



Antecedents and correlates of visual detection and awareness in macaque prefrontal cortex

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Abstract

We have investigated the neural basis of visual detection in monkeys trained to report the presence or absence of a visual stimulus that was rendered intermittently detectable by backward masking. Neurons were recorded in the frontal eye field (FEF), an area located in prefrontal cortex that is involved in converting the outcome of visual processing into a command to shift gaze. The behavioral and neuronal data were analyzed in terms of signal detection theory. We found that the initial visual responses in FEF provided signals that could form the basis for correct or erroneous detection of the target. A later phase of prolonged elevated activity occurred in many visual neurons and all movement neurons that was highly correlated with the monkey's report of target presence. When observed in movement cells that project to oculomotor structures, this period of activation is interpreted as a motor command leading to the behavioral response. When observed in visual cells that do not project to oculomotor structures, the later period of activation does not admit to the motor command interpretation. Because the visual neurons likely contribute to the feedback pathway to visual cortical areas, we hypothesize that the later selective activation in the prefrontal visual neurons interacts with ongoing activity in visual cortical areas contributing to the process by which a particular sensory representation receives enhanced activation and thereby engages attention and awareness. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The search for neural correlates of visual awareness has received considerable interest. Ambiguous stimuli have been used to dissociate the presentation of a stimulus from perception of that stimulus in neurophysiological (Logothetis & Schall, 1989; Sengpiel, Blake-more & Harrad, 1995; Leopold & Logothetis, 1996; Britten, Newsome, Shadlen, Celebrini & Movshon, 1996; Fries, Roelfsema, Engel, Konig & Singer, 1997; Sheinberg & Logothetis, 1997; Bradley, Chang & Andersen, 1998; Kim & Shadlen, 1999), neuroimaging (Tong, Nakayama, Vaughan & Kanwisher, 1998; Lumer, Friston & Rees, 1998; Lumer & Rees, 1999), and event-related potential studies (e.g. Brown & Nor-

cia, 1997; Tononi, Srinivasan, Russell & Edelman, 1998; Kaernbach, Schroger, Jacobsen & Roeber, 1999). Implicit in such studies of awareness is the subject's voluntary response to an environmental event that allows an inference about the subject's perceptual state.

We investigated the neurophysiological link between sensation and the report of perception by training macaque monkeys to shift gaze to a visual target that was rendered intermittently perceptible by backward masking (Thompson & Schall, 1999). The experiment was designed to discourage guessing by requiring monkeys to report either the perceived presence or absence of a target. We recorded neural activity in the frontal eye field (FEF). Because it receives thalamic innervation from the mediodorsal nucleus of the thalamus (e.g. Huerta, Krubitzer & Kaas, 1986; Stanton, Goldberg & Bruce, 1988) and has a granular layer 4 (e.g. Stanton, Deng, Goldberg & McMullen, 1989), the FEF is properly considered part of prefrontal cortex in macaque monkeys. In general terms, this cortical area partici-

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pates in the transformation of visual signals into saccade motor commands (reviewed by Schall, 1997).

FEF is connected in a topographic fashion with extrastriate visual areas in both the dorsal and ventral streams (e.g. Baizer, Ungerleider & Desimone, 1991; Schall, Morel, King & Bullier, 1995b). As a result of the extensive innervation from extrastriate visual cortical areas, physiological recordings in the FEF of monkeys trained to shift gaze to visual targets have found that roughly half of the neurons have visual responses (Mohler, Goldberg & Wurtz, 1973; Bruce & Goldberg, 1985; Schall, 1991). Although FEF visual neurons do not respond selectively for stimulus features such as color or orientation, recent research has demonstrated how these visually responsive neurons in FEF participate in the selection of visual targets for saccades (reviewed by Schall & Thompson, 1999; see also Schall, Hanes, Thompson & King, 1995a; Thompson, Hanes, Bichot & Schall, 1996; Bichot & Schall, 1999; Kim & Shadlen, 1999).

In fact, we have found that visually responsive neurons in FEF select the salient oddball stimulus in an array of visual elements even when monkeys are instructed not to shift gaze (Thompson, Bichot & Schall, 1997). Coupled with the evidence that attention is allocated automatically to the pop-out oddball in a search array (see Egeth & Yantis, 1997), this finding suggests that FEF may play a role in covert orienting of visual attention. This conclusion is supported by recent brain imaging studies showing that a region including FEF in human frontal cortex is activated in association with both attention and saccade tasks (Nobre, Sebestyen, Gitelman, Mesulam, Frackowiak & Frith, 1997; Corbetta, Akbudak, Conturo, Snyder, Ollinger, Drury et al., 1998). Thus, FEF may function as a salience map in which stimulus locations are distinguished based on visual conspicuousness as well as prior knowledge or expectancy.

FEF is also known to play a direct role in producing saccadic eye movements. Low intensity microstimulation of FEF elicits saccades (e.g. Bruce, Goldberg, Bushnell & Stanton, 1985). This direct influence is mediated by a subpopulation of neurons that discharge specifically before and during saccades (Bruce & Goldberg, 1985; Hanes & Schall, 1996). When planned saccades are canceled, these movement-related neurons exhibit modulation of activity sufficient to cancel the movement (Hanes, Patterson & Schall, 1998). The neurons in FEF that generate movement-related activity innervate the superior colliculus (Segraves & Goldberg, 1987) and the neural circuit in the brainstem that generates saccades (Segraves, 1992). Recent work has demonstrated that reversible inactivation of FEF impairs monkeys' ability to make saccades (Dias, Kiesau & Segraves, 1995; Sommer & Tehovnik 1997) and complements earlier observations that ablation of FEF

causes an initial severe impairment in saccade production that recovers over time (e.g. Schiller, Sandell & Maunsell, 1987; Schiller & Chou, 1998).

The experiment we will review was designed for two purposes. The first was to evaluate the hypothesis that neurons in prefrontal cortex respond only to stimuli that are behaviorally relevant. Many studies have shown that visual responses in frontal cortex are dictated more by the meaning or value than by the visual features of a stimulus (e.g. Yajeya, Quintana & Fuster, 1988; Sakagami & Niki 1994; Watanabe, 1996; Rainer, Asaad & Miller, 1998). In fact, Crick and Koch (1995) have hypothesized that visual awareness arises from the activity of a particular population of neurons in extrastriate visual areas that project to frontal cortex to guide voluntary behavior. This hypothesis can be tested by examining the activity of neurons of prefrontal cortex that mediate the transformation from a sensory representation to a voluntary motor command. The second purpose of our investigation was to expand on the earlier studies of visual cortex using ambiguous stimuli by monitoring the neural process that links sensation to action. This was accomplished by describing how, over the course of a trial with no imposed delays, a stimulus is detected and a behavioral response is generated.

We will describe the results in terms of objective detection and localization of masked visual stimuli. We will also offer an interpretation in broader terms of subjective visual awareness. Our interpretation will be based on the premise that visual awareness is a phenomenon that can be investigated physiologically because it is caused by reasonably circumscribed events in the brain that have definite properties. One key property is that the activity of neurons that mediate awareness must be of necessary magnitude and must remain active for a minimum duration of time (Libet, Pearl, Morledge, Gleason, Hosobuchi & Barbaro, 1991; Ray, Meador, Smith, Wheless, Sittenfeld & Clifton, 1999; see also Koch & Crick, 1994; Gomes, 1998). Other properties such as temporal patterning (Llinas, Ribary, Contreras & Pedroarena, 1998; Singer, 1998) or coherence (Tononi & Edelman, 1998) may also be necessary.

Visual masking has been considered one model phenomenon with which to explore the nature of consciousness (e.g. Dennett, 1991; Flanagan, 1992). Neurophysiological data can inform these discussions. We believe that progress on identifying the neural correlates of visual awareness is necessary to clear the way for understanding more complex cognitive phenomena. Put simply, if we cannot understand the neural correlates of the primitive mental content associated with the awareness of a spot of light, then how will we understand the neural correlates of cognitive phenomena with more complex mental content such as decisions or intentions?

2. Methods

Data were collected from two *Macaca mulatta* weighing 8 and 10 kg. Behavioral and physiological methods have been described (Schall et al., 1995a; Thompson et al., 1996; Thompson & Schall, 1999) and conformed to NIH guidelines.

2.1. Task

Using operant conditioning with a juice reward as positive reinforcement, monkeys were trained to shift gaze to a dim peripheral target presented alone or to a dim target that was followed by a bright mask. The detection task without the mask stimulus was used to determine cell type and to map the spatial extent of the receptive field. The simple detection task and the visual masking task were run in separate blocks of trials. The trial sequence of the visual masking task is illustrated in Fig. 1. Each trial began with the appearance of white fixation spot at the center of the screen. After the monkey fixated the spot for 500–700 ms a dim blue target appeared (CIE $x = 161$, $y = 73$, $Y = 0.3$ cd/m²) at one of four or eight possible target locations around the fixation spot on about 70% of trials. On the remaining trials no target appeared. On average, on 32.6% of trials no target appeared (the percentage of target absent trials ranged from 16 to 48% across sessions). At a

short interval following the appearance of the target a bright white mask stimulus (CIE $x = 276$, $y = 284$, $Y = 83$ cd/m²) equal in size to the target appeared at each of the possible target locations. The interval of time between the appearance of the target and the appearance of the mask was called the stimulus onset asynchrony (SOA). The monkeys were rewarded for correctly reporting whether or not the target was present; absence of a reward provided error feedback. The monkey indicated ‘yes’ (target present) by shifting gaze to the target location. The monkey indicated ‘no’ (target not present) by maintaining fixation on the central spot. To report ‘yes’, the saccade to the target location had to occur within 500 ms of target presentation. To report ‘no’, fixation had to remain on the central spot for at least 750 ms following target presentation. Single trials were scored according to the conventions of Signal Detection Theory as either hits (correctly responding ‘yes’), misses (incorrectly responding ‘no’), correct rejections (correctly responding ‘no’), or false alarms (incorrectly responding ‘yes’) (Green & Swets, 1966).

Using a staircase procedure, the SOA was adjusted before each trial according to the monkeys’ performance on the previous trials. If the target was present and the monkey correctly reported its presence, the SOA was reduced one step. If the target was present but the monkey failed to report its location, the SOA was increased one step. Performance on no-target trials did not influence SOA adjustment. The minimum SOA step was limited by the 16.7 ms scan time of the video monitor. The SOA was typically adjusted after three correct trials or three incorrect trials in a row in which the target appeared. This approach insured that on approximately half of the target present trials the monkeys reported the detection of the target. The maximum SOA allowed was 66.7 ms (or four video scan cycles) to discourage the monkeys from continually maintaining fixation on the central spot on every trial until the SOA reached intervals for which the target was easily detected. Thus SOAs stepped between 16.7, 33.3, 50.0 and 66.7 ms. After the SOA converged on a level that resulted in 50% performance (usually 33.3 or 50.0 ms) on target present trials, significant changes in SOA occurred only when the monkey’s behavioral response criterion changed.

2.2. Neuronal activity analysis

The analysis of the neural activity consisted of several steps. First, the visual response latency of each neuron to the mask stimulus on correct target absent trials was determined using a Poisson spike train analysis. This time will be referred to as the mask response latency. The theoretical basis and details of this analysis have been described (Hanes, Thompson & Schall, 1995; Thompson et al., 1996). For each neuron, occurrences

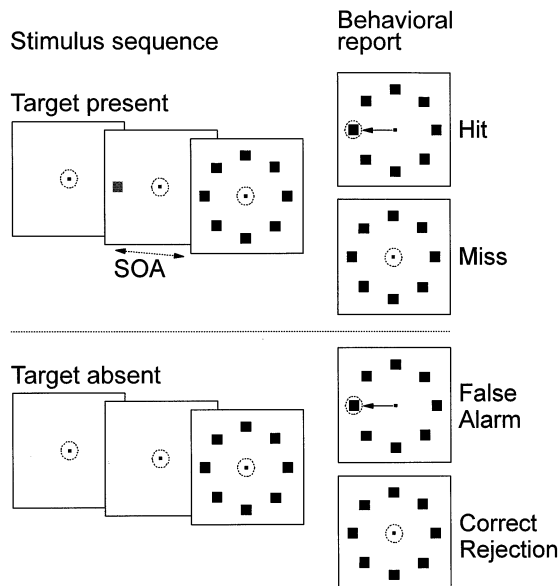


Fig. 1. Visual backward masking task. The target appeared followed after an adjustable stimulus onset asynchrony (SOA) by a mask in *target present* trials. A saccade directly to the location where the target had been was scored a *Hit*. Continued fixation was scored a *Miss*. Only the mask appeared on *target absent* trials. A saccade to any location was scored a *False Alarm*. Continued fixation was scored a *Correct Rejection*. Monkeys were rewarded for Hits and Correct Rejections.

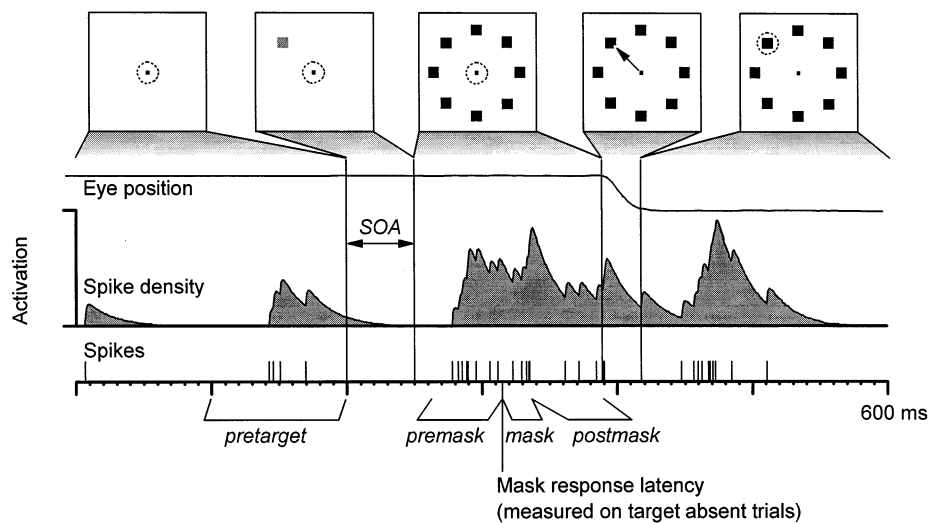


Fig. 2. Trial sequence and periods of neural activity analyzed. The sequence of visual displays and gaze locations are indicated by the top panels which are synchronized on the eye position trace and spikes with the associated spike density function. The spike density function was calculated by convolving the spike train with a filter resembling a post-synaptic potential. Spikes that occurred before the target appeared (or would have appeared in target absent trials) were counted for the *pretarget* activity. The latency of the visual response to the mask determined during target absent trials (*mask response latency*) was used to partition spikes into *premask*, *mask* and *postmask* intervals.

of action potentials were counted during four separate time intervals illustrated for a single trial in Fig. 2. The first interval, termed the *pretarget* interval, was the 100 ms before target presentation on target present trials or the corresponding interval on target absent trials. The *pretarget* interval measured the level of background activity present before the target was presented. The second interval, termed the *premask* interval, was equal in duration to the SOA and began at the time of target presentation plus the mask response latency and ended at the time of the mask response latency. The *premask* interval on target absent trials was identical to the *premask* interval on the target present trial that immediately followed. The *premask* interval measured the visual response to the target stimulus on target present trials and the activity present in the same period of time on target absent trials. The third interval, termed the *mask* interval, was the first 20 ms of the response to the mask stimulus beginning at the mask response latency. The *mask* interval measured the magnitude of the visual response to the mask stimulus. The fourth interval, termed the *postmask* interval, began at the end of the *mask* interval and ended at the time of saccade initiation on trials that ended with a saccade (hits and false alarms). For trials on which no saccade was made (misses and correct rejections), the *postmask* interval ended at the average time of saccade initiation calculated from hits and false alarms. The *postmask* interval measured activity occurring later in the trial following the initial visual responses to the target and mask stimuli.

Neuronal activity was measured as the sum of the action potentials counted across all trials divided by the

total amount of time in which action potentials were counted. For each neuron, the average firing rate was calculated in this manner for each of the four intervals (*pretarget*, *premask*, *mask*, and *postmask*) separately for each of the trial classes (hits, misses, false alarms and correct rejections). As well as calculating the average activation for each class, the average activation was also calculated separately for groups of trials with the same SOA within each class. Any group with less than three trials were not included in the analysis.

3. Results

The psychophysical measure of perceptual sensitivity, d' , was calculated for each of the two monkeys used in this investigation (Thompson & Schall, 1999). For both monkeys, d' increased with increasing SOAs. This indicates that the monkeys were using the target stimulus to guide their behavior.

Sixty-seven neurons from the FEF of two *M. mulatta* provided the data. Sixty of these neurons were classified as visual because they exhibited activity following flashed visual stimuli without eye movements. The remaining seven neurons exhibited only movement-related activity before a gaze shift. We have recently reported the properties of the visual responses to the target (*premask* interval) and mask (*mask* interval), as well as the pretrial activity (*pretarget* interval), in FEF during visual masking (Thompson & Schall, 1999). Here we will review these findings and then describe for the first time the enhanced activation after the mask response during the *postmask* interval that occurred

when the monkeys reported that the target was present, whether or not it actually was.

3.1. Visual responses to the masked target

Contrary to the hypothesis that prefrontal cortex only registers sensory activity that reaches awareness to guide voluntary behavior, we found that virtually all visually responsive neurons in frontal eye field responded at short latencies to the target stimulus whether or not the monkey reported its presence. Fig. 3 shows the activity of an FEF visually responsive neuron during misses — trials on which the target appeared but was not detected, and on correct rejections — trials on which no target appeared and the monkey correctly reported that no target was present. For both trial types, the monkey's behavior was the same, fixation remained on the central spot. The increase in discharge rate that occurred before the mask response latency on trials when both the target and the mask were presented is a response to the target stimulus. This initial visual

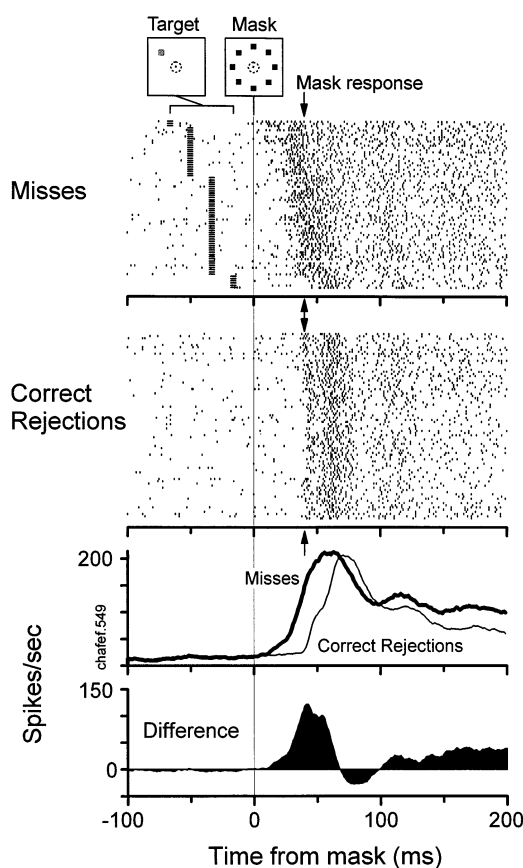


Fig. 3. Comparison of activity of an FEF visual neuron between miss (top raster and thick spike density) and correct rejection (bottom raster and thin spike density) trials. The activity is aligned on the time of mask presentation. The time of target presentation is indicated by the horizontal tickmarks. Vertical arrows show the latency of the mask response on target absent trials. The difference between miss trial and correct rejection trial activity is shown in the bottom panel.

response to the masked target, which was observed in 97% of visually responsive FEF neurons, demonstrates that a significant response was evoked in FEF by the target when it was presented but not detected.

3.2. Small differences in visual responses predict the behavioral report

Fig. 4 compares the activity evoked by the target and mask during hits and misses (left) with the activity evoked by the mask during false alarms and correct rejections (right). This figure compares the activity on physically identical trials with opposite behavioral reports. The difference plots shown at the bottom of Fig. 4 illustrate three new findings. First, a slightly stronger initial visual response occurred 50–100 ms following stimulus presentation when the target was detected and localized behaviorally. For nearly every visually responsive FEF neuron, the early sensory responses were slightly greater on trials that the target was reported as being present. This difference was small, often only 1–2 spikes per trial. We believe it is unlikely that the differences in initial visual activation arise *de novo* in FEF. Most likely, the differences observed reflect variations in visual activation in earlier stages of the visual pathway, perhaps even originating in the retina and propagating throughout the visual system.

3.3. Pretarget biases may influence evoked visual responses

Many of the FEF neurons exhibited slightly elevated discharge rate specifically before trials on which the monkey reported a target in the receptive field. This bias before target presentation can be observed in the small positive values in the difference plots in Fig. 4 before a stimulus appeared in the receptive field. This small difference amounted to just one to four spikes in each trial. Across the sample of neurons recorded, a pretarget bias before 'yes' trials was observed only before trials with saccades into the neurons' receptive field. Therefore, the small bias before target presentation cannot be a result of a non-specific motor readiness. Instead, it appears that the increased neural responsiveness before 'YES' trials contribute to the monkeys' decision to move the eyes to a specific target location.

The source of this pretarget bias is unknown. It may be due to a random fluctuation in neural discharge rates. Recent work has shown that the responsiveness of visual cortex is modulated by variations in local activation levels, although this variability does not account for all of the variability in spike generation (Arieli, Sterkin, Grinvald & Aertsen, 1996; Azouz & Gray, 1999). The pretarget bias may also be due to a systematic adjustment related to the monkeys' perfor-

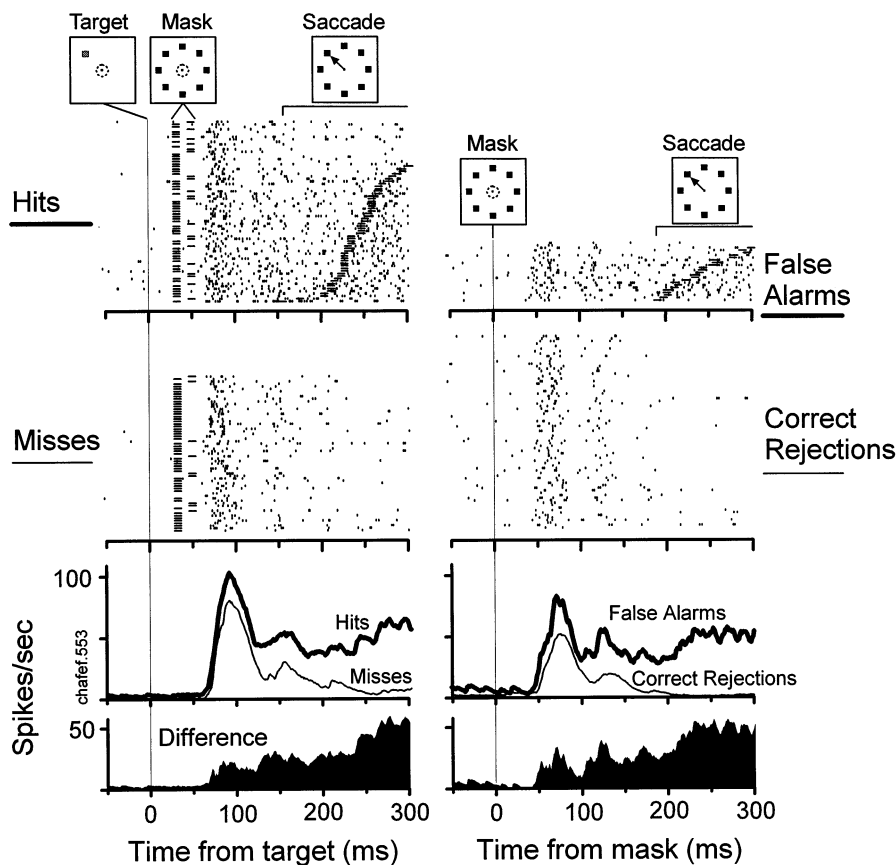


Fig. 4. Activity of an FEF visual neuron. The left panels compare the activity during target present trials leading to hits and misses. The right panels compare the activity during target absent trials leading to false alarms and correct rejections. Trials are aligned on the time of target presentation in the left panels and on time of mask presentation in the right panels. Conventions as in Fig. 3.

mance. We believe these alternatives can be distinguished in further work. Evidence for a strategic adjustment of performance would be provided by observing sequential relationships between pretrial activity and trial history. Evidence for simple random fluctuations would be provided by observing that the pretarget activity level does not relate to previous performance and the same bias is observed at early levels of the visual system.

3.4. Large differences in late activation lead to the behavioral report

Except for a preliminary report (Thompson & Schall, 1998) we now present for the first time neural events in FEF that may lead to the report and may correlate with visual awareness. We found that many of the visually responsive FEF neurons exhibited a prolonged phase of elevated activity that occurred specifically during trials on which the target was reported as being present (hits and false alarms) but not during trials on which the target was reported as being absent (misses and correct rejections). For the neuron shown in Fig. 4, this second phase of differential activity began around

100 ms following target presentation and continued until the saccade. We have termed this the postmask activity because it occurs after the visual response to the mask stimulus. Postmask activity on 'yes' trials was significantly greater than the postmask activity on 'no' trials in 62% of the visually responsive neurons and in all of the movement neurons.

What does this late, enhanced activation on hits and false alarms represent? As reviewed above, FEF is commonly regarded as a motor area. Thus, one must ask whether the late activation after the mask response is related to visual processing or to motor programming. To address this question, we compared the selective activity of movement neurons to that of visual neurons.

Fig. 5 shows the activity of a movement neuron during the visual masking task. Movement neurons in FEF are distinguishable from the visual neurons such as that shown in Figs. 3 and 4. Movement neurons exhibited little or no modulation of activity on misses or on correct rejections but exhibited strong activation specifically associated with the saccade in either hits or false alarms. Further, the magnitude and pattern of movement-related activity was the same for hits as it

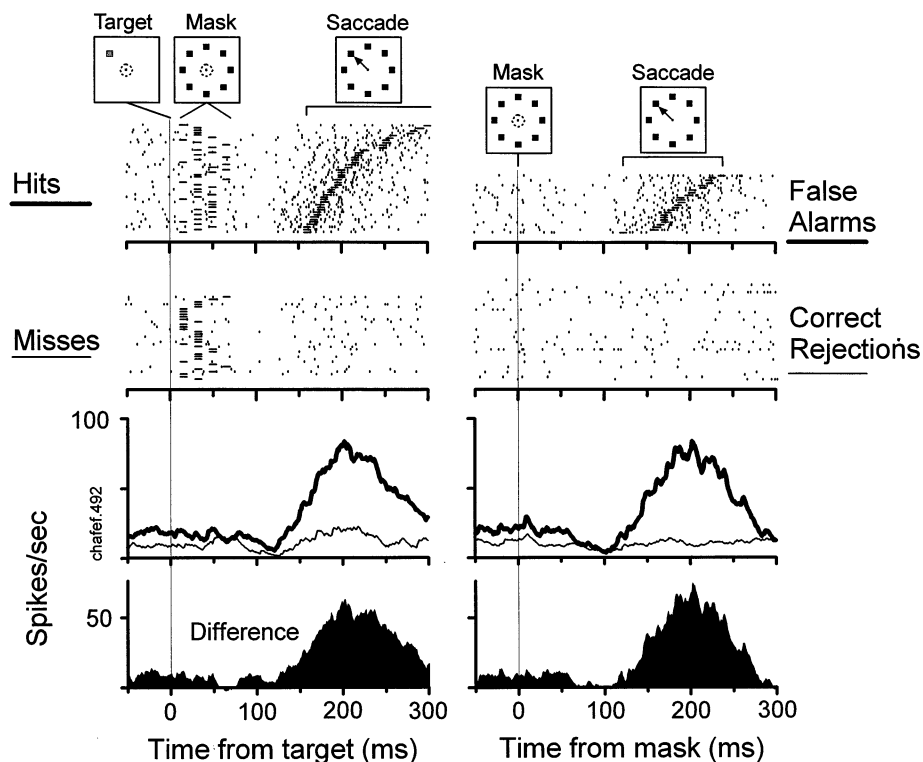


Fig. 5. Activity of an FEF movement neuron associated with identical stimulus conditions having different behavioral report. Conventions as in Fig. 4.

was for false alarms (Fig. 6). Thus, FEF provides a motor command appropriate to complete the task, to produce the overt behavioral report of a gaze shift. We suppose that if the report had been a manual movement, then similar movement-related activity would be observed in motor cortex.

Now, while it seems clear that the movement neurons in FEF generate activity directly related to saccade production (Bruce & Goldberg, 1985; Hanes & Schall, 1996; Hanes et al., 1998), we believe we should ask whether the postmask activation of all FEF neurons can necessarily be regarded as a motor command. One avenue to address this question is to determine whether the time of the postmask selective activity is synchronized on the time of saccade initiation or on the time of stimulus presentation (Commenges & Seal, 1986; Hanes et al., 1995; Thompson et al., 1996). The variability of behavior response times permits a temporal dissociation of sensory and motor-related neural events.

To investigate the possibility that the postmask response may only be associated with saccade production, we related the time of onset of the postmask activity to the time of target presentation and to the time of saccade initiation in a subset of neurons that exhibited a strong postmask response. Sixteen visually responsive neurons with significant postmask activity and with at least 30 target-detected trials were identified. The trials that were scored as hits were collected

from each of these 16 neurons and divided into three equal groups based upon reaction time. For each group of trials the onset of postmask activity on hits was judged as the time of the second phase of elevated activity following the initial visual response that was different from the activity on misses. This second period of activation can be seen beginning 125 ms after target presentation for the neuron in Fig. 4. The statistical analysis we use has been described (Hanes et al., 1995; Thompson et al., 1996).

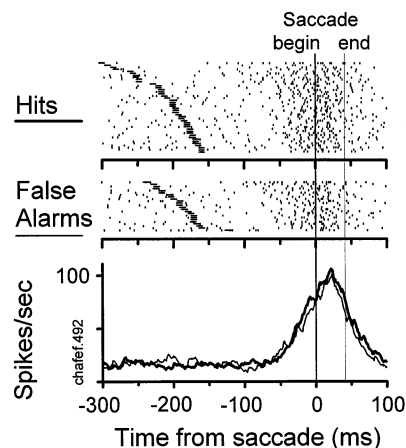


Fig. 6. Saccade-related activity of a FEF movement neuron associated with hits and false alarms. The trials are aligned on the time of saccade initiation.

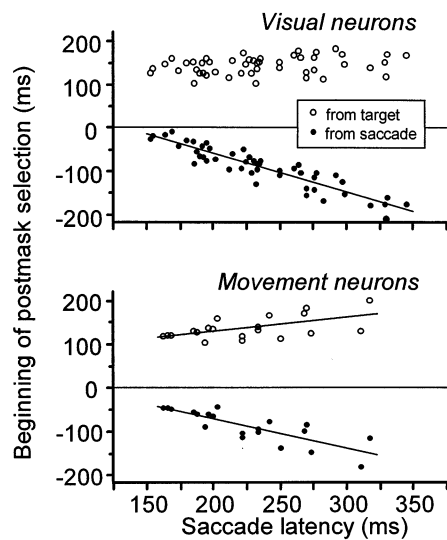


Fig. 7. Timing of postmask selection. Top — scatter plot of the time of the beginning of the postmask activity in visual neurons during hit trials measured relative to target presentation (open circles) and measured relative to saccade initiation (solid circles) as a function of saccade latency. The time of postmask selection measured relative to saccade are plotted as negative values because they occur before saccade initiation. Bottom — scatter plot of the time of the beginning of movement activity in FEF movement neurons during hits measured relative to target presentation (open circles) and measured relative to saccade initiation (solid circles) as a function of saccade latency.

Fig. 7 shows the results of this analysis for groups of trials that had differing reaction times. For each group of trials, the mean reaction time was divided into two periods demarcated by the time at which the postmask selection began. This time will be referred to as the *selection time*. A regression analysis revealed that for visual neurons, the selection time did not change with increasing reaction time when measured relative to the time of target presentation ($F_{1,46} = 3.9$), but did change when measured relative to the time of saccade initiation ($F_{1,46} = 249.4$, slope = -0.95 , $P < 0.001$, $r^2 = 0.84$). Furthermore, the variance of the selection time measured relative to saccade initiation was significantly greater than the variance of the selection time measured relative to target presentation ($F_{47,47} = 5.9$, $P < 0.001$). This result demonstrates that the selection time of visually responsive neurons, like any visual response, was synchronized on the time of target presentation and did not predict when gaze would shift.

For comparison, the analysis of the timing of the postmask activity was performed on a sample of movement cells including the one shown in Figs. 5 and 6. We found that not only is the pattern of modulation different in movement neurons, the timing of the selective signal is also different. Because these movement neurons did not exhibit a pronounced visual response, we measured the time that the activity began to rise before saccade initiation. The onset of activation of the move-

ment neurons increased significantly with increasing reaction time when measured relative to target presentation ($F_{1,18} = 8.5$, slope = 0.32 , $P = 0.009$, $r^2 = 0.32$). In other words, the activation of the movement cells began progressively later on trials with progressively longer saccade latencies. However, the onset of movement-related activation was also not synchronized on saccade initiation. Movement neurons became active significantly earlier before progressively longer latency saccades ($F_{1,18} = 36.9$, slope = -0.67 , $P < 0.001$, $r^2 = 0.67$). The variance of the onset of movement activity measured relative to target presentation and the variance of the onset of movement activity measured relative to saccade initiation did not differ significantly ($F_{19,19} = 2.1$).

This result indicates that unlike the selective response in visual neurons, the movement-related activity leading to the behavioral response to the masked target began at a time that was not synchronized on either target presentation or saccade initiation. This timing relationship was qualitatively different from the selection signal observed in the visual neurons. To our knowledge, this is the first report of a specific modulation of neural activity during a sensorimotor task that is not synchronized on either stimulus presentation or on movement initiation. This observation indicates that the beginning of the movement-related activity was not triggered by stimulus events but was instead triggered by internal, self-generated events.

4. Discussion

To identify neural correlates of visual awareness, an experimental manipulation is required by which a visual input is constant but perception of that visual stimulus varies. For instance, to dissociate the visual stimulation from perceptual reports, physiological studies of visual cortex have utilized binocular rivalry (Logothetis & Schall, 1989; Leopold & Logothetis, 1996; Sheinberg & Logothetis, 1997), weak stochastic motion (Britten et al., 1996; Kim & Shadlen, 1999) and motion in depth (Bradley et al., 1998). We have utilized backward masking by light to manipulate the perceptibility of a visual target for a saccade. We have identified neural processes in FEF associated with the conversion through time of an ambiguous sensory input into a conclusive motor output. The results are summarized in Fig. 8 which compares the averaged activation of phasic visual neurons, tonic visual neurons with selective postmask activity and movement neurons during trials with 50 ms SOAs. In visual neurons there was an early sensory response to an undetected target but was slightly stronger when the target was detected. This early visual activity difference was evident when the target and mask were presented in succession on target

present trials, and also when the mask was presented alone on target absent trials. A later, longer phase of elevated activity occurred in some visual neurons that was associated with the selection of a visual target whether or not the target was actually there. This selective activity led to a growth of activity in movement neurons preceding an eye movement to the detected target. Also shown at the bottom of Fig. 8 is the distribution of reaction times to the reported target for both hits and false alarms. Measured from the time of mask presentation, reaction times were on average 48 ms longer on false alarms (mean = 219 ms; S.D. = 61 ms) than on hits (mean = 171 ms; S.D. = 49 ms). This

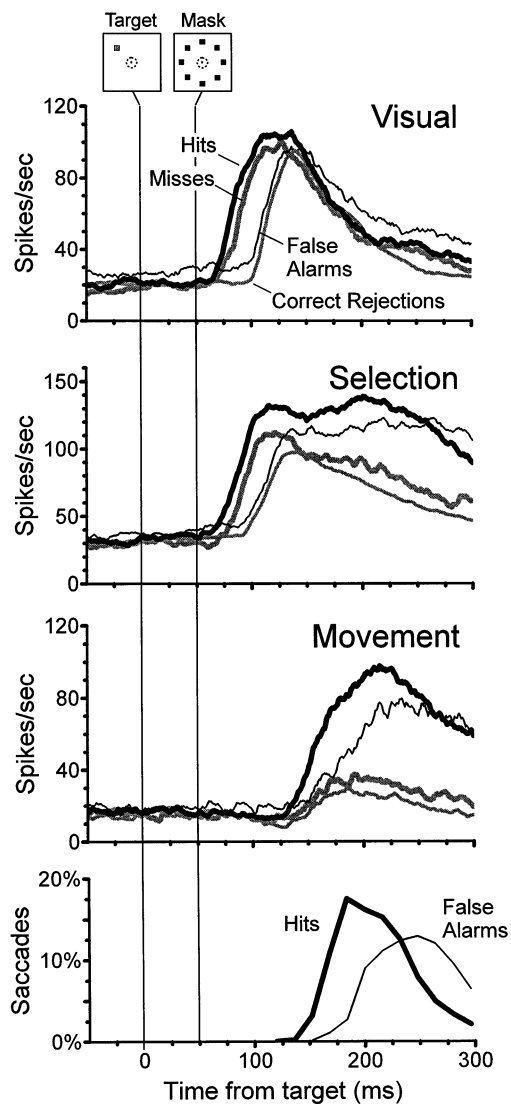


Fig. 8. Summary of FEF activity during visual backward masking. The overall average firing rate obtained from 17 transient visual neurons, 22 visual selection neurons and four movement neurons during hits (thick black), misses (thick gray), false alarms (thin black) and correct rejections (thin gray). Only trials with SOAs of 50 ms were included in the average. Bottom panel shows frequency distributions of saccade latencies across the same trials for hits and false alarms.

difference is about equal to the 50 ms SOA on hits. Therefore, the time it takes for the monkey to generate a response is about equal on hits and false alarms when measured relative to the appearance of the first visual stimulus. Nevertheless, the delay in movement initiation measured relative to the onset of the mask stimulus is predicted by the delay in movement-related activation in movement neurons.

4.1. Previous studies with visual masking

A number of investigators have made physiological recordings from different stations in the visual system during backward masking (Schiller, 1968; Fehmi, Adkins & Lindsley, 1969; Coenen & Eijkman, 1972; Bridgeman, 1975, 1980; Judge, Wurtz & Richmond, 1980; Rolls & Tovee, 1994; Rolls, Tovee, Purcell, Stewart & Azzopardi, 1994; Kovács, Vogels & Orban, 1995; Macknik & Livingstone, 1998). The primary purpose of these studies was to identify the neurophysiological basis of the backward masking phenomenon.

Previous studies of backward masking by light, in which the target and the mask occupy overlapping spatial locations, have been limited to the earliest levels of the visual system. Single unit recordings made in the optic tract (Coenen & Eijkman, 1972) and LGN of cats (Schiller, 1968; Coenen & Eijkman, 1972) and striate cortex of monkeys (Judge et al., 1980) all show that as the time between the target and mask (SOA) shortens, the responses to the target and to the mask merge. This pattern was also evident in evoked-potentials recorded in the optic tract, LGN, and striate cortex of monkeys (Fehmi et al., 1969). This merging of responses at shorter SOAs, which was evident as early as the discharge of retinal ganglion cells, was correlated with psychophysical measurements of masking in humans and led to the conclusion that backward masking by light has a retinal origin. We have found essentially the same pattern of visual responses in frontal cortex as has been found at early levels of the visual system. The visual responses to the target and mask are merged together and, as can be seen in Fig. 3, at longer SOAs there are more spikes before the mask response. We now extend these earlier reports of backward masking by light to investigate why two physically identical trials can lead to opposite reports of target presence.

Recently, backward masking with pattern stimuli was used to study the encoding of faces (Rolls & Tovee, 1994; Rolls et al., 1994) and shapes (Kovács et al., 1995) in monkey temporal cortex. Pattern masking occurs when the target and mask are patterned stimuli and are presented at the same spatial location. These studies showed that the presentation of a mask pattern over a stimulus abbreviated the selective response to the stimulus. At shorter SOAs, the responses were interrupted earlier. The decrease in activation was correlated

with psychophysical tests of recognition of the test stimulus performed on humans (Rolls & Tovee, 1994; Rolls et al., 1994; Kovács et al., 1995) and monkeys (Kovács et al., 1995).

The neurophysiological correlates of metacontrast masking has also been studied in the optic tract of cats (Bridgeman, 1975), LGN of cats (Schiller, 1968; Bridgeman, 1975) and striate cortex of cats (Bridgeman, 1975) and monkeys (Bridgeman, 1980; Macknik & Livingstone, 1998). Metacontrast masking refers to a backward masking effect when the presentation of two stimuli of equal intensity are offset in time and space and share a common contour — such as a disk followed by a ring, where the inner contour of the ring corresponds to the contour of the disk. The metacontrast backward masking function is ‘U-shaped’, there is no masking when the stimuli are presented simultaneously and reaches a maximum at SOAs between 50 and 150 ms. The findings of all of these studies were basically the same. The initial visual response to the masked stimulus was the same at all SOAs. However, in some of these studies the magnitude of a later response was shown to be correlated with psychophysical masking in humans (Bridgeman, 1975, 1980; Macknik & Livingstone, 1998). It is unclear if the late responses observed during metacontrast masking correspond to the late enhancement we observed in FEF. Metacontrast masking and masking by light involve somewhat different phenomena and probably different neural mechanisms (see Breitmeyer, 1984).

Our study was fundamentally different from all previous studies of masking. Earlier investigators were attempting to identify the physiological basis of masking, so they analyzed the differences in neural activity between masked and non-masked stimulus presentations and the changes in neural activity at different SOAs. In contrast, we were most interested in the differences in neural activity between trials that had exactly the same physical parameters in which monkeys generated opposite reports. In addition, all of the previous studies were indirect comparisons of psychophysical performance measured with humans or monkeys and physiology measured with monkeys or cats. In contrast, we correlated on a trial-by-trial basis the activity of neurons and the performance of the monkeys. Moreover, by including a high fraction of trials with no target, we were able to elevate the response criterion and observe a useful fraction of miss and false alarm trials. Therefore, we were able to analyze data relating neural activity to different behavioral reports produced in response to the same physical stimulus. This provided the operational dissociation of sensation and perception.

4.2. Early visual activation in FEF

Our results show that significant stimulus evoked neural activation in the prefrontal cortex does not necessarily lead to detection of that stimulus. We found that nearly all visually responsive neurons responded at short latencies to undetected targets. Crick and Koch have hypothesized that in order for a visual area to mediate visual awareness, it must provide the ‘best’ current interpretation of the visual scene directly to the parts of the brain that plan and execute voluntary movements, specifically the prefrontal and premotor cortex (Crick & Koch, 1995). A strong interpretation of this hypothesis is that the visual information that reaches prefrontal cortex has already been processed into an explicit representation sufficient to guide voluntary behavior. Contrary to this interpretation, our results indicate that FEF, which is located in prefrontal cortex, is accessed by primitive visual signals that have not been subjected to selective processing.

What is the origin of this early visual signal in FEF? Such a short latency response would not be predicted by the notion that visual information percolates sequentially through an extensive anatomical hierarchy of areas (e.g. Felleman & Van Essen, 1991). However, recent studies indicate that visual signals do reach FEF surprisingly quickly, at effectively the same time as they reach areas MT and MST (Nowak & Bullier, 1997; Schmolesky, Wang, Hanes, Thompson, Leutgeb, Schall et al., 1998). Area MT can convey the early visual responses to FEF because MT projects directly to FEF (Schall et al., 1995b), and neurons in MT are sensitive to dim, low contrast stimuli (Sclar, Maunsell & Lennie, 1990; Cheng, Hasegawa, Saleem & Tanaka, 1994). Alternatively, it appears that visual signals can reach FEF from the intermediate layers of the superior colliculus through the thalamus (Sommer & Wurtz, 1998).

Regardless of how the differences in activation came to be, the initial visual activation occurring immediately before the mask response predicts reasonably well whether monkeys will generate a ‘yes’ or a ‘no’ report (Thompson & Schall, 1999). We postulate that the initial visual responses in FEF represent the evidence upon which the detection decision is based. In terms of signal detection theory the early visual response is the dependent variable along a decision axis (Green & Swets, 1966). When this visual response is slightly greater than otherwise, it is high enough to cross a threshold on this axis such that the monkey responds that the target was there. Further studies are required to identify where in the visual system the differences in the initial visual responses arise as well as the nature and locus of the threshold.

Is this brief visual response a neural correlate of visual awareness? We believe not. The period in which the small initial differences in activity were observed

was always less than 100 ms and often as short as 10 ms. Based on the premise that a neural correlate of visual awareness must be a neural state of necessary magnitude and duration (Libet et al., 1991; Koch & Crick, 1994), the premask activity does not meet these criteria. Therefore, we interpret the initial visual response as an antecedent of visual awareness — part of a sensory representation of what will be the contents of awareness. This conclusion has also been reached by previous masking studies (Fehmi et al., 1969; Bridgeman, 1980; Rolls & Tovee, 1994; Rolls et al., 1994; Kovács et al., 1995). Now, the brief, small difference in activity probably supports only a fleeting representation, but then this is backward masking. Human subjects viewing the displays we used report a weak impression of a slight difference at one of the mask locations. Despite the quality of the impression, we would emphasize the conjoint fact that the impression was experienced. If this was so, and if the initial activity is not sufficient for visual awareness, then some other brain events must have transpired to convert the ambiguous sensory signal into an explicit interpretation of that signal. This representation leads to the preparation of the voluntary behavioral report of the perceptual experience.

4.3. Late selective activation in FEF

We observed a later phase of activation that occurred specifically when monkeys perceived the target as indexed by the behavioral report. We now turn to the interpretation of this period of selective activation in FEF.

The activation of movement neurons when the target was detected may be regarded as being directly linked to the execution of the motor response. This conclusion is based on the fact that movement neurons are directly involved in saccade production. Located in layer V of FEF, they project directly to the saccade generating regions of the superior colliculus and brainstem (Segraves & Goldberg, 1987; Segraves, 1992). As a result, microstimulation in the vicinity of movement neurons in FEF will elicit saccades with very low currents ($< 50 \mu\text{A}$) (Bruce et al., 1985). In addition, FEF movement neurons bear a consistent relationship to the time of saccade initiation (Hanes et al., 1995; Hanes & Schall, 1996). When a planned saccade is successfully canceled in a countermanding task, movement neurons are modulated in a manner sufficient to cancel the movement (Hanes et al., 1998). All of this evidence supports the uncontroversial claim that movement neurons in FEF contribute proximally to the causation of saccades.

Is the late, enhanced activation of visual neurons when the target was detected also linked to the movement? In a weak sense it must be the case because the activation of the visual neurons occurs specifically be-

fore the movement is made. However, is the relationship more than a distal correlation? To answer this question, we offer several lines of evidence. First, in other studies we have found that visually responsive neurons in FEF discriminate the oddball of a visual search array (Schall et al., 1995a; Thompson et al., 1996) regardless of when or even whether gaze shifts (Thompson et al., 1997). However, visual neurons do not play a direct role in controlling gaze; when a planned saccade is canceled, visual neurons are modulated not at all or too late to participate in the act of control (Hanes et al., 1998). Second, the population of visually responsive neurons in FEF does not innervate subcortical oculomotor structures (Segraves & Goldberg, 1987; Segraves, 1992; see also Sommer & Wurtz, 1998). Third, the remoteness of the visual cells in FEF relative to the motor system is confirmed by the fact that to elicit saccades with microstimulation, higher currents are needed at the sites of visual neurons ($> 50 \mu\text{A}$) (Bruce et al., 1985). Finally, in this experiment we found that unlike the onset of movement-related activity, the onset of the postmask selection in visual neurons was synchronized with the appearance of the target.

All of this indicates that visual neurons and movement neurons in FEF are functionally distinct such that any relationship of the postmask activity in visual neurons to saccade execution is distal to that of the movement neurons. Therefore, we believe that the postmask selection signal observed in the visual neurons represents a signal that is not just visual but not quite motor. In fact, two separate selection processes have been theorized to be necessary for the execution of a voluntary movement — the selection of the stimulus that guides the action and the selection of the action (e.g. Allport, 1987; see also Pashler, 1991). We conclude that both of these selective processes can be observed in the activity of FEF neurons. It seems clear that the activity of movement neurons corresponds to the preparation of the motor act. We hypothesize that the late, selective activity of the FEF visual neurons in this masking task may represent a process by which an ambiguous sensory signal is selected to guide action. Visual selection should be distinguished from motor selection. First, the time of visual selection is different from time of motor selection (Fig. 7). Second, visual selection does not necessarily lead to or cause motor selection. Indeed, a particular state of visual selection can lead to the selection of different motor responses (Di Pellegrino and Wise, 1993; Crammond & Kalaska, 1994; Schlag-Rey, Amador, Sanchez & Schlag, 1997; Shen & Alexander, 1997; Zhang, Riehle, Requin & Kornblum, 1997; Everling, Dorris, Klein & Munoz, 1999).

5. Neural correlate of visual awareness

Can we claim that the monkeys had any awareness associated with the target to which they shifted gaze? The answer to this question depends on the criterion for the report used to evaluate awareness. A number of studies using masking with humans have adopted criteria based on subjects' verbal report of their subjective state (see Breitmeyer, 1984). This criterion is clearly not applicable to non-human primates or non-verbal humans. Therefore, a more objective criterion based on psychophysical procedures seems necessary.

Previous studies with masked stimuli have concluded that motor responses can be directed to stimuli without visual awareness (Merikle, 1992) or that awareness indexed by verbal reports arises after a manual movement is initiated (Castiello, Paulignan & Jeannerod, 1991; MacIntyre & McComas, 1996). However, we would note that the design of our experiment was fundamentally different from that of earlier studies that reported localization without detection in three key ways. First, we provided feedback after every trial. Second, the inclusion of trials on which no target appeared provided the option of reporting the absence of a target. This strategy has been used to obtain reliable reports of blindsight in monkeys (Cowey & Stoerig, 1995). Third, the SOA between the target and the mask was continuously adjusted in a staircase procedure. These procedures led to an elevated response criterion because feedback was given, guessing was discouraged and the difficulty of the task was adjusted according to performance. Accordingly, for monkeys to respond 'yes', the sensory evidence had to reach higher levels. Our conclusion is that under the conditions we employed, production of the gaze shift was a reliable indicator that the monkeys had some kind of more or less distinct perceptual experience related to target detection.

What is the nature of that experience, the contents of awareness? Although the quality of the subjective awareness is ineffable, the fact that an awareness was experienced can be established. We can describe what human observers report when they look at the displays we used. The experience is not of a distinct blue target square. Rather, the experience is that one of the locations of the mask is different, more distinct from the rest. This occurs when the masked target is detected. But the sense of distinctness can occur on false alarm trials. Thus, we should not suppose that absence of the target must necessarily correspond to absence of a perception. The annals of cognitive psychology are full of cases of subjects seeing and reporting what was not there, e.g. illusory conjunctions (Treisman, 1982; Cohen & Ivry, 1989). Indeed, false alarms are a common occurrence during near threshold psychophysics.

Accepting, at least for the sake of argument, that the monkeys had some phenomenal awareness of the target location, what evidence can be offered that neural processes in FEF have something to do with bringing this about? We have argued above that the postmask activation observed in visual cells in hit and false alarm trials should not be interpreted as a motor command. We will now demonstrate that the signals generated by the visual neurons in FEF are in a position to modulate activity in extrastriate visual cortex.

FEF provides a strong feedback projection to extrastriate visual cortex (e.g. Schall et al., 1995b). As illustrated in Fig. 9, many neurons in the upper and lower cortical layers of FEF and surrounding prefrontal cortex provide a feedback projection to inferior temporal and posterior parietal cortex. Of course, we do not know the physiological properties of the labeled neurons, but we have some information about where neurons that participate in visual selection are located in FEF. Fig. 10 shows a reconstruction of recordings from the FEF of one monkey; it illustrates where neurons involved in visual selection during search were recorded (Thompson et al., 1996). Nineteen of 35 neurons were localized in the supragranular layers, with nine in the infragranular. Admittedly falling short of direct evidence, we believe it is plausible that at least some of the visual selection neurons we recorded in this study contribute to the feedback projection to extrastriate visual cortex.

Taken together with the work reviewed above on the properties of movement cells in FEF, these data suggest the diagram shown in Fig. 11. This diagram is derived from the well-known pattern of feedback connectivity between cortical areas (e.g. Felleman & Van Essen, 1991; Salin & Bullier, 1995; Rockland, 1997). Pyramidal cells in layer V send motor commands to subcortical oculomotor structures. Neurons in layer V also provide feedback to extrastriate visual cortex. Pyramidal cells in the supragranular layers do not project subcortically, but they project to extrastriate visual cortex and terminate in the upper and lower cortical layers.

Earlier studies have related the activity in extrastriate cortical areas with perceptual states while viewing ambiguous stimuli (Logothetis & Schall, 1989; Britten et al., 1996; Leopold & Logothetis, 1996; Sheinberg & Logothetis, 1997; Bradley et al., 1998; Kim & Shadlen, 1999). The results of this study identify another putative neural correlate of visual awareness. Under the conditions of the present study, it is possible that the selective postmask activation in FEF is correlated not only with 'yes' responses, but also with a perceptual experience of the target. The prolonged postmask activity when the monkeys responded 'yes' satisfies the condition of activity being of necessary magnitude and duration (Libet et al., 1991; see also Koch & Crick, 1994).

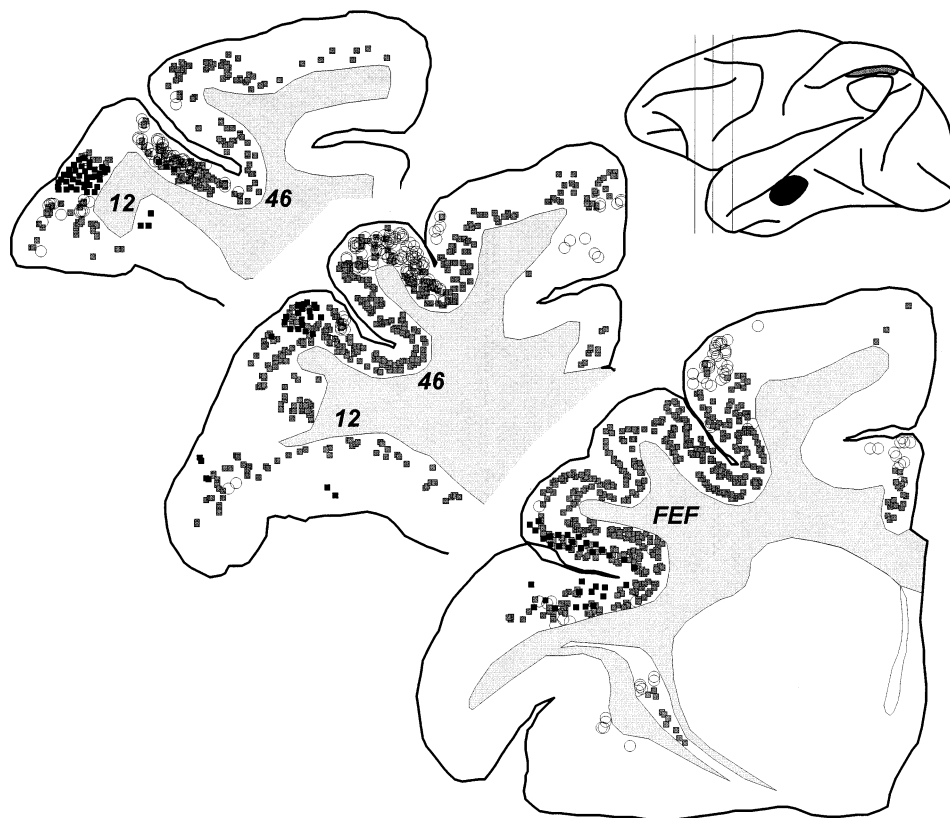


Fig. 9. Neurons in frontal cortex retrogradely labeled by tracer injections in inferior temporal cortex (black squares), the convexity of posterior parietal cortex (open circles), and the lateral bank of the intraparietal sulcus (gray squares). The locations of the injections are indicated on a lateral view of the brain as are the levels of the three coronal sections. Neurons in the supragranular and the infragranular layers in the frontal eye field (FEF) as well as in prefrontal areas 46 and 12 projected back to extrastriate visual cortex. (adapted from Schall et al., 1995b).

Many have suggested that enhanced activation of visual cortex corresponds to visual attention (e.g. Desimone & Duncan, 1995) and leads to visual awareness even during imagery (Farah, 1989; Kosslyn, Thompson, Kim & Alpert, 1995; Kosslyn, Pascual-Leone, Felician, Camposano, Keenan, Thompson et al., 1999). We hypothesize that the selective activation we observed in FEF visual neurons modulates ongoing processing in visual areas (Lamme, Super & Spekreijse, 1998; Tomita, Ohbayashi, Nakahara, Hasegawa & Miyashita, 1999). This modulation results in enhanced activity of neurons in visual cortical areas representing the location where the target was detected in hits and in false alarms and perhaps also the neurons signaling the properties of the stimulus. This top-down modulation, we hypothesize, is a critical event to make explicit the interpretation of the ambiguous sensory input.

Of course, we do not wish to claim that FEF is uniquely responsible for visual awareness. Nevertheless, evidence indicates that prefrontal cortex plays some role in awareness. First, fMRI studies have shown that areas of prefrontal cortex, possibly including FEF, exhibit activation associated with binocular rivalry (Lumer et al., 1998) even when subjects make no overt

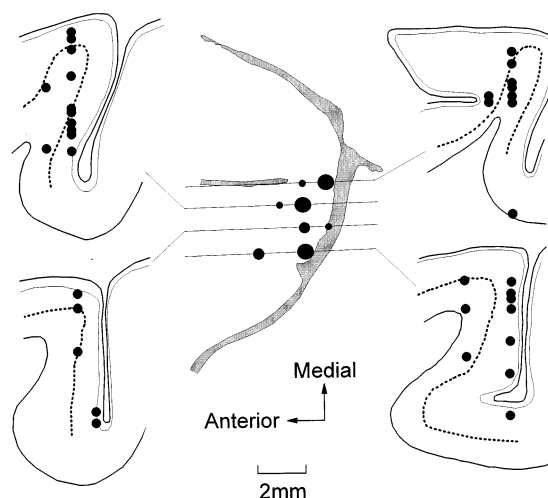


Fig. 10. Locations of neurons in FEF that contribute to saccade target selection during visual search. Circles indicate the locations of neurons in four sagittal sections through the arcuate sulcus. Layer 4 is shown by the dashed line in each section. The level of each section is indicated on the surface view of the arcuate sulcus region. (adapted from Thompson et al., 1996).

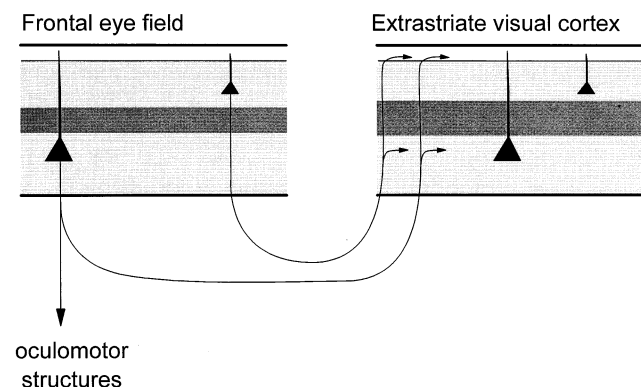


Fig. 11. Diagram of FEF output pathways. Pyramidal cells in layer V convey motor commands to oculomotor structures such as the superior colliculus and the pontine saccade generator. Neurons in layer V, possibly movement cells, project back to extrastriate visual cortex. Pyramidal cells in the layers II–III do not project to subcortical oculomotor structures but do convey signals back to extrastriate visual cortex. We propose that at least some of the visual selection neurons recorded during this study convey their signals to extrastriate visual cortex.

motor report (Lumer & Rees, 1999). Involvement of frontal cortex in rivalry dominance has also been demonstrated measuring neuromagnetic responses (Tononi et al., 1998). Second, in another fMRI study, activation of prefrontal cortex including FEF was observed specifically when a blindsight patient reported being aware of presented stimuli (Sahraie, Weiskrantz, Barbur, Simmons, Williams & Brammer, 1997). Fourth, the role of prefrontal cortex in working memory, which relates to visual awareness, is well-known in monkeys and humans (e.g. Courtney, Petit, Haxby & Ungerleider, 1998; Smith & Jonides, 1999; reviewed by Fuster, 1995). Moreover, recent neuroimaging has demonstrated a role for dorsolateral prefrontal cortex in explicit memory retrieval (Brewer, Zhao, Desmond, Glover & Gabrieli, 1998; Schacter, Buckner & Koutstaal, 1998). Thus, even if FEF is not directly responsible for generating visual awareness, we hypothesize that activation similar to the selective modulation we observed in FEF visual neurons occurs in whichever brain regions are related to the production of visual awareness.

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