Hand Modulation of Visual, Preparatory, and Saccadic Activity in the Monkey Frontal Eye Field

David Thura1,3, Fadila Hadj-Bouziane1,4, Martine Meunier1,2 and Driss Boussaoud1

1Institut de Neurosciences Cognitives de la Méditerranée, UMR 6193, Centre National de la Recherche Scientifique and Aix-Marseille Université, 13402 Marseille, France, 2Espace et Action, U864, Institut National de la Santé et de la Recherche Médicale and Université Claude Bernard Lyon 1, 69676 Bron, France, 3Current address: Groupe de Recherche sur le Système Nerveux Central, Département de Physiologie, Université de Montréal, C.P. 6128, succursale Centre-ville, Montréal, Québec, Canada H3C 3J7 and 4Current address: Laboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892-4415, USA

Address correspondence to Dr David Thura. Email: david.thura@umontreal.ca.

Behavioral studies have shown that hand position influences saccade characteristics. This study examined the neuronal changes that could underlie this behavioral observation. Single neurons were recorded in the frontal eye field (FEF) of 2 monkeys as they executed a visually guided saccade task, while holding their hand at given locations on a touch screen. The task was performed with the hand either visible or invisible, in order to assess the relative contribution of visual and proprioceptive information on hand position. Among the 224 neurons tested, the visual, saccadic and/or preparatory activity of more than half of them was modulated by hand position, whether the hand was visible or invisible. Comparison of lower (hand’s workspace) and upper (out of reach) visual targets showed that hand modulation was predominant in the hand’s workspace. Finally, some cells preferred congruency of hand and target in space, others preferred incongruency. Interestingly, hand modulation of saccadic activity correlated with hand position effects on saccade reaction times. We conclude that visual and proprioceptive signals derived from the hand are integrated by FEF neurons. These signals can modulate target selection through attention and allow the oculomotor system to use hand-related somatosensory signals for the initiation of visually guided saccades.

Keywords: attention, eye-hand coordination, frontal cortex, monkey, multisensory integration

Introduction

In our everyday life, our eyes and hands, the 2 crucial effectors with which we apprehend the world, must adapt their relationship to meet our current needs. They may have to move together toward a common target (look at and reach to grasp an object), to move separately each toward its own target (grasping a cup of tea while reading), or to move individually while the other remains temporarily static (exploring a painting, without touching it). Despite its apparent simplicity, the harmonious interplay of eye and hand movements relies in fact onto a complex brain machinery, which is yet to be understood (for reviews, see Bekkering and Sailer 2002; Carey et al. 2002). But, while most neurophysiological work has concentrated on how the brain uses eye-related signals to plan and execute accurate limb movements, little attention has been devoted to the reverse question, that is, how oculomotor centers of the brain use limb-related signals to generate eye movements. Yet, hand-to-eye influences are just as important to developing sophisticated computational models of sensorimotor transformations as are eye-to-hand effects.

At the behavioral level, perhaps the most remarkable evidence for close eye-hand interactions is the fact that, 1) static eye position can be used as a target for hand movements (e.g., point to where you are looking at, in the absence of a visual target; Bridgeman and Stark 1991; Blouin et al. 2002), 2) subjects can follow the displacement of their unseen fingertip with their eyes (Levine and Lackner 1979; Vercher et al. 1997; Ariff et al. 2002), and 3) gaze is anchored to the target of an ongoing pointing movement (Neggers and Bekkering 2000, 2001). These and various other observations (e.g., Carey 2000) indicate that the arm sensory (afferent) as well as motor (efferent) signals are used to generate and control eye movements and vice versa.

Since the eyes provide visual information which guides hand movements, effects of saccadic eye movements, and gaze direction on subsequent arm-reaching movements have been thoroughly studied (e.g., Prablanc et al. 1986; Abrams et al. 1990; Vercher et al. 1994; Song and McPeek 2009). By contrast, reverse influences of arm movement and/or static position on saccade-generating circuits remain relatively unexplored. A handful of behavioral studies have reported arm-reaching effects on saccade latencies (Mather and Fisk 1985; Lünenburger et al. 2000; Engel and Soechting 2003), peak velocity (Epelboim et al. 1997; Snyder et al. 2002), trajectory (Tipper et al. 2001), or accuracy (Lünenburger et al. 2000). A few others have demonstrated that saccades toward a hand-displaced visual target are less accurate than those made to memorized visual targets (Ren et al. 2006, 2007) or addressed hand-eye interactions in human subjects instructed to look at the location of their unseen hand (Ariff et al. 2002; Nanayakkara and Shadmehr 2003). At a lower level, Fisk and Goodale (1985) have shown that biomechanical parameters of limb movements affect the kinematics of eye movements. This body of evidence suggests that the oculomotor system estimates the position of the hand using proprioceptive feedback, an effereence copy of the skeletomotor command and an internal model of the limb.

At the neuronal level, it is well established that the networks formed by the parietofrontal circuits play a key role in eye-hand coordination (see e.g., Boussaoud and Bremmer 1999; Battaglia-Mayer et al. 2006; Pesaran et al. 2010), and computational models have been proposed to explain coordinate transformations and eye-hand coordination (e.g., Henriques et al. 2002). These models suffer from the lack of neurophysiological data on how hand-related signals modulate neuronal...
activity in brain areas specialized for eye movements. In an early study, Werner (1993) have reported the existence of arm-related neurons in the superior colliculus, a subcortical structure well known for its role in eye movements. Later, Mushiake et al. (1996) found that saccade-related activity of neurons in the supplementary eye field (SEF) is different when the saccades are made with or without a reaching arm movement to the saccade target.

Given the lack of knowledge on how the hand affects the neuronal circuits of eye movements, we have investigated this issue in a visually guided saccade task where the hand was held static close to or away from the saccade target. Our aim in using a static hand, instead of a hand reaching, was to reduce efferent signals (motor command) and leave afferent, sensory signals (proprioception). Furthermore, beyond the sensorimotor aspects of hand effects, we hypothesized that the hand in the workspace would affect orientation of attention and ocular exploration. This hypothesis is supported by behavioral data. Indeed, Reed et al. (2006) have shown in humans that the hand (even when invisible) influences the detection of a visual target appearing in its vicinity. More recently, we (Thura, Hadj-Bouziane, et al. 2008) showed that the static hand position affects strongly saccadic reaction times (SRTs), both in macaque monkeys and human subjects. Here, we provide clear evidence that, under these conditions, the hand, whether visible or invisible, modulates neuronal activity in frontal eye field (FEF), a key structure in the control of eye movement. This modulation is a widespread phenomenon, especially for targets located in the hand’s workspace, affecting the activity of more than half of FEF neurons, whether visual, visuomotor, or purely motor. Overall, this study shows that the initiation of visually guided saccades is influenced by hand-related somato-sensory signals, from target selection to saccade execution.

Materials and Methods

Subjects

The monkeys were 2 adult males, monkey A, a Macaca fascicularis, and monkey S, a Macaca mulatta. Both were implanted, under anesthesia and aseptic conditions with a bolt for head fixation and a recording chamber over the hemisphere contralateral to the hand that the animal used to perform the task, that is, the right hand for monkey A and the left one for monkey S (see Thura, Boussaoud, and Meunier 2008; Thura, Hadj-Bouziane, et al. 2008). Surgery, testing procedures, and animal care were in accordance with the European Community’s Council Directive for the Care and Use of Laboratory Animals (86/609/EEC).

Setup

Monkeys were seated in a primate chair with the head fixed to the chair. They were trained to perform visually guided saccades toward 1 of 4 possible targets while holding their preferred hand at 1 of 2 possible locations on a touch screen. They were also taught using their nonactig hand at rest under the screen. Their actual behavior during testing sessions was monitored via a video camera placed above their heads. Eye position was recorded using a scleral search coil (Fuchs and Robinson 1966; monkey A) or an infrared camera (ISCAN, monkey S). The testing apparatus consisted of a resistive touch screen (36 × 27 cm) inclined at a 45° angle under a mirror onto which stimuli were projected from an above computer monitor (Fig. 1A). The semireflective properties of the mirror made the visual stimuli appear as if located on the underneath touch screen together with the hand. In this condition (“hand visible”), saccades were made while both visual and nonvisual, that is, tactile, proprioceptive, and motor signals from the hand were present. Insertion of a black paper board under the mirror made it fully reflective. Under this “hand invisible” condition, visual stimuli still appeared on the touch screen, but the hand was invisible to the monkey. Saccades were thus made while only nonvisual, presumably proprioceptive information was available about hand position. The experiments, including presentation of stimuli and delivery of reward, were controlled using the CORTEX software (The National Institute of Mental Health), which also served for behavioral (hand and eye position) as well as neuronal (online digitalized action potentials, see below) data acquisition.

 Experimental Design

A trial began with the presentation of a white square (2 × 2°) at the bottom left or the bottom right of the screen (11° from the center). This stimulus instructed the monkey to put his hand at that location and was turned off when the hand contacted the touch screen (Fig. 1B). Then, a white circle, the fixation point (FP, 0.25° diameter) appeared at the screen center, which the monkey had to fixate without moving his hand. After 500 ms of fixation, a peripheral target (white square, 1 × 1°) appeared at 1 of 4 potential locations corresponding to the 4 screen corners (10.3° from the screen center). The 2 lower targets were located immediately above the hand positions, that is, within the hand workspace, whereas the 2 upper targets were out of the hand’s reach. The monkey had to wait for the extinction of the FP (Go signal) before executing a saccade to the target. For nondelayed saccades, the Go signal coincided with the appearance of the target (Fig. 1C). For delayed saccades, a 500- or 1000-ms preparatory delay was introduced between target onset and the Go signal. A correct saccade (duration <50 ms, 300-ms fixation within ±1.5° around the target center) triggered the delivery of a liquid reward. If the animal moved the hand, interrupted hand contact with the touch screen or made the saccade before the Go signal, the trial was aborted. Except for a few neurons tested with 3 delays duration intermixed (see Results), different preparatory delay durations and vision conditions were tested in separate blocks of trials. By contrast, target location and hand position varied pseudorandomly from trial to trial within each block. Daily testing sessions varied in length depending on the monkeys’ motivation and included several blocks of nondelayed and delayed saccades, with or without hand vision. For the 2 targets located in the lower visual hemifield (hand’s workspace), the hand-target spatial configuration was termed “congruent” when the hand was near the target and “noncongruent” when the hand was far from it.

FEF Localization

The recording chamber was placed above the arcuate sulcus of each animal using magnetic resonance imaging (MRI), and FEF was localized within the chamber by means of intracortical microstimulation (Fig. 1D,E). Neuronal activity was first recorded using tungsten electrodes (FHC Instruments, impedance: 0.5–2 MΩ) to detect the surface of the cortex. Then, microstimulation was applied every 250 μm, with currents ranging from 5 to 100 μA. Each pulse was 0.2 ms in duration, stimulation frequency was 500 Hz, and the train duration was 40 ms. Each site where microstimulation-evoked contralateral saccades with currents <50 μA was considered as part of FEF (Bruce et al. 1985). In monkey S, an extensive mapping of the FEF region was performed and 5 of the identified sites subsequently recorded while the monkey performed the experimental task; in monkey A, 3 recording sites were identified using microstimulation and 3 neighboring sites considered as part of FEF on the basis of their visual and saccadic activity during the task (Fig. 1D,E).

Data Collection and Analysis

Saccade analysis was performed by deriving the horizontal and vertical eye position signals (sampled at a minimum of 240 Hz) with the use of custom MATLAB routines (The MathWorks, Inc.) based on a detection threshold. Saccade onset, used to determine SRTs, was defined as the first measure after the Go signal for which eye velocity exceeded 50°/s. The end point, used to assess saccade accuracy, was defined as the first measure after saccade onset for which velocity fell below 50°/s. The highest velocity value during saccade execution was taken as the eye peak velocity. These 3 parameters were analyzed using a 5-factor
analysis of variance (ANOVA) (monkey × target × hand × delay × vision). Trials with reaction times <80 ms or >500 ms (i.e., anticipatory and no response, respectively) were excluded from the statistical analysis.

For neuronal activity, action potentials were isolated on line using a waveform-based sorting software (MSD, Alpha Omega) during the recording sessions. Later, during off line processing, epochs of interest for statistical analyses were inspected visually on raster displays and histograms of the firing rate. Visual activity was defined as any significant change of activity within a 150-ms interval, from 50 to 200 ms after target onset, relative to a baseline activity taken during the fixation period. For delayed saccades, delay-related activity was defined as any significant change of activity occurring at least 200 ms after target onset and 50 ms after the Go signal relative to the same baseline activity. Saccade-related activity was defined as any significant change of activity occurring from 150 ms before to 50 ms after saccade onset relative to the preceding preparatory period. Neurons were all recorded with the delay task in order to dissociate visual from saccadic activity.

Target location and hand position effects were tested on the mean firing rate for each event-related activity occurring within the time windows defined above using either 2-factor (target × hand for cells recorded in only one vision condition) or 3-factor (target × hand × vision for cells tested under both hand vision conditions) ANOVAs.

The latency of FEF visual responses was determined by computing for each cell the mean firing rate across trials in successive bins of 10 ms. The latency was defined as the second bin, after target onset, at which mean activity differed significantly (paired-samples t-test) from the reference activity measured in a reference bin (−20/−20 ms before target onset). Likewise, the onset of saccadic activity was calculated by computing in each cell the mean activity across trials in successive bins starting 30 ms before saccade onset. Saccade onset was defined as the second interval (bin) in time, relative to saccade onset, at which mean activity in a specific bin differed significantly from the mean activity calculated in a reference bin (−320/−300 ms before saccade onset).

Correlation between neuronal activity and behavior was explored trial-by-trial using Pearson’s product-moment correlation coefficient r. More precisely, we analyzed the correlation between 2 temporal parameters: SRTs and latencies of the peak of saccadic activity. We defined the latter as the time after the Go signal at which the spike density function (computed on each trial by convolving the spike train with a Gaussian of standard deviation equal to 20 ms) reached its maximal value. Thus, for each trial, 2 latencies were measured: one reflecting the monkey’s behavior and one directly related to neuronal activity. We tested the correlation between the 2 parameters for each neuron separately and across a population of selected cells in order to emphasize the effects of hand position on each of them. For all statistical analyses, the significance level was set to 0.05.

Results

Behavior
Hand position effects on saccade characteristics (latency, peak velocity, and end point) were tested on a total of 11 838 trials...
(5897 trials for monkey A and 5941 trials for monkey S). As the hand position had no reliable effects on the saccade velocity peak or its end point, the following results will focus on saccade latencies or SRTs. Most of the behavioral findings have been reported earlier (Thura, Hadj-Bouziane, et al. 2008). Briefly, we found that the presence of the static hand in the workspace did affect SRTs, whether it was visible or not. We also observed that this modulation was highly time dependent, as hand-target proximity retarded immediate saccades, whereas it had to hasten delayed saccades. We will describe additional behavioral effects not included in the previous paper and which are relevant to the neuronal data.

The Hand Modulates SRTs for Lower but not Upper Targets
Lower targets were located within the hand’s workspace, whereas upper targets were located outside the hand’s reach. We tested whether hand effects extended to saccades falling outside its workspace. Monkey A and monkey S, respectively, performed 1298 and 682 saccades to the 2 upper targets, all in the delay task, with their hand either visible or invisible (SRTs’ mean: 314 ms, range: 80–196 ms, standard deviation: ±82 ms). In both monkeys, hand position had no significant effect on the SRTs of delayed saccades toward the upper visual field (hand effect: $F_{1, 193} = 1.68, P = 0.19$), whether the hand was visible or invisible (hand × vision interaction: $F_{1, 193} = 0.004, P = 0.95$). The behavioral impact of hand position thus appeared largely, if not exclusively, limited to the hand’s workspace.

Neuronal Activity, General Properties
As detailed in Table 1, hand position effects were studied on a total of 96 cells with visual responses and 172 with saccadic activities. Each cell was recorded for 30–100 trials. Visual responses started on average 62.3 ± 13.8 ms (range: 40–100 ms) after stimulus onset, whereas saccadic activity appeared on average 86.5 ± 44.9 ms (range: −260 to +0 ms) before saccade onset. Most cells were spatially selective (visual: 80/96, 83%; saccadic: 149/172, 87%), with a preference for contralateral targets in 56% (45) of the visual cells and 70% (105) of the saccadic cells.

Hand Position Modulates the Magnitude of Neuronal Activity in FEF
More than half of the recorded neurons displayed significant differences in their firing rate depending on hand position in both monkeys (Table 2). Indeed, the hand modulated 64% of visually responsive cells in monkey A (59% in monkey S) and 52% of saccadic cells (63% in monkey S). There was a tendency for purely movement cells to be modulated by hand position more often than visuomotor cells (56 vs. 49%, respectively), whereas visual responses were equally modulated in purely visual cells and visuomotor ones. This hand modulation typically influenced the magnitude of neuronal response for the preferred target. Figures 2 and 3 illustrate examples of hand modulation of visual and saccadic activity, respectively. In Figure 2, the neuron responded preferentially to the target in the lower left quadrant, and the hand modulated specifically the neuron’s visual response to this target, not to the other ones. In Figure 3, the neuron’s preferred saccade direction is to the lower left target, and as for the visual response, the neuron’s activity for that particular direction was significantly modulated by hand position. For each neuron, the optimal activity could reflect a combination of factors, including hand-target congruency and/or hand visibility/invisibility (see below).

Both Visual and Nonvisual Signals Contribute to Hand Modulation
A sample of 98 cells (39 visual, 59 saccadic; Table 2) was successfully tested both with and without hand vision. For both visual and saccadic activity, a minority of cells (visual: 25% and saccadic: 20%) displayed the same magnitude of hand modulation, whether the hand was visible or invisible. In a large majority of cases, the hand effect was significant in only one hand vision condition. Interestingly, as in the examples illustrated in Figure 4, hand position affected visual responses of most cells (49% of the cases) only when it was visible, whereas saccadic responses were preferentially (54% of the cases) modulated by the invisible hand only. When only ‘purely’ motor cells (i.e., saccadic) were taken into consideration, the proportion favoring the invisible hand remained high (51%). By contrast, for strictly visual cells, the proportion of cells significantly modulated only under the visible condition increased markedly (8/11, 72%).

Hand Effects: Spatial Aspects

Hand Modulation Is More dominant in the Lower than in the Upper Visual Hemifield
The hand modulation of FEF visual and saccadic activity was not evenly distributed over the lower and upper visual fields (Table 2). In a subset of cells tested with the 4 targets and with a spatial preference for the lower targets ($n = 24$; 13 visual and

### Table 1

<table>
<thead>
<tr>
<th>Number of neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recorded</td>
</tr>
<tr>
<td>Task related</td>
</tr>
<tr>
<td>Monkey A</td>
</tr>
<tr>
<td>Monkey S</td>
</tr>
<tr>
<td>Visual (target)</td>
</tr>
<tr>
<td>Delay only</td>
</tr>
<tr>
<td>Movement (saccade)</td>
</tr>
<tr>
<td>Visual and movement</td>
</tr>
<tr>
<td>Visual and delay</td>
</tr>
<tr>
<td>Delay and movement</td>
</tr>
<tr>
<td>Total visual activities tested</td>
</tr>
<tr>
<td>Total delay activities tested</td>
</tr>
<tr>
<td>Total saccadic activities tested</td>
</tr>
</tbody>
</table>

Note: The first column reports the overall effect, the second, third, and fourth columns, respectively, specify the cells responding exclusively for the visible versus invisible hand, the lower versus upper visual targets, and the congruent rather than the noncongruent hand-eye spatial configuration.
11 saccadic), the response to the preferred target was significantly modulated by position of the hand for a majority of neurons (71%). By contrast, among the cells with a preference for the upper targets (n = 31; 9 visual and 22 saccadic), only 29% were significantly modulated by the position of the hand. Hand modulation of activity for the nonpreferred target was atypical but did occur (Fig. 5) and revealed a similar albeit less marked, spatial bias. Namely, 45% of the nonpreferred responses for lower visual targets (n = 20; 14 saccadic and 6 visual) were significantly affected by hand position. This proportion dropped to 23% for responses to nonpreferred, upper visual targets (n = 21; 13 saccadic and 8 visual). In other words, when the nonpreferred target is within the hand’s workspace, it is more likely to be modulated by hand position than when it is outside the workspace.

**Differential Effects of Hand-Target Spatial Congruency on Visual Versus Saccadic Activity**

Based on the close interactions between the eye and the hand, our prediction was that the spatial congruency of hand position and target would be systematically associated with optimal neuronal activity. Focusing our analysis on cells with spatial preference for the lower targets (85 visual cells and 134 saccadic cells), we found that this was not always the case (Table 2). Rather, some cells were preferentially activated in...
the congruent condition (i.e., when target was near hand location), whereas others were more activated in the non-congruent condition. Interestingly, the configuration with maximal firing rate was different for visual and saccadic activity, as illustrated in Figure 6 for all visual \((n=85)\) and saccadic \((n=134)\) cells. Indeed, analysis of hand effects in relation with the spatial relationship between hand and target showed that the magnitude of the visual response was significantly greater in the noncongruent condition in a majority of cells (70%). Examples are illustrated in Figures 2 and 4 A.

For saccadic activity, the preference for congruency/non-congruency was more balanced. Indeed, among a sample of 134 cells, saccadic activity was significantly modulated by hand position in 69 cells (51%), and in approximately half of them \((36/69, 52%)\), the activity was maximal when the hand was near the saccade target (see examples in Figs 3 and 4 B). Yet, this proportion of congruent cells within the FEF saccadic population tended to increase with longer preparatory delays, from 50% without delay and 51% for 500-ms delay to 60% for 1000-s delay.

**Delay-Related Activity and Temporal Aspects of Hand Modulation**

Among the 24 neurons with delay activity, most were spatially selective \((19/24, 79%)\), with a preference for saccades to the contralateral hemifield in 63\% \((12)\) of the cases. Hand position effects were tested on the mean activity measured in a window of 200 ms preceding the Go signal and were found to be significant in 9 neurons \((37.5\%, \text{see an example in Fig. 7 A})\). Among these neurons, 5 were tested both with and without hand vision. As far as it is possible to conclude with such a small sample of cells, we found that, as observed for visual and saccadic activity, hand modulation of delay-related activity occurred under both hand vision conditions (Table 2) and for both hand-target spatial configuration conditions, with a slightly higher number of modulated cells preferring the congruent configuration (Fig. 7 B).

The analyses of the temporal aspects of hand modulation revealed an interesting relationship between the preparatory delay duration and the upcoming saccade-related activity. A sample of 12 saccadic neurons were tested with variable preparatory delays \((0, 250, \text{and } 750 \text{ ms})\) mixed within the same block of trials. Saccadic activity averaged across both hand positions appeared to be delay dependent in 7 \((58\%)\) neurons, with generally greater firing rate \((5/7 \text{ neurons})\) for the short preparatory delay \((250 \text{ ms})\). Hand position effect also seemed delay dependent as 7 of the 10 neurons presenting this effect did so for one specific preparatory delay duration, whereas only 3 cells did so irrespective of the delay.

**From Modulation of Neuronal Activity to Behavior**

The question here is whether hand modulations found at the level of neuronal activity relate to the hand effects at the behavioral level. We attempted to answer this question by performing a trial-by-trial correlation on SRTs and FEF saccadic activity.

**Hand Modulation of Saccadic Activity Peaks Predicts Hand Position Effects on SRTs**

Given that both the mean saccadic activity and the SRTs are modulated by hand position, we sought to determine whether the latencies of saccadic activity peaks (time elapsed between
activity is higher when the hand and target were spatially congruent. The correlation was even stronger for this subset of cells (394 trials) recorded in monkey A with the 1000-ms delay analysis in a subset of 18 hand-modulated saccadic neurons. The effect of hand position for the same 394 trials, the analysis on onset; \( t \)-test, \( P > 0.05 \). Instead, it modified responses to the nonpreferred bottom targets which lie within its workspace (bottom left target: 46 vs. 37 sp/s; \( t \)-test, \( P = 0.039 \); bottom right target: 47 vs. 39 sp/s; \( t \)-test, \( P = 0.15 \)). Note that in this case, the activity is higher when the hand and target were spatially congruent.

**Discussion**

This study is, to our knowledge, the first to demonstrate that visual and visuomotor neuronal activity in FEF are strongly modulated by the position of the hand in the workspace and that this modulation is a widespread property, affecting all types of FEF neurons and all types of activity. The results can be summarized in 5 points: 1) hand modulation was present whether the animals could see their hand during task execution or not; 2) visual responses were preferentially modulated when the hand was visible, whereas saccadic responses were preferentially modulated when the hand was invisible; 3) hand position effects on both visual and saccadic neurons were stronger when targets were located in the hand’s workspace; 4) visual responses were stronger when the hand and the target were noncongruent, whereas saccadic responses did not show such bias for either condition, that is, spatial hand-target congruency/noncongruency was evenly represented; and 5) effects of hand position on FEF neuronal activity correlated with hand effects at the behavioral level. Based on these results, we suggest that part of the influence of the hand position on FEF neuronal activity could be explained in terms of attention and that overall, FEF neurons integrate both visual and proprioceptive information of hand position and might transform hand-related somatosensory signals into eye-related coordinates.

**FEF Receives Proprioceptive Information on Hand Position**

The brain uses different cues to determine hand position, but 2 of them are most crucial: the felt position (proprioception) and the seen position. Both these cues modulate the activity of FEF neurons. Interestingly, the visible hand increased the visual responses of FEF neurons, whereas the felt hand did so mostly for saccadic activity (see Table 2 and Fig. 5). This difference suggests that both visually responsive and saccadic FEF neurons contribute to the representation of hand position, but they do so using differentially visual and proprioceptive information. As we will argue in the following paragraphs, effects of the visible hand may be interpreted in terms of orientation of attention. Here, let us focus on the modulation due to the invisible hand. Because the hand was static, the contribution of a motor command of the hand (efferent copy) is presumably limited or absent. Therefore, the effects of hand position on neuronal activity, when the hand was invisible, are likely due to proprioceptive information of hand position (Vercher et al. 1997). This information may come from hand/arm-related cortical areas including the dorsal and ventral premotor areas, the supplementary motor area, and the somatosensory cortex, which all have anatomical connections with the FEF (Stanton et al. 2005).

Among previous studies that addressed the issue of eye–hand interactions in the oculomotor areas, very few have investigated the effects of hand movement/position on saccadic activity. Mushiake et al. (1996) used a saccade/pointing task.
and reported that the SEF, but not FEF, neurons vary their presaccadic activity depending on whether the saccade was made alone or together with a hand pointing movement. Although our findings may seem at odds with those of Mushiake et al. (1996), the apparent discrepancy relates to the fact the 2 studies did not address the same issues. Indeed, in order to observe hand modulation in FEF, it is necessary to vary the initial hand position, and this was not done in the experiment by Mushiake et al. (1996). Another study has shown that the lateral intraparietal area (LIP) receives feedback about limb motor plan (Oristaglio et al. 2006). These 2 studies, although not directly related to the issue addressed here, support the present findings in that they both suggest that at least some oculomotor areas (SEF and LIP) receive arm-related signals. Our results clearly show that the FEF is among these hand-modulated oculomotor areas.

Multisensory Integration within the Peripersonal Space

One of the striking findings in this study is that hand position affects saccade latencies and FEF neuronal activity, more so for targets presented in the lower visual field, that is, in the hand’s workspace than for targets presented in the upper field, that is, outside the hand’s workspace. This differential hand modulation is thus of particular interest and is reminiscent of the distinction between far and near (peripersonal) space (Rizzolatti et al. 1997). Contrary to those located out of reach, objects or targets within peripersonal space can be grasped and manipulated, making them particularly relevant for the visuomotor areas of the brain. For instance, recent studies on healthy subjects using functional MRI suggest that neural responses within brain areas coding actions (such as the superior parietal–occipital cortex) reflect automatic processing of reachable objects with the hand (affordance; Quinlan and Culham 2007; Gallivan et al. 2009). The present results suggest that, although the entire visual space is represented within FEF, both visual and proprioceptive information on hand position is processed by FEF neurons mainly within the hand’s workspace where it is more relevant, as it can interact with objects.

The Problem of Reference Frames

Although this study was not designed to examine the reference frames within which saccades are planned and executed, it is useful to discuss the present data in light of recent behavioral evidence suggesting that the saccade system might transform hand-centered somatosensory signals into eye-centered coordinates. For example, Ren et al. (2006, 2007) found that saccades to handheld object locations showed larger overshoots than visually guided saccades. On the basis of the

Figure 6. Global effects of hand-target configurations and hand vision on FEF activity. Each symbol represents the mean activity of individual visual (top panels) and saccadic (bottom panels) neurons showing a spatial preference for 1 of the 2 targets located on the lower part of the screen (85 visual cells and 135 saccadic cells). The data are presented for the congruent (abscissa) and noncongruent (ordinate) hand-target spatial configurations, when the hand is either visible (left panels) or invisible (right panels). In each panel, an open symbol illustrates a nonsignificant effect of hand position; a filled symbol depicts a significant hand modulation of FEF activity. For saccadic neurons (bottom panels), triangles represent those neurons recorded in the 1000-ms delay and circles mark cells recorded with the other delay durations (0 or 500 ms). The diagonal line represents the null hypothesis of no effect of hand position. The histograms on the diagonal lines illustrate the firing rate differences for all neurons. Black indicates significance, and the arrows point to mean value of the population. The saccadic cells fall into 2 relatively equal subpopulations, whereas most of visual cells are more active in the noncongruent configuration. In addition, the activity of visual cells was modulated mostly when the hand was visible, whereas the activity of saccadic cells was modulated mostly when the hand was invisible. Firing rate in congruent and noncongruent hand positions was compared using a t-test.
distribution of saccade endpoints, the authors suggested that
the saccade system transforms hand-centered somatosensory
signals into oculomotor coordinates. In another study
(Nanayakkara and Shadmehr 2003), saccades were examined
while perturbations were applied to the unseen hand. The
authors have suggested that proprioceptive feedback from the
arm is used to compute an estimate of hand position in eye-
centered coordinates. Based on the present results, FEF appears
to be an ideal brain site where the saccadic system might
compute such an integration of somatosensory signals into eye-
centered coordinates. Furthermore, we suggest that hand
modulation of visual and visuomotor activity in FEF represents
the counterpart aspect of what was previously reported in arm-
related somatosensory and motor areas, illustrating the close
and bidirectional interplay between the hand and the eye.
Graziano and colleagues have reported that neurons in ventral
premotor cortex, putamen, and some areas of the posterior
parietal cortex (Graziano and Gross 1993, 1995; Graziano et al.
Figure 7. Effect of hand position on delay activity in FEF. (A) Same convention as in Figure 2, except that activity is aligned on the Go signal and is shown for targets located
in the lower left (left panel) and lower right (right panel) corners of the screen in the visible hand condition. In both cases, the hand is either in the lower left (black) or in the
lower right part of the screen (red). For this neuron, hand modulation in favor of the hand-target congruent configuration steadily increases over the delay duration until and
after the Go signal (from −200 ms to Go signal; t-test, \( P = 0.004 \)). (B) As in Figure 5, the mean activity of those neurons with a delay-related activity is
represented for the congruent (abscissa) and noncongruent (ordinate) hand-target spatial configurations. Note that given the small sample size, we grouped the cases for
which the hand is either visible or invisible. Diamonds and circle symbols illustrate neurons recorded in the 1000- and 500-ms delay duration, respectively. The arrow indicates
the neuron shown in B.

Figure 8. Hand position effects on FEF neuronal activity predict SRTs. (A) Distribution of Pearson correlation coefficients \( r \) calculated with a trial-by-trial correlation analysis
between saccadic activity peak latencies and SRTs for the 172 saccadic cells. For each cell, all trials corresponding to the preferred target (including the 2 hand positions, both in
the hand vision and the no hand vision conditions) were included. For the few saccadic cells which did not show a spatial preference for 1 of the 2 or 4 targets (depending on
testing conditions), all trials were included to test the correlation. The results revealed a significant positive correlation in the majority of neurons (open bars; 141/172, 82%; the
arrow marks the mean \( r = 0.58 \)). (B) We show the result of the same trial-by-trial correlation analysis pooled across the 18 saccadic neurons (394 trials) recorded in monkey A
with 1000-ms delay (which shortens SRTs in the congruent hand-target spatial configuration) and preferentially tuned for the bottom right target. Here, each dot represents
a trial. A strong correlation \( (r = 0.66, P < 0.05) \) exists between the 2 temporal parameters with a majority of points falling under the dotted diagonal line (as shown on the
histogram above the diagonal line) meaning that activity peak latencies precede SRT (294 ± 6.3 vs. 320 ± 4.8 ms; t-test, \( P < 0.001 \)). (C) Similarity of the hand position effect on
neuronal activity and SRTs: the cumulative distributions of SRTs and saccadic activity peak latencies according to hand-target spatial configuration show that both parameters are
shorter when the hand is close to the target (congruent configuration, red curves).
1994, 1997, 2000) respond to visual and auditory stimuli in body parts coordinates. Here, we show that FEF neurons with visual receptive fields (visual responses) or with motor fields (saccadic activity) respond in a manner that is dependent upon hand location. Although we did not test the entire visual field to determine the receptive field, the data suggest that the preferred spatial locations of FEF neurons, which can be coded in terms of retinal coordinates, do not shift with hand position. Instead, only the response magnitude was affected by changes of hand position. This suggests that the representation of targets and saccades in the FEF is eye centered but modulated by hand position. Much as gain fields in other areas (see Boussaoud and Bremmer 1999) can create a flexible, task-dependent eye or head-centered representations of visual space, hand modulation of FEF neuronal activity may allow the emergence of eye- or hand-centered coordinates depending on the task at hand.

**Attention and Hand Modulation of FEF Activity**

Another, nonexclusive, interpretation of the results reported in this study relates to spatial attention, as FEF is known to play a key role in attentional processes and target selection (e.g., Schall and Hanes 1993; Thompson et al. 1996; Moore and Fallah 2001; Moore and Armstrong 2003; Wardak et al. 2006). Can attention account for part or all the results reported in the present study? We believe that modulation of visual responses by hand position might well reflect an attentional bias due to the hand, independently from sensory and/or motor processes per se. As stated in the Introduction, it was previously reported that the mere presence of the hand (even if invisible) can affect the detection of visual stimuli (Reed et al. 2006), confirming that viewing and/or feeling our hand contribute to the orienting of attention to the space surrounding it. This would explain the fact that, for many FEF cells, the firing rate was at its maximum when the hand was close to the saccade target. If we assume that attention would affect more predominantly sensory responses than motor activity, the attentional bias due to the hand may also account for the fact that hand modulation was found to affect visual responses mostly in the hand visible condition, whereas saccadic activity was modulated more often in the invisible condition. Furthermore, as will be discussed in the following paragraphs, attention can also account for the relative preference of visual cells for the noncongruent hand-target configuration.

However, if one assumes that the hand would bias attention more strongly when it is visible rather than when invisible, the fact that hand modulation is stronger (or even exclusive) in the invisible condition must be due to another phenomenon, namely the integration of nonvisual signals mentioned above. The same reasoning can be applied to hand modulation of saccadic and preparatory activity, which is more predominant when the hand was invisible than when it was visible.

**Temporal Dynamics of Hand Modulation and the Inhibition of Return**

Interestingly, hand modulation of FEF neuronal activity is dynamic throughout time. For saccadic cells tested under 3 different delay conditions (0, 250, and 750 ms), we found that the length of this preparatory delay did affect the hand modulation of activity associated with the upcoming saccade. During the delay period, transient attention shifts between the target and the location of the hand could occur, resulting in delay-related effects of hand position on both reaction times (Thura, Hadj-Bouziane, et al. 2008) and neuronal activity. This could be related to the phenomenon known as the inhibition of return, defined by Posner and Cohen (1984) as the tendency for observers to favor orienting attention toward new locations (for a review, see Klein 2000). In the saccade task used in the present study, the monkey’s attention presumably moves from hand location (after the monkey put its hand) to the FP. Yet, as sensory cues from the hand attract attention to its location (e.g., Spence et al. 2000), attention may shift back and forth between the hand and the other potential locations of the saccade target. This could explain the transient nature of hand modulation on saccadic activity as well as the higher visual responses in the noncongruent configuration. This would predict that shortening the delay between the hand contact with the screen and the onset of the saccade target would reverse the neurons’ preference. In other words, if the target is presented within 200 ms after the monkey puts the hand on the screen, the activity of the neurons will display a preference toward the targets presented near the hand location but not those away from it.

Overall, the modulation of the FEF neuronal activity strongly correlated with the behavioral effects of hand position. Indeed, the time of occurrence of the peak of saccadic activity correlates with saccade reaction times and their modulation by hand position. As the monkey’s motor behavior share many of the characteristics of its human counterpart (Roy et al. 2002, 2006), notably the hand position’s effects on SRTs (Thura, Hadj-Bouziane, et al. 2008), this insight likely extends to humans as well (Thura, Hadj-Bouziane, et al. 2008).

**Conclusions**

Taken together, the present findings suggest that hand position signals reach FEF, one of the major cortical areas involved in the generation of eye movements. Both visual and saccadic activities of FEF neurons reflected such hand-related signals. Integration of hand position information by FEF neurons is more predominant in the hand’s workspace than in the space out of the arm’s reach. Within this workspace, FEF functions in visual selection and saccade generation depend partly on hand position signals, derived from both vision and proprioception. We conclude that FEF represents one of key brain structures, where arm-related somatosensory signals could be transformed into eye-related coordinates, thereby contributing to the neuronal processes of eye-hand coordination within the peripersonal space.

**Funding**

National Center of Scientific Research (CNRS); University of Aix-Marseille II.

**Notes**

We thank Ivan Balansard, Magali Jacquier, and Mourad Mekaouche for veterinary assistance and Sébastien Barniaud, Anne Duhoux, and Ahmed Zellat for animal care. Conflict of Interest: None declared.


