determined the latency using the curve-fitting method described above. We repeated this procedure 10,000 times to estimate the 95% confidence interval.

**Measurement of the rate-covariation**

We measured the rate-covariation between MUA signals within area V1 and also the interareal rate-covariation between the V1 MUA and single units in area FEF (Figure 6). We measured the strength of the response in each trial by counting the number of spikes or measuring the amplitude of MUA in FEF and V1 in a spontaneous time window (from -300 ms to 0 relative to stimulus onset) and a time window during the neuronal responses (200-500 ms after stimulus onset). We excluded artefacts by removing trials with an activity level more than 6 times the standard deviations above the mean response (less than 1% of all the trials). Recordings in which more than 5 trials for each condition were available were included in our analyses. We measured the strength of coupling between the responses from different neurons with the Pearson correlation coefficients (\( \rho \)).

**Results**

**Behavioral Performance**

Figure 1A depicts the curve tracing task. A trial started as soon as the monkey fixated a small fixation point. After 300 ms, two curves and two circles at one of their ends appeared on the screen. One of the two curves (target curve, T) was connected to the fixation point and the other curve was a distracter (D). The monkey had to maintain fixation and mentally trace the target curve to locate the circle that was located at the end of this curve. The curves stayed on the screen for 500ms and then the fixation point disappeared cuing the monkey to make an eye movement. An eye movement towards the circle at the end of the target curve was counted as a correct response while a saccade to the circle connected to the end of the distracter curve was an error. We manipulated the difficulty of this task by varying the luminance contrast of the small initial segment of the target curve (Figure 1B). This segment could take one of three luminance contrasts: a high contrast equal to the rest of the curve (90%), an intermediate contrast of 16% or an even lower value of 8% Michelson contrast. As
expected, the performance of the monkeys decreased for lower values of the contrast because it became difficult to distinguish the target curve from the distractor (Figure 1C). The effect of task difficulty on psychophysical performance was statistically significant (ANOVA, $F(2,48) = 69, \ P < 10^{-10}$). We will therefore refer to these three conditions (with different contrast levels of the proximal curve segment) as “easy”, “intermediate” and “difficult”.

**Figure 1. Curve tracing task and behavioral performance**

A. Curve tracing task. The monkey first fixates on a small fixation point. After 300 ms, two curves appear on the screen. The curve that is connected to the fixation point is the target curve (T) and the other curve is distracter (D). After 500 ms the fixation point disappears and the monkey makes an eye movement to the circle that is connected to fixation point.

B. The difficulty of the task is manipulated by varying the luminance contrast of the short contour element that connects the target curve to the fixation point.

C. Behavioral performance of the monkey as a function of the luminance contrast of the proximal curve segment that connected the target curve to the fixation point. The accuracy of curve tracing was decreased if the segment had a lower contrast.

**The effect of task difficulty on the magnitude and latency of response modulation in FEF and area V1**

Figure 2 shows the response of an example FEF neuron (figure 2A) to the easy, intermediate and difficult stimulus configurations as well as responses of a V1 recording site that was recorded simultaneously (figure 2B). The appearance of the stimulus evoked a strong response in FEF as well as V1 neurons. In both areas, the initial responses did not discriminate between the target and the distracter curve. However, after a delay the responses evoked by the target curve became stronger than the responses evoked by the distracter curve, as has been described previously in area V1 (Roelfsema et al., 1998) and FEF (Khayat et al.,
Notably, the magnitude of this response modulation decreased as the task became more difficult. In order to quantify this effect we measured neuronal modulation indices (MI) in a time window from 200 to 500 ms after the stimulus onset (see Methods). In this example FEF cell, neuronal MI ranged from 1.3 to 0.87 and 0.3 in the easy, intermediate and difficult conditions, respectively. The response modulation of the V1 site was weaker than in area FEF and it showed a similar effect of task difficulty as the MI dropped from 0.35 in the easy configuration to 0.16 at the intermediate difficulty and to 0.14 in the difficult condition.

We next examined the latency of the response modulation. It can be seen that the response modulation started later when the task was more difficult. This effect was quantified by measuring the response latency using a curve fitting method similar to the methods used previously (Khayat et al., 2009; Roelfsema et al., 2007). We measured the start of the response modulation, $\text{Lat}_{\text{Start}}$, as well as the time when it reached 33\% of the maximum level, $\text{Lat}_{33}$. As shown in figure 2B, $\text{Lat}_{\text{Start}}$ of the FEF cell increased from 156ms in easy condition to 190ms and 280ms in intermediate and difficult conditions, respectively, and the $\text{Lat}_{33}$ showed a similar trend (increasing from 200ms to 220ms and then to 320ms). Likewise, the latency of the modulation of the response of the V1 site also increased with task difficulty (from 140ms, to 255ms and 305ms). The strength of the response modulation of this example V1 site reached a constant level soon after the initiation, and the $\text{Lat}_{33}$ values were close to the $\text{Lat}_{\text{Start}}$ values. A comparison between the latency of response modulation in FEF cell and V1 site suggests that in the easy condition response modulation starts almost at the same time in both areas, the modulation of FEF cell response in the intermediate and the difficult conditions may have preceded the response modulation of the V1 recording site. However, we cannot exclude that these latency differences were caused by the weaker and therefore noisier response modulation in area V1.
Figure 2. Example of a FEF single cell and a V1 multi-unit recording site

The upper panel shows the relative location of the FEF cell and V1 sites. The PSTHs depict neuronal responses of the FEF cell (A) and the V1 recording sites (B) to stimuli of three levels of difficulty. The red and blue traces correspond to the responses to the target and distracter curve respectively. The arrows intercepting the X-axis show either the time when the modulation initiated (magenta) or when it reached 33% of its maximum level (cyan). These latencies were computed based on fitting a function to the difference between responses to the target and the distracter curves. The grey area below each PSTH plot illustrates this response difference and the green curve depicts the fit of the function (see methods) to the data.
We next examined the population responses of the simultaneously recorded FEF and V1 neurons. Figure 3 shows the population responses of FEF cells and V1 sites. We confined our analysis to the visual and visuomovement cells in area FEF, including a total of 13 neurons. We recorded from a total of 22 V1 recording sites with a sufficiently strong visual response (see the Methods for inclusion criteria). Of these, 16 sites showed a significant response modulation in easy condition ($U$-test, $P < 0.05$) and the other 6 cells did not. Since we were interested in the dynamics of attentional modulation, we focussed our population analysis on the V1 recording sites with significant response modulation ($N = 16$).

**Figure 3. Population responses of FEF and V1**

Population responses of all the recorded FEF cells (A) and V1 sites (B). The red and blue traces correspond to the responses to the target and distracter curve respectively. The arrows intercepting the X-axis show either the time when the modulation initiated (magenta) or when it reached 33% of its maximum level (cyan). These latencies where computed based on fitting a function to the difference between responses to the target and the distracter curves. The grey area below each PSTH plot illustrates this response difference and the green curve.
The magnitude of response modulation decreased as the task became more difficult, both in FEF cells (average modulation index = 1.25, 1.1 and 0.66 in easy, intermediate and difficult conditions, respectively) and V1 sites (population modulation index = 0.34, 0.27 and 0.09). Overall the response modulation was stronger in FEF cells than V1 sites. We then examined the latency of population response modulation. In FEF cells the average \( \text{Lat}_{\text{Start}} \) was 106ms, 139ms and 196ms (with 95% confidence-intervals of 75-147ms, 83-174ms and 157-274ms) and it reached 33% of the maximum after 178ms, 230ms and 287ms (95% confidence interval of 140-200, 180-280, 260-320 ms). In area V1 the response modulation started at 125ms, 176ms and 254ms (95% confidence interval 84-147ms, 105-189ms and 95-430ms) and it reached 33% of the maximum at 132ms, 176ms and 255 ms (95% confidence interval of 101-147, 150-203, 184-315 ms) for the easy, intermediate and difficult conditions, respectively. Thus, the latency of modulation increased when the task became more difficult. Overall, the initiation time of response modulation tended to be earlier in FEF than in V1 but we note that the 95% confidence intervals were overlapping. Furthermore, the shape of the response modulation differed between in area FEF and V1. In area FEF the modulation tended to increase until the monkey made an eye movement to circle at the end of the target curve, while the modulation soon reached a plateau in area V1, and this explains why the \( \text{Lat}_{33} \) in area V1 tended to be shorter than that in area FEF. In fact when we measured distribution of the parameter \( b \) of the fitting function (a parameter that determines the time constant by which the modulation reaches its maximum) we observed a far larger variation in FEF (with standard deviation of 89 ms) than V1 (30 ms).

In order to test the statistical significance of the observed effects at the population level, we next compared the magnitude and latency of response modulation of individual FEF cells against individual V1 sites. Figure 4A depicts the distribution of MI values in FEF cells juxtaposed to the distribution in V1 sites. Two effects can be discerned from this figure. Firstly, at each task difficulty level the attentional modulation is stronger in FEF than in V1. Secondly, the MI decreases when the task becomes more difficult, more so for FEF cells than for V1 sites. The results of an ANOVA with MI as the independent variable and task difficulty (3 levels) and area (FEF or V1) as factors showed a significant effect of difficulty (\( F_{2,86} = 8.35, P < 0.0001 \) ) and area (\( F_{1,86} = 33, P < 10^{-10} \)).

Figure 4B depicts the distribution of \( \text{Lat}_{\text{Start}} \) in area V1 and FEF. An increase in task difficulty delayed the time of response modulation in both areas. However, at each task difficulty level the latency of the modulation did not differ between FEF and V1. Results of a two-way with area and difficulty as factors showed a significant effect of task difficulty (\( F_{2,86} = ...\).
= 24, P < 10^{-10}), while the effect of area (FEF or V1) did not reach statistical significance (F_{1,86} = 0.01, P = 0.94).

The effect of erroneous choices on neuronal activity in areas FEF and V1

We next examined the neuronal activity on trials where the monkey made an error. We limited our analysis to the most difficult configuration, where enough number of error trials (> 5) were available in every recording session. Figure 5 shows the FEF and V1 population responses in correct and error trials. When the monkey erroneously selected the distracter

**Figure 4. Comparison of the magnitude and the latency of response modulation between FEF cells and V1 sites**

A. The cumulative distribution of modulation indices (left) and modulation latencies (the initiation time, right) across all the recorded FEF single cells. On each panel green, blue and red traces correspond to the difficult, intermediate and easy conditions. The vertical dashed lines are the medians and the horizontal error bars are the standard deviations.

B. The cumulative distribution of modulation indices (left) and modulation latencies (the initiation time, right) across all the recorded area V1 sites. On each panel green, blue and red traces correspond to the difficult, intermediate and easy conditions. The vertical dashed lines are the medians and the horizontal error bars are the standard deviations.

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curve, the responses of FEF cells to the distracter were higher than the responses to the target curve (i.e. a complete reversal of response modulation in correct trials). Interestingly, the latency of response modulation in error trials was very similar to the latencies in correct trials (mean initiation time: 192 ms, 95% confidence interval: 157-273 and mean Lat33: 292 ms, 95% confidence interval 260-320). Therefore no matter whether the monkey made a correct or an erroneous choice, at a certain time after the stimulus onset the activity of FEF cells faithfully reflected the monkey’s behavioral choice.

In area V1, however, in error trials the response modulation became very weak compared to the correct trials and did not reverse. Therefore although previous studies from our lab have shown choice effects in the activity of V1 neurons (Roelfsema and Spekreijse, 2001), we did not observe this effect in our sample cells in monkey G. One possibility that can account for this inconsistency is the relative location of the receptive fields in this monkey. Since the receptive fields had a small eccentricity, they were clustered near the fixation point and in most instances were lying far away from the saccadic targets (the red circles connected to the target or the distracter curve). We reasoned that since these V1 RFs are distant from the saccade targets, they show a weaker choice probability effect. Indeed in a series of control experiment in the same animal, we observed that if V1 receptive fields area located on the saccade targets (by making the curves extremely short) correlates of monkeys choice (reflected as the reversal of the modulation in error trials) can also be observed in area V1.

**Rate-covariation between FEF and V1**
We next investigated whether the firing rate of neurons in FEF and area V1 are correlated across trials and if the correlation depends on the attentional state, the task difficulty and the relative location of FEF and V1 receptive fields.

We recorded from a total 114 pairs consisting of one FEF neuron and one V1 recording site with RFs on the same curve, and from 63 pairs with receptive fields on different curves. Figure 6A shows the average correlation coefficient between the FEF firing rates and the V1 response during the evoked responses (200-500ms after stimulus onset) and during ongoing activity while the monkey was maintaining fixation in anticipation of the stimulus (300-0ms before stimulus onset). In the fixation epoch, there was an influence of the relative location of the receptive fields on the rate-covariation (grey bars in Figure 6A). If the FEF and V1 receptive fields fell on the same curve, there was a weak positive correlation (mean 0.041) and there was a weak negative correlation if they fell on different curves, a difference that was
statistically significant ($t$-test, $P<10^{-8}$). We note that these effects that occurred before the presentation of the stimulus presumably reflect a selection bias because the RFs were generally closer together when a single curve could be placed the RFs than when different curve were placed in the RFs. It is also possible, however, that the increased rate-covariation in the spontaneous epoch with RFs on the same curve was induced by the configuration of the curves or the distribution of attention in previous trials.

The inter-areal correlation changed during stimulus presentation and was highest if the RFs fell on the same, attended curve. We believe that the reliable correlations between neurons in

**Figure 5. Population responses of FEF cells and V1 sites in error trials**

PSTHs of all the recorded FEF cells (A) and V1 sites (B) during correct (left) and erroneous (right) trials. Only the most difficult condition where enough error trials were available is included. The red and blue traces correspond to the responses to the target and distracter curve respectively. The arrows intercepting the X-axis show either the time when the modulation initiated (magenta) or when it reached 33% of its maximum level (cyan). These latencies were computed based on fitting a function to the difference between responses to the target and the distracter curves. The grey area below each PSTH plot illustrates this response difference and the green curve depicts the fit of the function (see methods) to the data. Note that in error trials the modulation in FEF reverses while in area V1 only the strength of the modulation is decreased (almost to zero). In error trials the modulation in FEF reverses while only the strength of modulation is decreased in area V1.

The inter-areal correlation changed during stimulus presentation and was highest if the RFs fell on the same, attended curve. We believe that the reliable correlations between neurons in
area V1 and area FEF, at the opposite ends of the visual processing hierarchy are a remarkable finding. In addition, we observed that different stimuli caused different correlations, although the curves falling in the receptive fields were always the same. To explore the pattern of correlations, we performed an ANOVA with attention (target or distracter on RF of V1 sites), task difficulty (three levels) and the relative location of receptive fields (RFs on the same or different curves) as factors. There was a main effect of task difficulty ($F_{2,1062} = 6.45$, $P < 0.002$) because the interareal rate-covariation decreased if the task became more difficult. There was also a main effect of the relative RF location ($F_{1,1062} = 4.01$, $P < 0.05$), because the rate-covariation was stronger when the RFs fell on the same curve, mirroring the effects that we observed in the fixation epoch, before the presentation of the stimulus. We did not obtain a main effect of attention ($F_{1,1062} = 0.03$, $P = 0.86$).

In addition, we obtained a number of significant interactions. Firstly, task difficulty had a stronger effect on the rate-covariation if the RFs fell on the same curve than if they fell on different curve ($F_{2,1062} = 6.63$, $P = 0.0014$). Secondly, the influence of task difficulty was more pronounced if the attended curve fell on the FEF-RF ($F_{2,1062} = 5.6$, $P = 0.004$). Thirdly, the effect of attention on the rate-covariation was stronger if the RFs fell on the same curve ($F_{2,1062} = 11.12$, $P = 0.0009$). It can be seen in Figure 6 that task difficulty tended to decrease the rate-covariation, except if the FEF RF fell on the distractor curve and the V1 RF fell on the target curve (blue bars in the right panel of Figure 6A). This rich pattern of effects on the strength of the rate-covariation awaits confirmation in a second monkey.

In addition to interareal correlation between FEF and V1 we also measured the rate-covariation between pairs of V1 recording sites (1140 pairs in total, note that in this initial analysis the same pairs were counted multiple times if they were tested on different days). Figure 6B shows the pattern of correlations between V1 pairs. The rate-covariation was weaker if the task became more difficult, just as was observed for the interareal correlation ($F_{2,6840} = 13.09$, $P < 10^{-10}$). We did not observe a significant effect of attention ($F_{1,6840} = 2.4$, $P = 0.1148$) and attention did not interact with the task difficulty ($F_{1,6840} = 0.96$, $P = 0.4881$). Because all V1 receptive fields fell on the same curve, we could not compare the rate-covariation between responses evoked by the same curve and different curves, but we note that this effect was previously explored in our lab (Poort and Roelfsema, 2009; Roelfsema et al., 2004).
We next compared the strength of interareal rate-covariation between FEF and V1 pairs with intra-areal rate-covariation within area V1 in the “easy” condition and averaging correlation coefficients between the two attention conditions. The average FEF-V1 rate-covariation was 0.06 while the average V1-V1 rate-covariation was 0.27. Given the large distance between the FEF and V1 cells this pattern of correlations is expected since the rate-covariation is higher between adjacent neurons than between the neurons farther apart (Zohary et al., 1994).

Figure 6. Rate-covariations between area FEF and area V1 and within area V1

A. Rate-covariation between FEF and V1 at three levels of task difficulty, easy (E), intermediate (I) and difficult (D) for neurons with an RF on the same curve (left panel) and on different curves (right panel). Red bars denote conditions where the FEF-RF fell on the target curve and blue bars where it fell on the distractor. Grey bars, correlation in the spontaneous window before the stimulus appeared.

B. Rate-covariation between V1 sites at different levels of task difficulty. Red bars show the conditions where the RFs fell on the target curve and green bars when they fell on the distractor.
Discussion

In this study we recorded the activity of neurons in the frontal eye fields (FEF) and area V1 of monkeys performing a curve tracing task. We manipulated the task difficulty and investigated the effect on the activity in the two areas and on the interaction between the areas. Our results show that the magnitude of attentional response modulation is decreased if the task becomes more difficult, both in FEF and in V1, while the latency of response modulation is increased. We found that the response modulation in area FEF was stronger than that in area V1, but that the latency of the response modulation was not significantly different between these two areas. As a measure of coupling between the responses of these two areas, we measured the rate-covariation. Our remarkable finding is that the activity of area V1 and area FEF is coupled, although these areas are at opposite ends of the visual cortical processing hierarchy. We found that the interareal correlations were higher for neuronal responses evoked by the same curve than for responses evoked by different curves. When the same stimulus was coded by FEF and V1 neurons the correlations were affected by attention and the task difficulty as reflected by a significantly stronger rate-covariation when both areas responded to the attended curve of an easy stimulus. As expected, the rate-covariation between FEF and V1, areas at opposite ends of the visual cortical processing hierarchy, was weaker than correlations between two V1 sites.

Comparison of attentional effects between FEF and V1

If the task is difficult, the response modulation was weaker, similar to previous studies in V1 (Roelfsema and Spekreijse, 2001) and in FEF (Bichot et al., 2001; Cohen et al., 2007; Thompson and Bichot, 2005; Thompson et al., 2005a). This effect also nicely fits with the idea of a salience map in FEF (Thompson and Bichot, 2005) that has originally been proposed for the neuronal activity of this area during visual search. The longer latency of attentional modulation as the task becomes more difficult has also been described both in area V1 (Chen et al., 2008) and in FEF (Cohen et al., 2007; Thompson et al., 2005a).

A unique finding emerges from the direct comparison between latency of the response modulation in FEF and V1. Previous studies have compared the timing of visual responses across frontal and visual cortex (Schmolesky et al., 1998; Khayat et al., 2009) but the present study is the first to directly compare the timing of attentional effects in these two areas with simultaneous recording in a task that is associated with attention shifts. Our results suggest that FEF and V1 jointly and simultaneously participate in the selection of a behaviourally relevant target, without a substantial difference in the timing of the attentional effects across
the different levels of task difficulty. These results therefore cast doubt on models of attention in which the selection of a target primarily occurs in frontoparietal cortices and then is fed back to the visual cortex into question (Corbetta and Shulman, 2002). Instead our findings are in line with models proposing reciprocal interactions between higher and lower visual areas (Usher and Niebur, 1996; Hamker, 2005). In such a network target selection is akin to settling of a network into an attractor state and the correlates of this relaxation can occur simultaneously across many areas. In this view, task difficulty could modulate the speed of convergence into one of the attractor states, with slower convergence for stimuli that are harder to interpret.

A recent study from our lab (Roelfsema et al., 2007) demonstrated that different aspects of a cognitive task are processed at different times in area V1. The present results are complementary by showing that neuronal correlates of a single processing step, the attentive selection of contour elements that belong to the same curve, occur simultaneously in areas in visual and frontal cortex. Taken together, these studies provide a novel view on cortical organization of visual information processing. Classical hierarchical views tried to map the processing phases onto areas (Felleman and Van Essen, 1991), for example attempting to determine the cortical areas responsible for pre-attentive and attentive processing. We have previously shown that the neurophysiology is incompatible with such a framework, since correlates of both preattentive and attentive processing can be found in a single area (Roelfsema et al., 2007; Shapley, 2007). The present results indicate that different stages of processing, like feature extraction and attentional selection rely on the coordinated effort of multiple interacting cortical areas, which may jointly contribute to each of the processing steps.

**Rate-covariation between FEF and V1**

The emerging view that different areas interact during the various processing phases implies that the activity in different areas is coupled. The rate-covariation is a measure for this coupling. Indeed, neuronal activity in area V1 turned out to be coupled to activity in area FEF. As expected, the rate-covariations between FEF and V1 were weaker than the correlations within area V1, in accordance with previous studies showing that the strength of the correlation depends on cortical distance (Gawne et al., 1996; Poort and Roelfsema, 2009; Roelfsema et al., 2004; Zohary et al., 1994). We found that the rate covariation between FEF and V1 was stronger when (1) the neurons had nearby receptive fields and (2) they responded to the same curve, although we have not yet dissociated these two factors. We showed
previously that rate covariation in area V1 does not only depend on the RF distance but also on the stimulus, because it is stronger between neuronal responses that are evoked by the same object (Roelfsema et al., 2004). In some instances we observed positive correlations when a pair of neurons both coded the same stimuli and negative correlation when they responded to different stimuli. This latter finding is in line with the results of a recent study (Cohen and Newsome, 2008) showing that the correlation between two MT neurons can be positive or negative depending on whether they take part in a cooperative (responding to the same direction of movement) or competitive (responding to different directions of movement) interaction.

An interesting new finding is that the interareal rate-covariation as well as rate-covariation within area V1 depends on the task difficulty. The correlations were overall weaker when the task was more difficult. It has been shown that increasing the task difficulty, increases the variability of neuronal firing rates in FEF (Cohen et al., 2007) and MT (Shadlen et al., 1996). This latter finding is in accordance with the present findings, as correlations between pairs of neurons were weaker in the more difficult conditions. We will investigate the rate-covariations in more detail when data from an additional monkey becomes available.

In conclusion, we have shown that area FEF, which is one of the higher stages of the visual system involved in the generation of eye movements, and V1 which is the first cortical stage of visual processing have strong interaction and jointly take part in the intricate task of attentional selection.

Reference List


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