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SCHOOL OF SOCIAL SCIENCES  
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**THE INFLUENCE OF SALIENT, DISTRACTING  
STIMULI ON NEURONAL RESPONSES IN FRONTAL  
AND VISUAL CORTICAL AREAS DURING  
ENDOGENOUSLY DRIVEN ATTENTION**

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# CONTENTS

CONTENTS.....	3
ABSTRACT.....	5
ΠΕΡΙΛΗΨΗ.....	6
CHAPTER 1.....	8
INTRODUCTION.....	8
1.1.The frontal eye fields.....	9
1.2.Visual area V4.....	11
1.3.Goal of the present study.....	12
CHAPTER 2.....	14
MATERIALS AND METHODS.....	14
2.1. Laboratory animals.....	14
2.2. Behavioral task.....	14
2.3. Electrophysiological recordings.....	16
2.4. Receptive fields mapping.....	16
2.5. Firing rate analysis.....	18
2.6. Experimental conditions.....	19
CHAPTER 3.....	21
RESULTS.....	21
3.1. Main aims and experimental conditions studied.....	21
3.2. Effect of a stimulus color change inside the RF on neuronal responses in FEF and area V4 when attention is directed either inside or outside the RF.....	22
3.2.1. <i>Effect of spatial attention on FEF neuronal responses before the color change</i> .....	24
3.2.2. <i>Effect of a color change inside the RF on FEF neuronal responses</i> .....	25

3.2.3. <i>Effect of spatial attention on FEF neuronal responses following the color change</i> .....	26
3.2.4. <i>Effect of a color change on sustained responses in FEF. Comparison of firing rates before and after the color change</i> .....	27
3.2.5. <i>Effect of spatial attention on V4 neuronal responses before the color change</i> .....	29
3.2.6. <i>Effect of a color change inside the RF on V4 neuronal responses</i> .....	30
3.2.7. <i>Effect of spatial attention on V4 neuronal responses following the color change</i> .....	31
3.2.8. <i>Effect of a color change on sustained responses in V4. Comparison of firing rates before and after the color change</i> .....	32
3.3. <i>Effect of a stimulus color change outside the RF on neuronal responses in FEF and area V4 when attention is directed inside the RF</i> .....	33
3.3.1. <i>Effect of spatial attention on FEF neuronal responses before the color change</i> .....	34
3.3.2. <i>Effect of an irrelevant color change outside the RF on FEF responses</i> .....	35
3.3.3. <i>Late effects of an irrelevant color change on FEF neuronal responses</i> .....	36
3.3.4. <i>Effect of spatial attention on V4 neuronal responses before the color change</i> .....	37
3.3.5. <i>Effect of an irrelevant color change outside the R on V4 responses</i> .....	38
3.3.6. <i>Late effects of an irrelevant color change on V4 neuronal responses</i> .....	39
CHAPTER 4.....	40
DISCUSSION.....	40
BIBLIOGRAPHY.....	46

## ABSTRACT

In crowded visual scenes only a limited number of items can be processed by our brain at any given time due to the limited capacity of our visual system. Visual attention is employed to select those stimuli that are more salient or more relevant to the current behavioral goals for further processing. When attention is driven by external sources, such as the physical salience of the stimuli, we refer to it as bottom-up or exogenously driven attention, whereas when it is driven by internal inputs such as expectations and behavioral goals, we refer to it as top-down or endogenously driven attention. In everyday life endogenously and exogenously driven attention often interact to affect our perception and guide our actions. In this study, we examine such interactions. Specifically, we ask whether endogenously driven attention can be affected by exogenous, salient stimuli. We assess whether and how highly salient but behaviorally irrelevant visual events can affect neuronal responses in a paradigm of endogenously driven attention.

We focused on prefrontal (frontal eye fields-FEF) and mid-level visual areas (area V4), two areas that are known to modulate their activity with spatial attention. We addressed three main questions: First, we asked whether highly salient events are encoded by FEF and V4 neurons even when they are behaviorally irrelevant. We provide evidence that neuronal responses in both areas encode salient events outside the locus of attention. Secondly, we examined the magnitude and duration of this effect. We found that the magnitude depends on the locus of attention and we show that salient, behaviorally irrelevant events can have a prolonged effect on neuronal responses. Finally, we compared the effect of such salient events on the activity of neuronal populations encoding locations in the same hemifield with or the opposite hemifield to the location of the salient event. We show that suppressive interactions between neuronal populations encoding different locations are stronger within the same hemisphere compared to those across hemispheres.

## ΠΕΡΙΛΗΨΗ

Το οπτικό μας πεδίο κατακλύζεται από πλήθος αντικειμένων από τα οποία ο εγκέφαλός μας μπορεί να επεξεργαστεί μόνο έναν περιορισμένο αριθμό σε κάθε δεδομένη στιγμή, λόγω της περιορισμένης δυναμικότητας του οπτικού μας συστήματος. Η οπτική προσοχή βοηθάει να επιλεγούν για περαιτέρω επεξεργασία εκείνα τα ερεθίσματα τα οποία ξεχωρίζουν ή είναι πιο σχετικά με την τρέχουσα συμπεριφορά. Όταν η προσοχή κατευθύνεται από εξωτερικά χαρακτηριστικά των ερεθισμάτων, όπως η φωτεινότητά τους ή το αν ξεχωρίζουν από τα περιβάλλοντα ερεθίσματα, αναφερόμαστε σε «εκ των κάτω προς τα άνω» ή εξωγενώς κατευθυνόμενη προσοχή. Αντίθετα, όταν καθοδηγείται από ενδογενείς παράγοντες, όπως οι προσδοκίες μας ή οι τρέχοντες στόχοι της συμπεριφοράς, αναφερόμαστε σε αυτήν ως «εκ των άνω προς τα κάτω» ή ενδογενώς καθοδηγούμενη προσοχή. Στην καθημερινή ζωή, ενδογενή και εξωγενή σήματα αλληλεπιδρούν για να κατευθύνουν την προσοχή μας επηρεάζοντας την αντίληψη μας και τις πράξεις μας. Σε αυτή τη μελέτη, εξετάζουμε τέτοιες αλληλεπιδράσεις. Συγκεκριμένα, θέτουμε την ερώτηση εάν η ενδογενώς καθοδηγούμενη προσοχή μπορεί να επηρεαστεί από εξωγενή, εμφανή/προεξέχοντα ερεθίσματα. Εξετάζουμε εάν και πώς προεξέχοντα, αλλά άσχετα με την τρέχουσα συμπεριφορά οπτικά συμβάντα μπορούν να επηρεάσουν τις νευρωνικές αποκρίσεις, σε ένα παράδειγμα ενδογενώς καθοδηγούμενης προσοχής.

Εστίασαμε στον προμετωπιαίο φλοιό (πρόσθια οφθαλμικά πεδία-FEF) και σε μία μεσαίου επιπέδου οπτική περιοχή(V4), δύο περιοχές που είναι γνωστό ότι μεταβάλλουν τη δραστηριότητά τους με τη χωρική προσοχή. Εξετάσαμε τρία βασικά ερωτήματα: Πρώτον, ρωτήσαμε αν ιδιαίτερα εμφανή/προεξέχοντα οπτικά ερεθίσματα κωδικοποιούνται από νευρώνες στα FEF και τη V4, ακόμη και όταν είναι άσχετα με την τρέχουσα συμπεριφορά. Παρέχουμε ενδείξεις ότι οι νευρωνικές αποκρίσεις και στις δύο περιοχές κωδικοποιούν εμφανή/προεξέχοντα ερεθίσματα ανεξάρτητα από τη θέση της προσοχής. Δεύτερον, εξετάσαμε το μέγεθος και τη διάρκεια αυτών των επιδράσεων. Βρήκαμε ότι το μέγεθος εξαρτάται από την θέση της προσοχής και δείχνουμε ότι εξέχοντα οπτικά συμβάντα, άσχετα με την τρέχουσα συμπεριφορά, μπορεί να έχουν παρατεταμένες δράσεις στις νευρωνικές αποκρίσεις. Τέλος, μελετήσαμε πώς τέτοια εξέχοντα ερεθίσματα επηρεάζουν τις αποκρίσεις νευρωνικών πληθυσμών που κωδικοποιούν θέσεις στο ίδιο ή στο απέναντι ημιπέδιο. Τα αποτελέσματά μας δείχνουν ανασταλτικές/ανταγωνιστικές αλληλεπιδράσεις μεταξύ

πληθυσμών νευρώνων που κωδικοποιούν διαφορετικές θέσεις. Οι αλληλεπιδράσεις αυτές είναι ισχυρότερες μεταξύ νευρωνικών πληθυσμών εντός του ίδιου ημισφαιρίου σε σύγκριση με αυτές μεταξύ νευρωνικών πληθυσμών σε διαφορετικά ημισφαίρια.

## CHAPTER 1

### INTRODUCTION

We are constantly bombarded by far more visual stimuli than the number of stimuli our visual system can process at a given time. We employ visual attention to select those stimuli that are either more relevant to current behavioral goals or more salient than other concurrently present stimuli. Thus, visual attention functions as a selection mechanism that filters out irrelevant and unnecessary information and enables selective processing of specific stimuli or specific features of stimuli. As William James defined it, attention "...is the taking possession of the mind, in clear and vivid form, of one out of what may seem several simultaneously possible objects or trains of thoughts...It implies withdrawal from some things in order to deal effectively with others." (James, 1890).

Attention largely determines what we become aware of at any given moment and is therefore a critical element of normal cognition. It is known to be disturbed in several disorders and known diseases including Attention Deficit Hyperactivity Disorder, Alzheimer's disease, and schizophrenia as well as in normal aging. Despite the profound influence of attention on our perception, the exact neuronal mechanisms that mediate the selective processing of specific elements in our visual field and the suppression of irrelevant information are far from clear.

Neuropsychological studies in healthy humans and human patients, neuroimaging studies in humans as well as electrophysiological and lesion studies in animals have demonstrated that during attention tasks an extended network of areas across the brain is activated including areas in the frontal, parietal, temporal, and



occipital lobes (for relevant reviews see Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002). In agreement with a role of attention in facilitating processing of selected stimuli, neurophysiological studies have shown that when attention is directed toward the receptive field (RF) of a neuron it typically results in increased visual responses (Moran and Desimone, 1985). This attentional effect on firing rates has been reported in several visual areas (Motter, 1994; Treue and Maunsell, 1996; Luck et al., 1997; McAdams and Maunsell, 2000) as well as in frontal and parietal areas implicated in attentional control (Bisley and Goldberg, 2003; Thompson et al., 2005; Buschman and Miller, 2007; Gregoriou et al., 2009). Frontal and parietal areas in particular are thought to control the gain of signals in early visual areas through top-down signals. This way, they can modulate the sensitivity of selective visual neuronal populations for incoming visual information (Kastner and Ungerleider, 2000; Corbetta and Shulman, 2002; Armstrong and Moore, 2007). Thus, a selective increase in firing rate for stimuli at the locus of attention relative to stimuli outside the locus of attention leads to an enhanced representation of the former and consequently a preferential processing of attended versus unattended stimuli.

### **1.1. The Frontal Eye Fields**

One prefrontal area that has been extensively studied in neurophysiological studies in the context of attention is the frontal eye fields (FEF). The FEF (Figure 1) is located in prefrontal cortex (PFC) and was first described in the primate brain as the cortex occupying the anterior bank of the arcuate sulcus (Bruce and Goldberg 1985). Neurons in this area display both visual and oculomotor properties (Bruce and Goldberg 1985; Bruce et al 1985). Specifically, fast eye movements called saccades

can be elicited by microstimulation of the FEF using low currents (Bruce et al 1985), and reversible inactivation of the same area leads to saccadic deficits (Dias et al 1995; Peel et al 2014). These results and the known anatomical connections of the FEF to brainstem areas associated with the control of saccades (Stanton et al 1988) have established the critical role of FEF in oculomotor behavior.

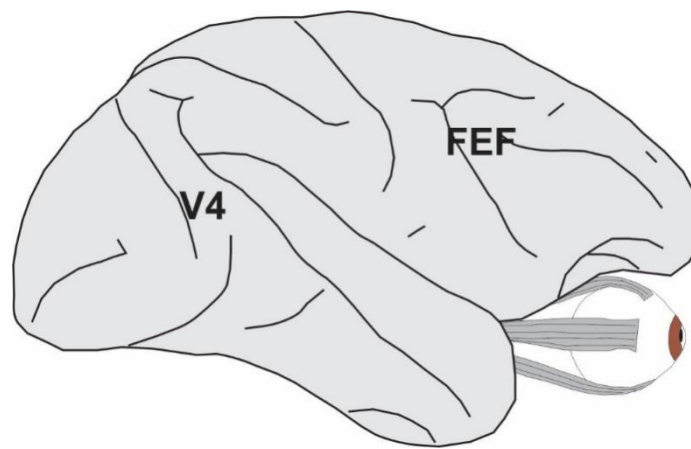


Figure 1. Lateral view of the right hemisphere of a macaque monkey brain. Area V4 is marked on the prelunate convexity, and the FEF is depicted in the anterior bank of the arcuate sulcus.

Besides the early established role of FEF in the control of saccades, later studies showed that the FEF have an equally important role in visual spatial attention. FEF neurons have visual responses (Bruce and Goldberg 1985) and share connections with visual areas both in the dorsal and ventral visual stream (Schall et al 1995; Stanton et al 1995; Anderson et al 2011; Ninomiya et al 2012). FEF visual neurons can distinguish a target from a distractor in both covert and overt attention tasks (Thompson et al 1996; Thompson et al 1997). This finding indicates that FEF neurons modulate their responses according to the behavioral relevance of the stimulus in their receptive field and can thus participate in visual selection of behaviorally relevant

stimuli. Neurons in FEF can change their responses according to the physical salience of a stimulus (Bichot et al 2001) as well as according to the behavioral relevance of a stimulus responding stronger to stimuli that share common features with the target (Zhou and Desimone 2011). These properties are in agreement with the proposal that FEF holds a saliency map of the visual world, where stimuli are represented by a level of activity that reflects their behavioral relevance (Thompson and Bichot 2005).

Several studies have provided evidence in agreement with a role of FEF in the control of the gain of sensory responses in earlier visual areas. Specifically, in humans, transcranial magnetic stimulation (TMS) in combination with functional magnetic resonance imaging showed that the FEF influence the activity of retinotopic visual areas V1-V4 and that TMS in the FEF affects visual perception (Ruff et al., 2006). Moreover, in monkeys, Moore and colleagues, in a series of experiments, underscored the causal role of FEF in guiding attention as well as in modulating responses and receptive fields in visual area V4 (Moore and Fallah 2004; Armstrong et al 2006; Armstrong and Moore 2007). Specifically, subthreshold electrical stimulation of FEF mimics the effects of attention by enhancing responses of V4 neurons with similar receptive field locations and by improving detection of subtle changes.

## **1.2. Visual area V4**

Area V4 (Figure 1) is part of the extrastriate cortex. Concerning its anatomical connections, the part of V4 representing central vision receives direct signals from V1 and is also interconnected with downstream areas TE and TEO. The part of V4 where peripheral vision is represented is mostly connected with dorsal stream areas

(Roe et al., 2012). Moreover, V4 is directly connected to visual areas V2, V3, MT as well as parietal area LIP and the FEF (Ungerleider et al 2008). Neurons in V4 encode features of stimuli that are essential for object recognition including their color, shape, orientation etc. (Desimone and Schein 1987; Schein and Desimone 1990).

Neurons in V4 modulate their responses both with spatial and feature attention (for reviews see Desimone and Duncan 1995; Chelazzi et al 2011). Numerous studies have shown that attention to a location in space increases the responses of V4 neurons with receptive fields at this location (Moran and Desimone, 1985; Desimone and Duncan, 1995; Reynolds et al., 1999; Kastner and Ungerleider, 2000; McAdams and Maunsell, 2000; Gregoriou et al 2009). During feature attention, attention is drawn to specific features e.g. to a certain color or to specific objects. In these paradigms, it has been shown that V4 neurons selective for the particular feature that attention is drawn to, enhance their responses throughout the visual field, i.e. irrespective of the locus of attention (Motter, 1994; Bichot et al., 2005; Chelazzi et al., 1998, 2001; Zhou and Desimone, 2011). This mechanism allows selective processing of the relevant feature, while other features/objects are filtered out.

### **1.3.Goal of the present study**

The goal of the present study was to examine how neuronal responses in V4 and FEF are influenced by spatial attention in the presence of salient irrelevant stimuli in a covert attention paradigm. Although several of the studies mentioned above have examined the modulation of neuronal responses by spatial and feature attention both in tasks requiring endogenous attention (when the target is defined by specific cues) and in tasks driven by exogenous attention (when the target captures attention

automatically), little is known about the influence of highly salient stimuli on neuronal responses in conditions in which endogenous attention is employed.

Accordingly, the questions that we asked in this study were:

1) Are highly salient events encoded by FEF and V4 neurons even when they are behaviorally irrelevant?

2) What is the magnitude and duration of such an effect if present?

3) How do salient events influence activity of neuronal populations encoding locations in the same hemifield and in different hemifields? Here, our goal was to examine whether suppressive interactions are stronger within or across hemispheres.

## **CHAPTER 2**

### **MATERIALS AND METHODS**

Experiments were carried out at the National Institute of Mental Health (NIMH), NIH (Bethesda, U.S.A.) and have been described previously (Gregoriou et al 2009; Gregoriou et al 2012). We briefly describe the behavioral tasks and electrophysiological procedures below. In this study, we focused on analysis of conditions that had not been examined in previous work.

#### **2.1. Laboratory Animals**

Experiments were performed in two male rhesus monkeys (*Macaca mulatta*) weighing 8-10 kg. Surgeries were performed under aseptic conditions to implant two recording chambers over the frontal eye field (FEF) and area V4, respectively, as well as a head holder. For the exact location of the implantation in FEF and V4, MRI scans were used before the surgery. All animal experimentation was conducted in accordance with the NIH guidelines and were approved by the NIMH Institutional Animal Care and Use Committee.

#### **2.2. Behavioral Tasks**

During training and electrophysiological recordings, the monkeys were seated facing a computer screen (resolution: 800x600 pixels, refresh rate: 100Hz) at 57 cm distance. Presentation of the visual stimuli and behavioral parameters were controlled by the CORTEX software package. Eye position was monitored by an infrared based eye-tracking system (ISCAN) at 60 Hz.

The monkeys had to hold a bar to initiate each trial. Following that, a small spot, 0.4x0.4 degrees of visual angle, appeared at the center of the computer screen and the monkeys had to keep their gaze on that spot within a 3 x 3 degrees window for the next 1500ms. If the monkeys failed to maintain fixation for the required time, the trial was aborted and the fixation spot disappeared (Figure 2).

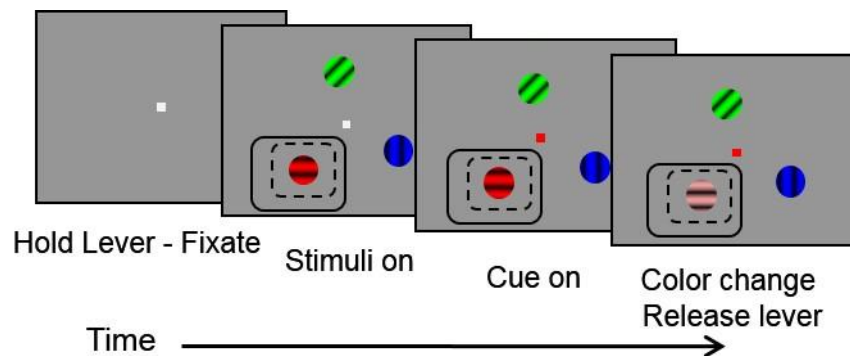


Figure. 2. Attention task. At the beginning of each trial, monkeys had to hold a bar in order for the trial to begin. Subsequently, a white fixation spot appeared at the centre of the screen. Following successful fixation for 1500ms, three sinusoidal drifting gratings (red, blue and green) appeared on the screen. They were distributed at 120° interval around the fixation spot. The monkey had to maintain fixation of the central spot. After a variable period of time the central fixation spot was replaced by a cue, which had the same color with one of the drifting gratings. The color of the cue indicated the target stimulus. Monkeys had to shift their attention to the target stimulus covertly and wait for it to change color while maintaining fixation of the central cue. When the target stimulus changed color, they had to release the bar. Color changes of the distractors had to be ignored. Successful completion of the trial was rewarded by a drop of juice. Inability to maintain central fixation, failure to respond to the color change of the target or response to the color change of a distractor resulted in the trial being aborted and a new trial was initiated.

If the monkeys successful fixated the fixation spot for 1500ms, three colored (red green and blue), isoluminant, sinusoidal, drifting gratings appeared subsequently on the screen. Each grating had a diameter of 2degrees and a drifting rate of 1cycle/s. They were positioned at the same distance from the central spot, at 120 degrees intervals. In the next 0-1000ms, a small square cue was presented at the center of the

screen. The color of the cue (red, green or blue) indicated the target stimulus to which attention should be directed covertly e.g. a red cue indicated that attention should be directed to the red grating.

Monkeys had to respond to a color change of the target stimulus by releasing the bar. The color change could occur any time between 250 – 3000 ms following the cue onset. The distractor stimuli could also change color before the target (at least 400ms before the target's color change). The monkeys were required to ignore color changes of distractors and release the bar following the target's color change. Successful responses were rewarded with a drop of juice. If the monkeys failed to release the bar within 600ms of the target's color change, released the bar following a distractor color change or failed to maintain fixation of the cue, the trial was terminated without a reward, and a new trial began.

### **2.3. Electrophysiological Recordings**

Electrophysiological recordings were carried out in FEF, in the anterior bank of the arcuate sulcus, and in V4 on the prelunate gyrus, simultaneously, using one to four electrodes in each area. Electrodes were lowered through the intact dura in each session at a distance of 650 or 900  $\mu\text{m}$  from each other both in FEF and V4.

Spikes from multi-units were obtained after amplification and filtering (250 Hz to 8 kHz) of the recorded signals and were digitized at 40 kHz through a Multichannel Acquisition Processor system by Plexon Inc. In the current study we relied on multi-unit activity by setting a threshold offline that distinguished noise from real spikes.

### **2.4. Receptive Fields Mapping**



To optimally position the grating stimuli in the covert attention task we first mapped the visual receptive fields (RFs) of the recorded neurons.

To this end, monkeys performed a memory - guided saccade task while we recorded multi-unit activity in the two areas (Figure 3). At the beginning of each trial, monkeys were required to fixate centrally at a fixation spot. While monkeys maintained central fixation, a stimulus was briefly flashed peripherally for 100 ms in one out of six possible locations distributed radially at 60 degrees intervals at the eccentricity that evoked a clear visual response. After 750 ms the central fixation spot was extinguished, giving the signal to the monkeys to make a saccade towards the memorized position of the flashed stimulus.

This task served two purposes. Firstly, it allowed us to map the extent of the response fields of the recorded multi-units. Secondly, it allowed us to dissociate visual from motor responses, which are both known to exist in the FEF (Bruce and Goldberg 1985).

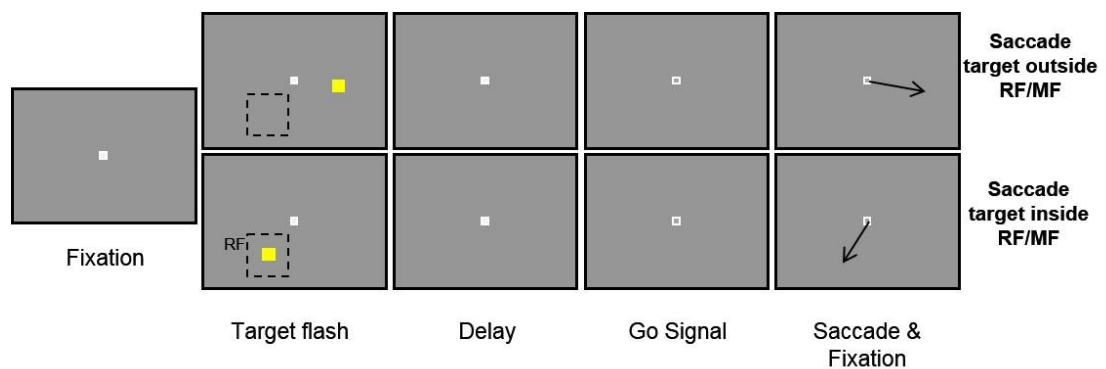


Figure 3. Memory – guided saccade task. At the beginning of each trial monkeys had to fixate at a white fixation spot at the centre of the screen. Subsequently, a yellow rectangle was briefly flashed (100ms) in one out of six possible locations, arranged on a circle at 60° distance from each other. A 750ms delay period followed, during which the monkeys had to maintain fixation of the central spot. At the end of the delay period the fixation spot was turned off signaling to the monkeys that they had to execute a saccadic eye movement towards the memorized location of the yellow rectangle. Successful completion of the trial was rewarded with a drop of

juice. Example trials in which the stimulus could appear inside (lower sequence) or outside (upper sequence) the response field of the recorded neurons are shown. The dotted rectangle indicates an example receptive field. Arrows depict the correct saccade.

## 2.5. Firing Rate Analysis

In this study we examined how a behaviorally relevant color change (that of the target) or a behaviorally irrelevant color change (that of a distractor) influences neuronal responses when attention is inside the RF of the recorded neurons or elsewhere. All analyses were performed on multi-unit data using custom made codes in Matlab. Firing rates were calculated at a millisecond resolution for the period around the color change of the target or distractors. For each signal, firing rates were averaged across trials for each of the conditions under study. For visual presentation firing rates were smoothed using a Gaussian kernel ( $\sigma=10$  ms). To obtain firing rate population averages, the firing rate data collected from each electrode were normalized to either the peak response obtained from this electrode across conditions or to the mean response within 400ms before the color change. To this end, for each signal, the mean firing rate across trials at each millisecond was divided by either the peak response or the mean response within the 400ms window before the color change.

Statistical comparisons of firing rates in different conditions were carried out at the population level using either analysis of variance (ANOVA) and repeated measures ANOVA (for comparisons among three conditions) or unpaired and paired t-test (for comparisons between two conditions). Comparisons were made a) between responses before and after a color change with attention within the neurons' RF or at a position outside the neurons' RF (on the same hemifield or on the contralateral hemifield), b) among responses in the three attention conditions (inside the RF, on the

ipsilateral position and on the contralateral position) before the color change and c) among responses in the three attention conditions (inside the RF, on the ipsilateral position and on the contralateral position) after the color change (see next section for more details on the conditions considered). The null hypothesis was that the spatial location of attention or the color change of a stimulus did not influence the activation of the recorded neurons. For the statistical comparisons firing rates were averaged within windows at different time periods (before and after the color change of the target or of a distractor) to assess how spatial attention and the color change affected the activity of neurons in different conditions.

## **2.6. Experimental Conditions**

As it has already been mentioned, the main goal of this study was to assess how attention and salient visual events influence the responses of FEF and V4 neurons, with known receptive fields' locations. In order to examine neuronal responses in different conditions that had not been previously examined, we wrote two different codes in Matlab for data analysis.

We developed the first code in order to calculate and display the modulation of firing rates of the recorded neurons when the stimulus inside the RF (target or distractor) changed color. Three conditions were considered based on the location of attention. The first condition included trials in which attention was directed inside the RF. In this condition we were interested in the time period around the target color change when the target was inside the RF. The second and third conditions included trials in which attention was directed outside the RF of the recorded neurons. More specifically, in the second condition we examined neuronal responses around the time the distractor in the RF changed color, when attention was directed to the position

contralateral to the neurons' RF. Accordingly, in the third condition we examined neuronal responses around the time of the color change of the distractor inside the RF, when attention was directed to the position ipsilateral to the RF.

Our second aim was to study how neuronal responses were affected by an irrelevant color change (inside the RF, outside the RF at the opposite to the RF hemifield and outside the RF at the position on the same hemifield with the RF), when attention was directed outside the RF (either at the contralateral or the ipsilateral position) or inside the RF, respectively. To this end we developed a second code. In this case, we specifically looked around the time that the earliest distractor color change occurred in order to examine the temporal evolution of the responses following the change.

In the following section we present the results of these analyses for the FEF and V4 neurons, separately.

## CHAPTER 3

### RESULTS

#### 3.1. Main aims and experimental conditions studied

We first examined how the locus of attention affects neuronal responses *when the stimulus inside the RF changes color*. We included trials from three different conditions based on the locus of attention. In the first condition attention was directed inside the RF to the stimulus that changed color. Thus, both distractors were located outside the RF of the recorded neurons. In the second and third condition attention was directed outside the RF whereas the stimulus that changed color was inside the RF. The difference between these two conditions was that in the second condition attention was directed to the stimulus on the contralateral hemisphere relative to the RF, whereas in the third condition attention was directed to the ipsilateral to the RF stimulus. This way, we were able to

1) examine how a salient event inside the RF affects neuronal responses when attention is directed to that location vs. when it is directed elsewhere. We hypothesized that a color change inside the RF can lead to a similar increase in activation in all conditions regardless of the locus of attention due to the saliency of a color change. To test this hypothesis we assessed whether the activation induced by a color change inside the RF was similar when attention was voluntarily directed to that location and when attention was voluntarily directed to a different location.

2) assess possible differences in activation levels for contralateral vs ipsilateral attention shifts, to gain insight into the competitive interactions within and across hemispheres.

In a second set of conditions we tested *the influence of the color change outside the RF*, when attention was inside the RF. Our goal was to examine in more detail whether a salient event can capture transiently attention even when the subjects have been instructed to ignore this change and maintain attention on a different stimulus. To this end, we compared neuronal responses in trials in which the color change occurred outside the RF in the contralateral hemifield, with those that the color change occurred outside the RF but on the same hemifield with the RF, with attention inside the RF in both cases. This set of conditions is complementary to the one listed above. Here we also included a control condition with attention outside the RF (either to the ipsilateral or the contralateral location) and the color change occurring inside the RF.

We also compared firing rates in the same condition before and after a color change. This allowed us on one hand to assess whether any effect the color change had on neuronal responses was long lasting and when its influence was eliminated and the activation returned to the level before the color change occurred.

All comparisons were made for neuronal responses in both V4 and FEF in order to assess possible differences between the two areas. Similarities in the two areas would indicate the same effect on both areas and thus a global role of this factor (e.g. attention or encoding of salient events) on several areas in the brain. Possible differences on the other hand would highlight the differential contributions of the two areas on attention mechanisms.

### **3.2. Effect of a stimulus color change inside the RF on neuronal responses in FEF and area V4 when attention is directed either inside or outside the RF**

To examine the effect of a salient event on neuronal responses when attention is voluntarily directed away from the location of the salient event, we studied neuronal responses around the time the stimulus inside the RF changed color when attention was directed either inside or outside the RF. We included three conditions: the first condition included trials in which attention was inside the RF, and so was the color change. The second condition included trials in which, attention was directed outside the RF to the contralateral to the RF location, whereas the third condition included trials in which attention was directed outside the RF but ipsilaterally to the RF. In both cases the event of interest, the color change, occurred inside the RF. The population average responses of the FEF neurons for the three conditions are shown in Figure 4, whereas those of V4 are shown in Figure 5.

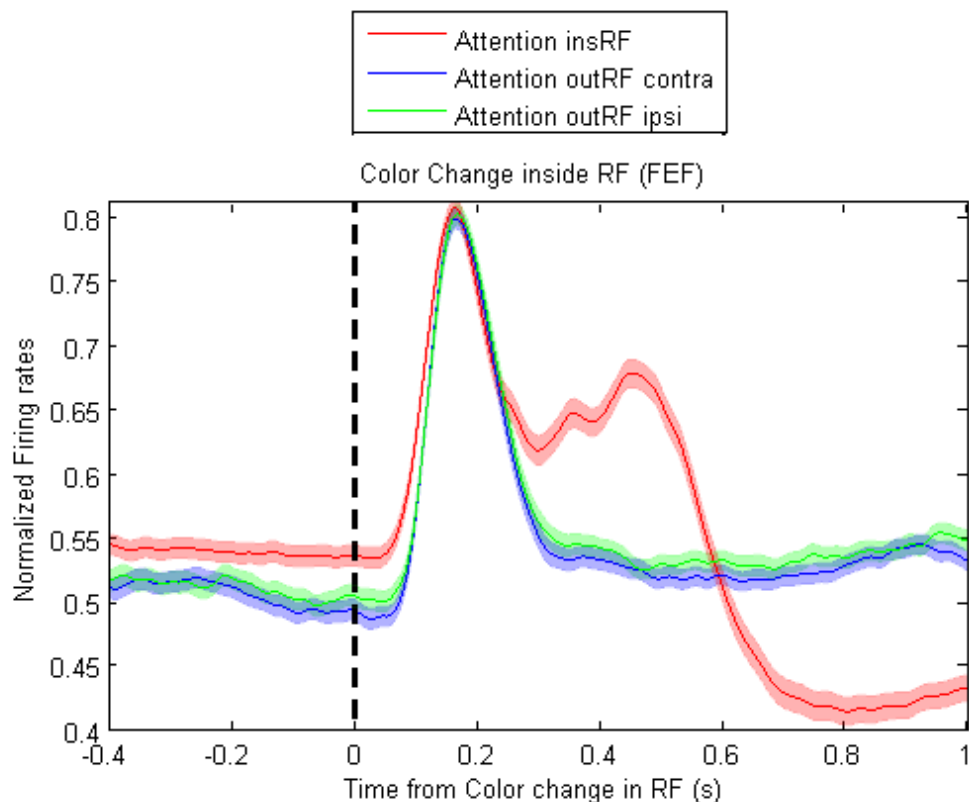


Figure 4. Normalized (to the peak response) firing rate population averages of FEF neuronal responses. Vertical dashed line indicates the time of color change inside the RF. Responses are shown for the period 400ms before the color change up to

1000ms after the color change. Red line depicts population response with attention inside the RF; blue line response with attention directed outside the RF on the contralateral hemifield; green line, response with attention directed outside the RF ipsilateral to the RF.

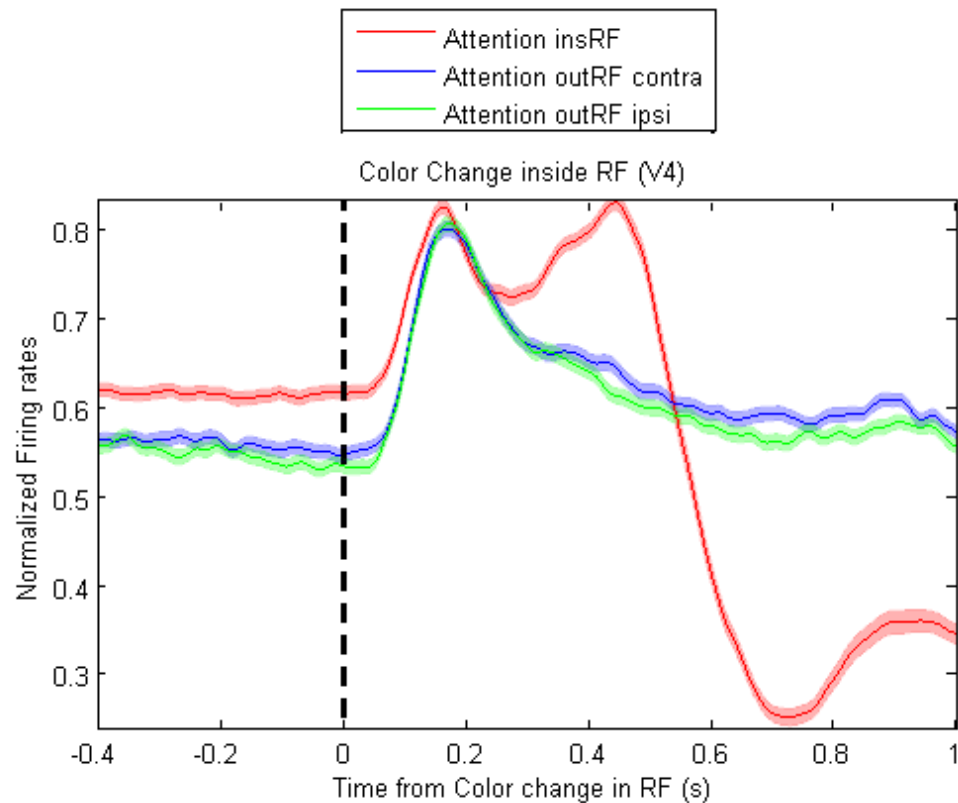


Figure 5. Normalized (to the peak response) firing rate population averages of V4 neuronal responses. Color change inside the RF is indicated by the vertical dashed line. Responses are shown for the period 400ms before the color change up to 1000ms after the color change. Red line depicts population response with attention inside the RF; blue line response with attention directed outside the RF on the contralateral hemifield; green line, response with attention directed outside the RF ipsilateral to the RF.

### ***3.2.1. Effect of spatial attention on FEF neuronal responses before the color change***

We examined the differences in activity between the three conditions in a 400ms window before the color change. During this period time differences in activity can only be attributed to the influence of spatial attention. In agreement with the expected



effect of spatial attention we found differential activation levels in the different attention condition (Figure 4; time period -0.4-0s) and this effect was statistically significant (one way ANOVA  $p < 0.05$ ). We found a significant increase when attention was directed inside the RF compared to the other two conditions (post hoc Tukey - Kramer test,  $p < 0.05$  for both comparisons) but not between the two conditions that attention was directed outside the RF (post hoc Tukey - Kramer test,  $p > 0.47$ ). The latter result indicates that before the color change the critical factor that influences activation levels is whether attention is inside or outside the RF and that when attention is outside the RF the effect of hemifield (contralateral or ipsilateral to the RF) is negligible. The result was the same both when the non-normalized data were considered as well as when the normalization was done to the mean response before the color change.

### ***3.2.2. Effect of a color change inside the RF on FEF neuronal responses***

We next examined FEF responses to the stimulus color change inside the RF. To this end, we compared firing rates 110 to 230ms following the color change. This period of time includes the peak in neuronal responses due to the visual effect of the color change inside the RF. We found no statistically significant differences among the three conditions during this interval (one-way ANOVA,  $p = 0.88$ ). We found the same result for non-normalized data as well as for data normalized to the mean pre-color change response.

This is an interesting finding. Although neuronal responses before the color change were lower when attention was directed outside the RF compared to the condition that attention was inside the RF, they reached the same level right after the

color change. This result indicates that a salient visual event is encoded by FEF neurons equally strongly irrespective of the locus of attention. Whether this is also perceived with the same sensitivity regardless of the locus of attention cannot be assessed with the present experimental paradigm.

### ***3.2.3. Effect of spatial attention on FEF neuronal responses following the color change***

Our results so far show that whereas spatial attention modulates neuronal responses in FEF initially in our task, so that the locus of attention (inside vs outside RF) can be inferred by the level of neuronal activity, a subsequent color change inside the RF is encoded by the same level of activity irrespective of the locus of attention. We next asked whether following this color change neuronal responses are again modulated by spatial attention. To this end, we considered the time period 300-500ms after the color change. As shown in Figure 4, neuronal responses in the three conditions are differentiated according to the location of attention and this difference is statistically significant (Figure 4; one-way ANOVA,  $p < 0.05$ ). More specifically, following the color change, neuronal responses were significantly higher when attention was directed inside the RF compared to the other two conditions (post hoc Tukey - Kramer test,  $p < 0.05$ ). It should be noted that with attention inside the RF, the monkey is required to respond by releasing a bar right after the color change inside the RF, whereas in the other two conditions the monkey should wait until the target (located outside the RF) changes color. It is thus possible that this increase in activity right before the monkey's response reflects a cognitive aspect related to the realization that the color change is a behaviorally relevant one. Neuronal responses in

the other two conditions with attention outside the RF were not significantly different (post hoc Tukey - Kramer test,  $p > 0.34$ ). A small enhancement in activity in the condition in which attention is directed ipsilateral to the RF relative to that when attention is directed to the contralateral hemifield can be seen in Figure 4 (compare green to blue line) but the difference between the two conditions did not reach significance. Given that FEF RFs can sometimes extend to both quadrants in the same hemifield we cannot rule out that this small enhancement reflects responses of neurons with slightly larger RFs. Similar results were obtained from the non normalized data as well as when normalization to the mean response was used. Note that by 600ms following the color change of the target the monkey had released the bar and the trial was terminated. This is the reason why responses in the attend inside RF condition drop at approximately 600ms after the color change (Figure 4, red line).

#### ***3.2.4. Effect of a color change on sustained responses in FEF. Comparison of firing rates before and after the color change***

An important question that one can ask in our experimental paradigm is whether neuronal responses during sustained attention are similar before and after a distractor color change. One could expect that with attention directed outside the RF neuronal responses before the color change and after the color change should be similar reflecting the activation levels during sustained spatial attention. Alternatively, given that following a distractor color change and as time progresses it becomes more likely that the target will change color, one could expect higher responses following a color change indicative of increased anticipation or vigilance.

To explore this issue further we measured the difference in response levels before and after the color change for the two “attend outside RF” conditions. Moreover, we compared the responses in these two conditions after the color change with those of the “attend in RF” condition before the color change. To this end, we measured firing rates in a 400ms window before the color change (Figure 4, -0.4-0s) and in a window 400-800 ms after the color change (Figure 4, 0.4-0.8s). We found that neuronal responses in the attend in RF condition (Figure 4, red line) before the color change were significantly higher compared to those in the “attend outside RF” on the contralateral hemifield (Figure 4, blue line), both before and after the color change (repeated measures ANOVA  $p < 0.05$  and post hoc Tukey - Kramer test  $p < 0.05$  in both cases; compare Figure 4 red line -0.4-0s to blue line -0.4-0s and to blue line 0.4-0.8s). Moreover, firing rates in the “attend outside RF” condition after the color change were significantly higher compared to those before the color change (post-hoc Tukey - Kramer test,  $p < 0.05$ , Figure 4, compare blue line before and after the color change). These results indicate that the color change of a distractor results in an increase in sustained activity of neurons with RFs at the distractor’s location even though attention is voluntarily directed to the contralateral hemifield. This could be due to increased vigilance as mentioned above. However, neuronal responses remain well below the level of activity they attain when attention is directed inside their RF.

Results were largely similar for the condition in which attention was directed outside the RF but to the ipsilateral to the RF hemifield. Responses were significantly different across the three conditions before and after the color change (repeated measures ANOVA,  $p < 0.05$ ) with the pre-color change “attend in RF” response displaying a significant enhancement compared to the pre-color change “attend outside RF” (ipsilateral hemisphere) response (Figure 4, compare red and green lines,

post hoc Tukey - Kramer test,  $p < 0.05$ ). Moreover, responses in the “attend outside RF” (ipsilateral hemifield) condition were significantly higher following the color change compared to those before the color change (Figure 4, compare green line before and after the color change, post hoc Tukey - Kramer test,  $p < 0.05$ ). The only difference here was that following the color change and with attention outside the RF in the ipsilateral hemisphere, responses did not differ significantly from those in the “attend inside RF” condition before the color change (post hoc, Tukey - Kramer test,  $p = 0.18$ ). This could be due to the larger FEF RFs, which for some neurons may encompass both quadrants in the same hemisphere.

### ***3.2.5. Effect of spatial attention on V4 neuronal responses before the color change***

The effect of attention on V4 neuronal responses was also examined in the same way as outlined in paragraphs 3.2.1-3.2.4 for FEF neuronal responses. Firstly, we compared neuronal responses among all three conditions in a 400ms window before the color change to assess the effect of spatial attention. As expected, directing attention to different locations led to statistically significant changes in neuronal responses (one way ANOVA  $p < 0.01$ , Figure 5; time period -0.4-0s).

In more detail, directing attention inside the RF caused a significant increase in neuronal activity compared to the other two conditions (Figure 5, compare red to blue and green lines, -0.4-0s; post-hoc Tukey-Kramer test,  $p < 0.01$  for both comparisons). Contrary to FEF neuronal responses, directing attention to the contralateral hemifield also caused a statistically significant difference in activity between the two “attend outside RF” conditions (Figure 5, compare blue to green line, post-hoc Tukey-Kramer test,  $p < 0.01$ ). Consequently, the results indicate that neuronal responses before the

color change are influenced not only by whether attention is directed inside or outside the RF, but also by the exact locus of attention relative to the RF's position (contralateral or ipsilateral to the RF). The same results were obtained when the statistical analysis was carried out on the non-normalized data as well as on the normalized to the mean response data.

This is an important albeit not unexpected finding. Our results show that in V4 with attention at one location, all representations of stimuli located at a distance but within the same hemifield are more suppressed compared to those on the other hemifield. This could be explained by stronger competitive interactions between neuronal populations within the same hemisphere as compared to those across hemispheres and will be further discussed in the Discussion section.

### ***3.2.6. Effect of a color change inside the RF on V4 neuronal responses***

Following the examination of V4 neuronal responses before the color change, we examined their activation levels 110 to 230ms after the stimulus' color change inside the RF. Similar to FEF neuronal responses, this time window includes the peak activation of the V4 neurons, due to the color change inside the RF. Our results showed that neuronal firing rates were influenced by the locus of attention (inside vs outside RF). Specifically, we found a significant increase when attention was directed inside the RF compared to the other two conditions, in which attention was directed outside the RF (one-way ANOVA,  $p < 0.05$ , post-hoc Tukey - Kramer test,  $p < 0.01$  for both comparisons, Figure 5, compare red to blue and green lines, right after the color change at peak activation). The difference was not significant between the two

conditions in which attention was directed outside the RF (post - hoc Tukey –Kramer test,  $p=0.98$ ).

Thus, contrary to FEF, where the color change inside the RF induced the same activity regardless of the locus of attention, neurons in V4 maintain a higher level of activity during the color change when attention is directed to that location. This could indicate that during maintenance of attention to a location V4 neurons can still discriminate whether a salient event occurring at any location is behaviorally relevant or not.

### ***3.2.7. Effect of spatial attention on V4 neuronal responses following the color change***

The results on V4 neuronal responses so far highlight the strong effect of spatial attention on the magnitude of neuronal responses even during a highly salient event such as a color change. We next asked whether the effect of spatial attention continues to similarly affect neuronal responses 300-500ms after the color change. Indeed, we found a statistically significant difference among the three conditions during this time period (Figure 5; one-way ANOVA,  $p<0.05$ ). In particular, neuronal responses were higher when attention was directed inside the RF (post hoc Tukey - Kramer test,  $p<0.05$  for both comparisons). Interestingly, a second peak in activity occurred at approximately 450ms following the color change inside the RF in the “attend inside RF” condition (Figure 5; red line). This most probably corresponds to a cognitive aspect of the realization that the color change was the behaviorally relevant event that required a response. However, we cannot rule out the possibility that this

increase in activity was related to the upcoming response since the monkey in this case had to respond by releasing a bar.

Comparison of neuronal responses between the two “attend outside RF” conditions showed that neuronal responses were relatively higher when attention was directed to the contralateral to the RF location compared to the condition where attention was directed ipsilateral to the RF (post-hoc Tukey-Kramer test,  $p < 0.05$ ; Figure 5; blue and green line respectively). As mentioned above this most probably reflects the stronger competition between same hemisphere populations, which results in stronger suppression of neuronal responses for stimuli located outside the RF within the same hemifield with the locus of attention.

### ***3.2.8. Effect of a color change on sustained responses in V4. Comparison of firing rates before and after the color change***

Similar to our analysis in the FEF, we also examined the effect of the color change on sustained responses of V4 neurons. To this end, we compared firing rates before and after the color change (Figure 5, -0.4-0s and 0.4-0.8s respectively). These comparisons showed that with attention outside the RF, neuronal responses significantly increased following the color change compared to the pre-color change levels both for the ipsilateral and the contralateral to the RF position (repeated measures ANOVA  $p < 0.05$ , post-hoc Tukey - Kramer test,  $p < 0.05$ ; Figure 5, compare blue line before and after the color change and green line before and after the color change). This could be due to increased vigilance as mentioned above as the monkeys expected that the next color change might be the relevant one to which they should respond.



Moreover, we compared responses in the “attend outside RF” conditions after the color change to responses before the color change in the “attend inside RF” condition. When attention was directed to the ipsilateral to the RF location responses following the color change although higher than before the color change remained lower than those before the color change in the attend inside RF condition (repeated measures ANOVA,  $p < 0.05$ , post-hoc Tukey - Kramer  $p < 0.05$ ; Figure 5 compare green line following the color change to the red line before the color change). By contrast, when attention was directed to the contralateral to the RF location, responses following the color change were not significantly different compared to those before the color change in the “attend inside RF” condition (repeated measures ANOVA,  $p < 0.05$ , post-hoc Tukey - Kramer  $p > 0.05$ ; Figure 5 compare blue line following the color change to the red line before the color change).

### **3.3. Effect of a stimulus color change outside the RF on neuronal responses in FEF and area V4 when attention is directed inside the RF**

The second set of conditions we studied aimed at exploring further the effect of an irrelevant color change on neuronal responses when attention is directed inside the RF. We included trials from three conditions as described in the first paragraphs of section 3. In two conditions we included trials in which attention was directed inside the RF and the distractor outside the RF, on the contralateral or ipsilateral to the RF position, respectively, changed color. In a third control condition we included trials in which attention was outside the RF, at either the ipsilateral or contralateral to the RF position, whereas the color change occurred inside the RF. The population average responses for FEF and V4 are shown in Figures 6 and 7, respectively.

### 3.3.1. Effect of spatial attention on FEF neuronal responses before the color change

In the time period before the color change we found significant differences among the three conditions (one-way ANOVA,  $p < 0.05$ ). As expected neuronal responses were significantly enhanced in the two “attend inside RF” conditions relative to those in the “attend outside RF” condition (-0.4-0s, Figure 6, compare blue and green lines to red line; post hoc Tukey-Kramer test,  $p < 0.05$  in both cases).

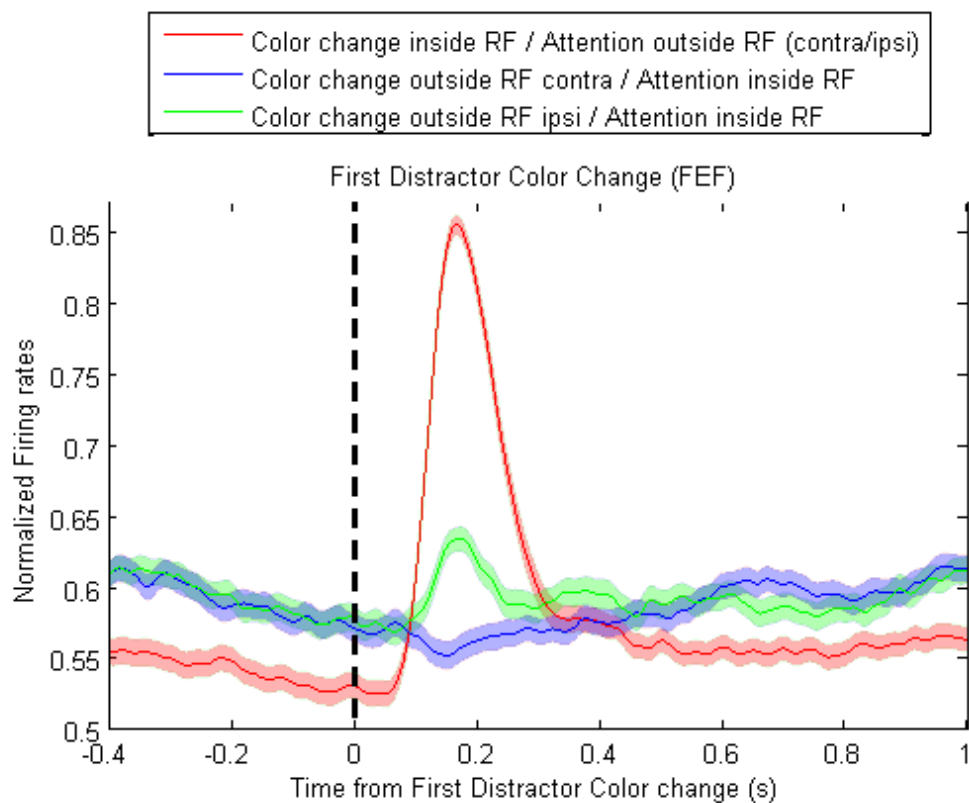


Figure 6. Normalized (to the peak response) firing rate population averages of FEF neuronal responses. Vertical dashed line indicates the time of color change of the first distractor that changed color. Red line depicts population response with attention outside the RF around the time that the distractor inside the RF changed color; blue line, response with attention directed inside the RF and the distractor’s color change occurring on the contralateral to the RF hemifield; green line, response with attention directed inside the RF and the distractor’s color change occurring outside the RF at the ipsilateral to the RF location.

During the same period we found no significant difference between the first two conditions in which attention was directed inside the RF (Figure 6 green and blue lines; post hoc Tukey - Kramer test,  $p = 0.82$ ). Results were the same for the non normalized data as well as when they were normalized to the mean response.

### ***3.3.2. Effect of an irrelevant color change outside the RF on FEF responses***

We next compared neuronal responses in the three conditions in a time window right after the color change, namely 100-300ms after the color change (Figure 6). This is typically the period during which visual neurons exhibit their peak response when visually stimulated. Although in two out of the three conditions studied there was no visual change inside the RF we sought to see whether the non stimulated neurons would show a transient decrease in activity indicative of attention being transiently captured by an event occurring outside the RF. For comparison, we also plotted the response when the color change occurred inside the RF and attention was directed outside the RF. As expected, due to this transient increase in activity significant differences were found between the three conditions (one way ANOVA,  $p < 0.05$ ). All three pairwise comparisons showed significant differences (post hoc Tukey-Kramer test,  $p < 0.05$  in all three cases). The transient increase in activity in the condition where the color change occurred in the ipsilateral to the RF position (Figure 6; green line) is attributed to the larger RFs, which most probably encompassed this position.

More importantly, however, we wanted to examine, whether activity decreased when the change occurred outside the RF on the contralateral hemifield. To this end, we compared the average firing rate in the “attend inside RF – Color change contra” condition, 110-250ms after the color change to the firing rate in the same condition

within a 150ms window before the color change(-0.15-0s). We found that, indeed, activity was significantly lower after the color change (paired t-test,  $p < 0.05$ ). This result indicates that an irrelevant color change can momentarily withdraw attentional resources to the location of the irrelevant change. Thus, even under voluntary control of attention, salient distracting events can decrease the attentional focus and this is manifested by a decrease in the activity of neurons encoding the attended location/object.

### ***3.3.3. Late effects of an irrelevant color change on FEF neuronal responses***

To assess how the irrelevant color change affected FEF neuronal responses long after the color change and whether activity returned to the pre-color change level, we examined activity in a window 600ms up to 900ms after the color change (Figure 6). We will refer to this as the late period after the color change. We compared neuronal responses during this late period to the activity levels within a 300ms window before the color change (-0.3-0s) for the “attend outside RF” condition (Figure 6, red line). The statistical analysis showed that following the color change neuronal responses were higher compared to the levels before the color change (paired t-test,  $p < 0.05$ ). This confirms our previous findings indicating that even when attention is located outside the RF, changes inside the RF can have long – lasting effects on neuronal responses. This could mean that attention remains within the RF or is now divided between two positions for at least 600-900ms. Alternatively, this increased activation could reflect increased vigilance as the probability that the next color change is that of the target increases.

### 3.3.4. Effect of spatial attention on V4 neuronal responses before the color change

In V4, neuronal responses before the color change depended on the locus of attention as expected (-0.4-0s before the color change, one way ANOVA,  $p < 0.05$ ; Figure 7). There were no significant differences between responses in the two “attend inside RF” conditions (Figure 7; green and blue lines, post-hoc Tukey-Kramer test,  $p = 0.11$ ), but responses in both were significantly higher than those in the “attend outside RF” condition (Figure 7, compare blue and green lines to red line before the color change; post-hoc Tukey - Kramer test  $p < 0.0001$ ). Analyses of both the non normalized data and the normalized to the mean response data confirmed the above results.

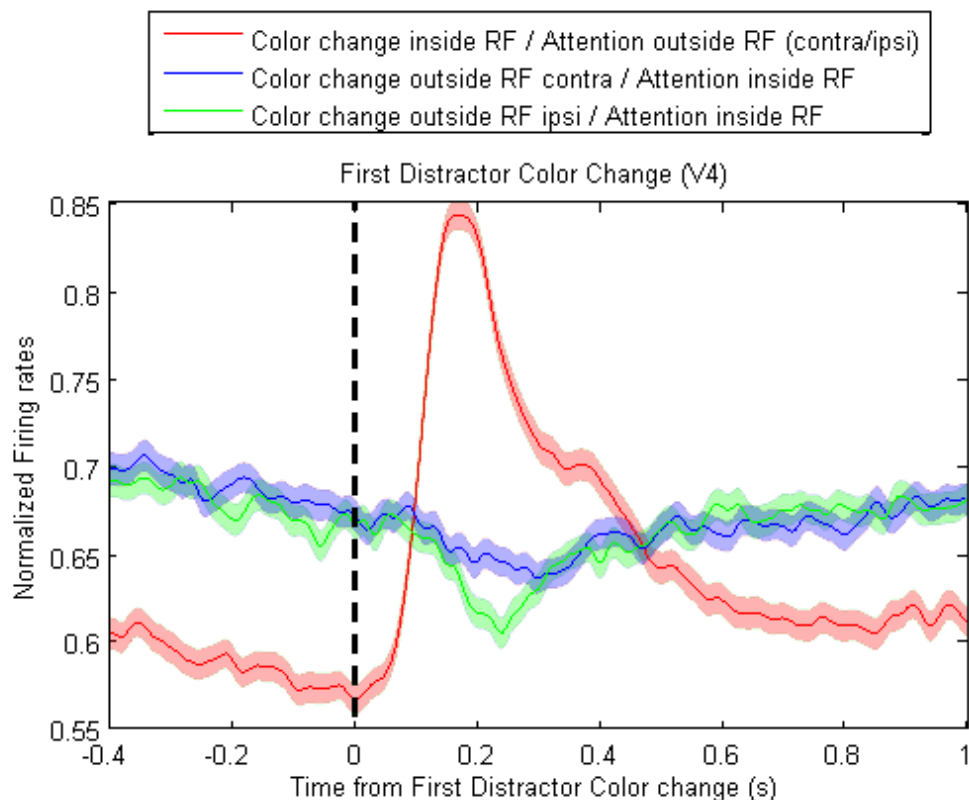


Figure 7. Normalized (to the peak response) firing rate population averages of V4 neuronal responses. Vertical dashed line indicates the time of color change of the first distractor that changed color. Red line depicts population response with attention outside the RF around the time that the distractor inside the RF changed color; blue

line, response with attention directed inside the RF and the distractor's color change occurring on the contralateral to the RF hemifield; green line, response with attention directed inside the RF and the distractor's color change occurring outside the RF at the ipsilateral to the RF location.

### ***3.3.5. Effect of an irrelevant color change outside the RF on V4 responses***

The next step was to compare the V4 neuronal responses 100 - 300ms after the color change in the three conditions. As expected, due to the transient increase in activity in the "attend outside RF" condition where the distractor inside the RF changed color (Figure 7, red line) significant differences were found between the three conditions (one way ANOVA,  $p < 0.05$ ). All three pairwise comparisons showed significant differences (post hoc Tukey - Kramer test,  $p < 0.05$  in all three cases).

Our main goal, however, was to examine, whether with attention inside the RF, activity decreased when an irrelevant color change occurred outside the RF. To this end, we compared the neuronal responses in each "attend inside RF" condition within a 250ms window before the color change (-0.25-0s) to its respective responses within a 200ms window after the color change (0.1-0.3s). We found that firing rates were significantly lower in both conditions (paired t-test  $p < 0.05$ ). This confirms our FEF results and indicates that even when attention is guided voluntarily to an object, an irrelevant salient event that occurs outside the locus of attention can momentarily capture our attention. This is manifested as a transient decrease in activity of the neurons that encode the location where attention is voluntarily directed. Interestingly, this decrease in activity was stronger for the condition in which the color change occurred in the ipsilateral to the RF position (post hoc Tukey - Kramer test  $p < 0.05$ ; Figure 7, compare green to blue line right after the color change). This finding is in

agreement with our earlier suggestion that positions ipsilateral to the locus of attention engage in stronger competitive interactions.

### ***3.3.6. Late effects of an irrelevant color change on V4 neuronal responses***

Finally, we examined the possible long-lasting effect of an irrelevant color change on V4 neuronal responses. To this end, we compared neuronal responses within a 300ms time window (0.6-0.9s following the color change) in the “attend outside RF” condition (Figure 7; red line) to the response in the same condition before the color change (average response-0.3-0s before the color change). Neuronal responses were significantly higher following the color change (paired t-test,  $p < 0.001$ ) indicating again a possible effect of vigilance.

## CHAPTER 4

### DISCUSSION

The present study provides additional evidence on the role of FEF and V4 in visual attention. More specifically, this study examined how V4 and FEF neuronal responses are modulated by spatial attention, as well as by salient behaviorally irrelevant events during covert attention processes.

In a typical attention experiment, subjects are presented with an array of different stimuli one of which is the target they are supposed to attend to. In such experiments many different features can be employed to guide attention and dissociate targets from distractors. Which features are the most appropriate to be used in cognitive research studies is still a controversial issue. However, color is probably the most commonly used feature in such experimental procedures. Hamker (2004) suggests that color is salient, and thus it is not only easier to be detected by the observer, but also has a stronger effect than other features, such as shape. Based on these, in the current study, we also defined the target stimulus based on its color on a trial by trial basis. Moreover, since V4 neurons are known to be color selective (Shein and Desimone, 1990), we expected that they would be driven more strongly by the attended color.

Both FEF and V4 have been shown to modulate their responses with attention. For instance, several studies have established the role of FEF in spatial selection and attention (Schall et al 1995; Thompson et al 1997; Moore and Fallah 2001; Gregoriou et al 2009). These studies have mainly shown that FEF neurons with receptive fields at the attended location increase their firing rate. Psychophysical studies have also



suggested that in oculomotor tasks the effect of areas implicated in spatial selection may also be exerted through inhibition of locations associated with the distractor stimulus (Van der Stigchel et al., 2007). Whether this is also the case for covert attention and whether such an effect can be seen in FEF neuronal responses has not been studied. Similarly, area V4 is one of the most studied visual areas in attention paradigms. Both spatial and feature attention have been shown to modulate neuronal responses in V4 (Moran and Desimone, 1985; Motter, 1994; Treue and Maunsell, 1996; Luck et al., 1997; Reynolds et al., 1999; McAdams and Maunsell, 2000; Burrows et al., 2014).

Attention is considered to function as a selection mechanism, which filters out irrelevant information. However, the neural mechanisms of this selection process are far from clear. On the one hand, even when attention is guided by specific behavioral demands in what is commonly called a “top-down” manner, salient stimuli that can occur unexpectedly should still be encoded even when irrelevant to the current behavioral goals. For example, while driving and looking for a specific restaurant it is important to notice the cat that may suddenly jump in front of your car. How such salient events are encoded in the brain when attention is guided by behavioral goals has not been studied. On the other hand, although a selection mechanism involves competitive interactions between different stimuli (Desimone and Duncan, 1995) it is not known how these are implemented across and within the two hemispheres. The goal of this study was to address these issues from extracellular recordings in FEF and V4.

We found that neuronal responses were enhanced when attention was directed within the neurons' RF in both areas during a period that sustained attention on a visual stimulus was required. This is in accordance with results from previous studies,

which have shown that both FEF and V4 neurons increase their firing rate and that neuronal populations are more active when attention is directed to stimuli located inside their RFs (Thompson et al., 1997; Reynolds et al 1999, Kastner et al 2001; Gregoriou et al 2009). Although the effects of attention are more prominent with multiple stimuli inside the RF (Moran and Desimone, 1985) here, we confirm that increased activity with spatial attention can also occur in less crowded scenes when a single stimulus occupies the RF (Kastner et al 2001; Kastner and Ungerleider 2001).

Although the effect of spatial attention during sustained attention was similar for the two areas, we found that a salient event affected neuronal responses in FEF and V4 differently. More specifically, when a color change occurred inside the RF of the recorded neurons, responses in the FEF were the same regardless of where attention was directed before the salient event. On the contrary, in V4, neuronal responses were significantly higher when attention had been directed inside the RF of the recorded neurons and lower when the salient event occurred at a non-attended distractor location, i.e. it followed the same pattern to that observed during sustained attention.

The difference between the two areas in their responses to highly salient events is shown for the first time and suggests that FEF and V4 have distinct roles in encoding salient stimuli, at least when attention is guided voluntarily to specific stimuli. The fact that V4 responses encode the location of the target even in the presence of distracting salient events indicates that V4 neurons are capable of filtering out salient stimuli when they are irrelevant to behavior. On the other hand, the fact that FEF neurons respond to salient events regardless of their behavioral relevance is in agreement with the suggested role of FEF in the construction of a saliency map (Thompson and Bichot, 2005). According to this idea, the FEF represent the locations of stimuli in the visual field by a level of activity that represents their physical and

behavioral saliency, i.e. their ability to stand out in a crowded scene and their similarity to the target. The pattern of FEF responses we observed could contribute to the allocation of attention to salient events outside the current behavioral goals that could nevertheless, be important for the organism's survival.

To assess whether there is any neuronal evidence that attention can indeed be captured by a salient irrelevant event occurring outside the locus of attention, we examined neuronal responses with attention inside the neuronal RF during a color change outside the RF. If attention is reflected on the neuronal responses of FEF and V4 one would expect to see a decrease in activity of the neurons that encode the location of the target when the color changed of a distractor occurred. Indeed, both in V4 and FEF we found a significant transient decrease in activity in neurons encoding the RF location during the color change outside the RF. This could indicate that attention was transiently captured by the salient irrelevant color change of the distractor and was therefore transiently shifted to the distractor stimulus. Therefore, based on the neuronal evidence it is tempting to suggest that even under top-down guidance, when attention is voluntarily directed on an object, salient events occurring elsewhere can transiently capture attention. However, we do not have any behavioral evidence that this was indeed the case, as we did not test whether the animals were still able to respond to the target location during this time.

Nevertheless, our data demonstrate that a salient event occurring outside the RF of a neuron results in a decrease in the neuron's firing although nothing changed inside the RF. At the neuronal level, this could be achieved through inhibitory, competitive interactions between neuronal populations encoding the different locations. Such competitive interactions have been suggested to underlie selective attention and experimental data have provided additional support to this idea

(Desimone and Duncan, 1995; Reynolds et al 1999). Initially, competitive interactions between neuronal populations encoding different stimuli were described in visual areas with larger RFs, which stand higher up in the visual hierarchy. It has been suggested that larger RFs can accommodate several objects and thus that competitive mechanisms are stronger locally between neurons that represent stimuli within a single RF (Desimone and Duncan 1995, Reynolds et al 1999). However, although the sensory suppression is more effective inside the RF, such competitive mechanisms can also be found between neuronal populations with non-overlapping RFs (Kastner et al., 2001, Kastner & Ungerleider, 2001).

Interestingly, when we compared the strength of these competitive interactions in V4 within one hemisphere and across the two hemispheres we found that competition was more prominent in the former case. Specifically, with attention inside the RF there was a larger decrease in activity when the distractor color change occurred at the location ipsilateral to the attended stimulus, compared to the decrease associated with a color change at the contralateral location. This indicates stronger competition between neuronal populations encoding different locations within the same hemisphere. We were not able to address the same question in FEF. FEF neurons have larger RFs, which often encompassed two of our stimuli. Thus, it was not easy to assess the effect of hemifield with our three stimuli paradigm in the FEF, since only one location was clearly outside the RF.

Finally, we also examined how neurons in the two areas modulated their responses with attention outside their RF. One interesting finding concerns the period long after a color change inside the recorded neurons' RF (more than 500ms following the color change). We found that neurons encoding an unattended location increased their firing rates in both FEF and V4 after a color change of a distractor

inside their RF. This result was surprising as these neurons did not encode an attended location and the observed increase was too late to be attributed to the color change. The most parsimonious explanation for this finding is that the observed increase reflected enhanced vigilance/alertness and anticipation for the next color change that was more likely to be that of the target.

This suggestion is in agreement with studies that have shown enhancements in firing rates in several brain areas due to increased alertness. Cano and colleagues (2006) found increased neuronal responses during alert (compared to non-alert) states in the lateral geniculate nucleus (LGN) of rabbits. Moreover, imaging studies, have shown that several frontal, parietal, thalamic and brainstem areas are activated during intrinsic alertness or arousal (Sturm and Willmes, 2001). It is thus possible that the enhanced activation we observed in FEF and V4 has a thalamic origin and can contribute to global arousal through modulations of brainstem circuits known to directly control general arousal.

All in all, our results show that neuronal responses in both FEF and V4 are modulated by several different factors. To name a few these include the spatial locus of attention, the behavioral relevance of visual events, the location of conspicuous visual events relative to the attended location and anticipation and global arousal. We have highlighted similarities and differences in the way FEF and V4 responses are affected by these factors. Future studies using experimental designs that employ behavioral measures of distractibility could further explore how the above mentioned factors affect behavior and how behavioral measures correlate to the modulation in activity we observed in our paradigm.

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