DISSOCIATION OF SPATIAL VISUAL ATTENTION AND SACCADE PREPARATION IN MACAQUE FRONTAL EYE FIELD

By

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CHAPTER I

INTRODUCTION

Numerous studies have investigated the link between eye movements and attention. Some researchers have suggested that shifts of attention and eye movements are tightly linked (Shepherd and others 1986; Henderson 1992; Sheliga and others 1994, 1995; Chelazzi 1995; Kowler and others 1995; Hoffman and Subramaniam 1995; Deubel and Schneider 1996; Hunt and Kingstone 2003; Peterson and others 2004). This view is known as the oculomotor readiness hypothesis (Klein 1980; Klein and Pontefract 1994) or, in its more extreme form, the premotor theory of attention (Rizzolatti 1983; Sheliga and others 1994, 1995). According to the premotor theory of attention, shifts of attention are equivalent to subthreshold activation of neurons that program saccades (Sheliga and others 1994; Moore and Fallah, 2004). Others have argued that the mechanisms for preparing eye movements and for shifting attention are distinct but interact (Klein 1980, 1994; Corbetta 1998; Juan and others 2004). While the behavioral evidence for a relationship between attention and saccades is convincing, the evidence that the neural mechanism producing saccades is identical to that shifting attention is much more rare and not as convincing.

To test the premotor theory of attention, it is necessary to dissociate states of attention from states of motor preparation. To give an example of how this might be done, Sato and Schall (2003) trained monkeys on a search task that

required a saccade either towards (prosaccade) or directly opposite (antisaccade) a color singleton based on its orientation. This paradigm dissociates the locus of attention from the endpoint of a saccade at least momentarily because monkeys must attend to but not look at the singleton in antisaccade trials. On a neural level, most visually responsive neurons in the frontal eye fields (FEF) select the singleton in prosaccade trials as observed previously (Sato and Schall 2003). In antisaccade trials, interestingly, most visual neurons in FEF select the singleton and then the endpoint of the saccade (Figure 1). The neurons in FEF that selected the singleton in antisaccade trials were designated *Type I* to distinguish them from other visually responsive neurons that only selected the endpoint of the saccade in antisaccade trials; these were designated *Type II*. Further evidence that these two populations of neurons instantiate different functions was obtained in prosaccade trials. Type I neurons selected the singleton in prosaccade trials at a time synchronized on array presentation and unrelated to when the saccade was initiated. In contrast, Type II neurons selected the singleton in prosaccade trials at a time unrelated to array presentation and partially predictive of when the saccade was initiated.

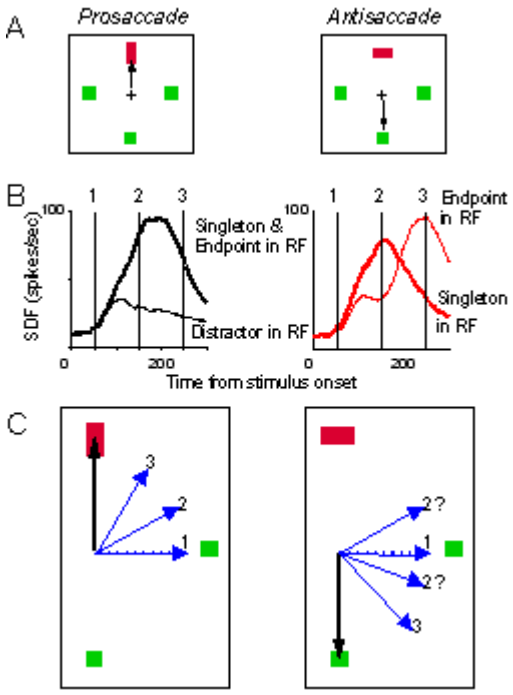

Figure 1. Schema of the task, typical FEF neural activity, and predictions made by the hypothesis.

Experimental design. *A*: Vertically oriented singleton required a saccade towards the singleton (left, prosaccades). Horizontally oriented singleton required a saccade towards the opposite location (right, antisaccades). *B*: Average firing rate of neurons that fire selectively for the singleton and then the correct endpoint in antisaccade trials (Type I neurons, n = 23) from Sato and Schall (2003). *Left*: Visually responsive neurons fire selectively for the singleton in prosaccade trials. The time at which activity becomes significantly greater for the singleton is the singleton selection time (SST). *Right*: Most visually responsive neurons first fire selectively for the singleton and then fire selectively for the correct endpoint of the saccade in antisaccade trials. The time at which activity becomes significantly greater for the endpoint is endpoint selection time (EST). Vertical lines 1-3 indicate representative times at which microstimulation was applied. *C*: The horizontal-rightward dotted blue line represents the average direction of microstimulation-evoked saccade endpoints in the dark. This direction varied across sites, and the stimulus array was rotated in each session to accommodate this variability. In sessions in which the singleton was presented at two locations, represented here, the array was tilted such that one distractor was at the location of the direction of saccades evoked in the dark and the two singleton locations were orthogonal to this location. Blue arrows represent the predicted deviation of evoked saccades when microstimulation was applied at each of the three times indicated in *B*, supposing that the microstimulation-evoked endpoints in the dark were horizontal-rightward. Black arrows represent the correct saccade. In both prosaccade (left) and antisaccade (right) trials, saccades evoked before the singleton is selected should not deviate (time 1). Saccades evoked shortly before saccade initiation (time 3) should deviate toward the correct endpoint of the saccade, which is the singleton in prosaccade trials and is opposite the singleton in antisaccade trials. Saccades evoked between the singleton selection time and endpoint selection time (time 2) in antisaccade trials could deviate either towards the singleton or the correct endpoint, either supporting or refuting the premotor theory, respectively.

Although these results suggest that the activity of different neurons in FEF may correspond to separate attentional and motor states, it is prudent to examine whether other results agree with this claim. Several lines of evidence support the conclusion that visual activity in FEF corresponds to the allocation of attention. First, in Sato and Schall (2003), the monkeys by design had to locate and discriminate the singleton to perform the task; when humans perform similar tasks, color singletons automatically capture attention (e.g., Theeuwes and Godijn 2002; Theeuwes and others 2003), even when not task-relevant. Second, perhaps through spatially-specific modulation of visual responses in area V4 (Moore and Armstrong 2003), electrical stimulation of FEF improves detection of a stimulus in the movement field of the stimulated site when competing visual stimuli are present (Moore and Fallah 2000, 2004). Third, transcranial magnetic stimulation over FEF in humans can influence visual detection (Grosbas and Paus 2002, 2003) and performance in a visual search task in which eye movements were not required (Muggleton and others 2003). Fourth, numerous functional imaging studies have shown that FEF is modulated in covert and overt orienting tasks in humans (Sweeney and others 1996; Corbetta 1998; Corbetta and others 2002; Cornelissen and others 2002; Donner 2002; Lepsien and others 2002; Matsuda and others 2002; Shulman and others 2003; Koyama and others 2004; Makino and others 2004). Finally, in a visual search task that required a forelimb and not an eye movement response in monkeys, Thompson and others (2005) found complete inhibition of saccade-related movement neurons but enhancement of visual activity that was consistent with attention allocation.

The FEF is also widely known to be involved in saccade production in both monkeys (reviewed by Schall and others 1997, Bruce and others 2004, Munoz and Schall 2003; Tehovnik and others 2000) and humans (Blanke and others 2000; Connolly and others 2004). Presaccadic movement-related neurons are modulated sufficient to control saccade initiation, but visual neurons are not (Hanes and others 1998). Similar distinctions exist in the superior colliculus (SC) (Horwitz and Newsome 1999; Paré and Hanes 2003; McPeek and Keller, 2004). Applying the premotor theory to entire areas is too general because of the diversity of neuron types within the FEF and SC. Thus, because both attentional and motor activity occur in the FEF, it is an ideal area in which to test the premotor theory of attention.

The evolution of saccade preparation can be probed using a property of saccades evoked by microstimulation of FEF or superior colliculus. Saccades evoked in one direction when monkeys are preparing a saccade to a stimulus in another direction exhibit a systematic deviation in the direction of the partially prepared saccade (Sparks and Mays 1983). This property has been used to probe the preparation of saccades during various tasks (Kustov and Robinson 1996; Gold and Shadlen 2003; Barborica and Ferrera 2004; Opris and others 2005). Juan, Shorter-Jacobi, and Schall (2004) used this method to investigate saccade preparation in monkeys performing singleton visual search with prosaccade or antisaccade responses (Figure 1). The premotor theory of attention was tested by applying microstimulation at times in antisaccade trials when visually responsive neurons have selected the singleton. Deviation of

microstimulation-evoked saccades toward the singleton in antisaccade trials would be evidence for the premotor theory, showing that allocation of attention to the singleton influences saccade preparation. Deviation of microstimulation-evoked saccades only towards the correct endpoint would be evidence against a strong interpretation of the premotor theory because saccade preparation was not influenced by the allocation of attention to the singleton. Juan and others found that saccades evoked during prosaccade trials deviated towards the singleton, but saccades evoked during antisaccade trials deviated only towards the saccadic endpoint.

The Juan and others (2004) study had a limitation, though, because the singleton was presented only at the two locations orthogonal to the evoked saccade. Consequently, the latency difference between prosaccades and antisaccades that is typically observed (Hallet and Adams 1980) was minimal in one monkey and absent in the other. This is not unusual in macaque neurophysiology experiments. Other neurophysiological studies using antisaccades with macaque monkeys have included data with minimal or absent latency costs (Gottlieb and Goldberg 1999; Gold and Shadlen 2003) or even latency benefits (Amador and others 1998; Gottlieb and Goldberg 1999) for antisaccade trials. However, prosaccade and antisaccade latencies are modifiable by practice (Dyckman and McDowell 2005; Amador and others 1998), by task conditions (Fischer and Weber 1997; Kristjansson and others 2001, 2004; Olk and Kingstone 2003) and top-down expectations (Gmiendl and others 2005). Sato and Schall (2003) found a significant antisaccade latency cost using

the same task with two of the same monkeys. Microstimulation, combined with practice, may have sped up antisaccades but led to an overall slowing of prosaccades when comparing Sato and Schall (2003) with Juan and others (2004; see Figure 3).

The time between the selection of the singleton and selection of the endpoint in antisaccade trials is crucial, however, to this experimental test of the premotor theory of attention. It is during this time, between the presentation of the array and the saccade, that attention is allocated to the singleton. Sato and Schall (2003) defined the time at which neurons differentiated the singleton from the distractors as singleton selection time (SST) and the time at which neurons differentiated the endpoint from the singleton in antisaccade trials as endpoint selection time (EST). The lack of a clear latency cost for antisaccades in our original microstimulation investigation introduces the possibility that the interval between the SST and EST might have been too short or even absent, unlike what occurred during the original physiology study of Sato and Schall (2003). This is a problem insofar as the hypothesis concerns what happens when microstimulation is applied during the interval between SST and EST. Therefore, the present experiment introduced more uncertainty in the singleton location by presenting the singleton at four locations with equal probability. Target location uncertainty is correlated with antisaccade latency costs (Evkokimidis and others 1996); higher target probability results in decreased prosaccade and antisaccade latencies (Gmiendl and others 2005). As expected, the increased uncertainty of

singleton or endpoint location reinstated the antisaccade latency cost, and the pattern of deviations reported in Juan and others was replicated.

CHAPTER II

METHODS

Surgical and Stimulation Procedures

A detailed description of procedures have appeared previously (Schall and others 1995; Sato and Schall 2003). Two adult macaque monkeys (*Macaca mulatta* and *M. radiata*) were prepared for neurophysiological stimulation and eye movement monitoring by placing a recording chamber over the frontal eye fields, a titanium restraint post on the skull, and a scleral search coil in one eye (Robinson 1963) aseptically under isofluorane anesthesia. All procedures complied with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals* and were approved by the Vanderbilt University Institutional Animal Care and Use Committee.

Monkeys were trained to fixate squares presented on a Sony Trinitron Color Graphic Display (vertical refresh rate 90 Hz) and to make saccades to eccentric visual targets. Monkeys were then trained in a visual search task in which four stimuli were presented (Figure 1). If the color singleton was a vertically oriented rectangle, monkeys were rewarded for making a saccade

towards the stimulus. If the singleton was a horizontally oriented rectangle, monkeys were rewarded for making a saccade directly opposite the singleton.

Suprathreshold microstimulation was delivered through tungsten microelectrodes (FHC, 2-4 MΩ; 40-60 ms trains of 20-30 0.3 ms biphasic pulses, 500 Hz) at 50-90 μA through a FHC Pulsar 6b stimulator and two FHC bp isolators that created optically isolated, constant-current, biphasic pulses.

Experimental Design

Monkeys searched a four-stimulus array of isoluminant stimuli (14.2 cd/m^2 on a black background) for a red singleton (CIE x = 638, y = 335) among green (CIE x = 272, y = 617) distractors or vice versa. These color complements randomly alternated across trials. Distractors subtended 1° at 57 cm. Singleton aspect ratio ranged from 1.3 to 2.1, and singletons were of equal area as the distractors. Eccentricity of the search array was typically 10º, corresponding to the movement field of the evoked saccades. Monkeys first performed an eye calibration procedure to map the analog signal to visual field coordinates in visual degrees. The procedure consisted of making saccades to a stimulus presented in four locations on orthogonal axes. The axes were tilted relative to the horizontal meridian in increments of 15° of polar angle`. Monkeys performed the calibration procedure and visual search until a site was found at which microstimulation reliably evoked saccades.

Electrodes were lowered into the left frontal eye field of both monkeys. At each depth, stimulation was delivered after the monkey foveated a visual

stimulus. If saccades were reliably evoked with a threshold around 50 μA or less (Bruce and Goldberg 1985), the site was considered adequate for further investigation. Approximately 60 saccades were evoked at random times from each site while the monkey sat in the dark. The average direction of the saccades evoked in the dark was measured. The stimuli in the search task were located on orthogonal axes, with two stimuli 45° from the average direction of the saccades evoked in the dark.

The monkey then performed the search task. The monkey was required to fixate the center of the screen for 400-700 ms. Four stimuli were then presented with equal eccentricities and uniform spacing, and the fixation point was simultaneously extinguished. In sessions in which the singleton was presented at four locations, the array was tilted such that two stimuli locations were each 45º away from the direction of the saccades evoked in the dark. For 11 of the 15 sites in monkey P, the singleton was presented at only two of four possible locations, both orthogonal to the angle of the dark-evoked saccades. 33 sites were obtained from monkey L.

Stimulation was delivered at one of three times after the display presentation (Figure 2). The three times were constant within a session but varied across sessions to test the effects of stimulation at 0-200 ms subsequent to array presentation. The first stimulation time ranged from 10-60 ms, the second from 70-120 ms, and the third from 130-180 ms, in 10 ms increments. In 11 of the 15 sessions for monkey P, stimulation was also delivered synchronously with array onset either at the beginning or in the middle of the

session. Half of all trials were stimulation trials, with stimulation times evenly distributed across all three categories.

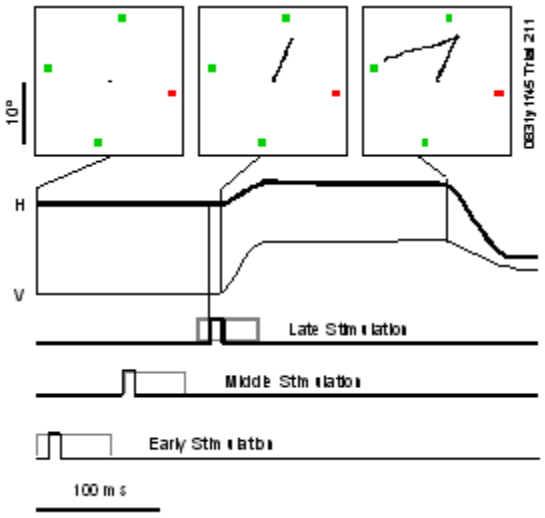

Figure 2. Sample antisaccade trial with microstimulation-evoked and voluntary saccades illustrated.

Example of a trial in which microstimulation was applied 130 ms after the presentation of the array. Search stimuli and eye position in display are drawn to scale; singleton aspect ratio was 1.3-2.1. Horizontal (thick) and vertical (thin) eye position. Microstimulation evoked a saccade up and to the right. It was followed by a self-generated saccade towards the correct endpoint location. The top pulse indicates the time of microstimulation for this trial. The other two black pulses indicate the other two times of microstimulation for this session. The intervals marked in gray indicate the times at which microstimulation could be applied across all sessions.

The monkeys were permitted 1,000 ms to initiate a saccade from the fixation point to the endpoint specified by the singleton. The monkeys then had to fixate the stimulus at the correct endpoint for 500 ms to receive a juice reward. A punish time of 1 second was imposed if the monkey failed to perform as specified above. All trial types were randomly interleaved.

Data Analysis

Eye movement data were recorded at a sampling rate of 250 Hz. Saccades were defined as the beginning and end of the monotonic change in eye position surrounding an eye velocity that exceeded 30°/s for at least 16 ms. The analog voltage of eye movements was converted into visual field coordinates by means of a nonlinear polynomial of the following form:

$$H_{Degrees} = a + b \cdot H_{Voltage} + c \cdot V_{Voltage} + d \cdot H_{Voltage} \cdot V_{Voltage}$$

$$V_{Degrees} = a + b \cdot V_{Voltage} + c \cdot H_{Voltage} + d \cdot V_{Voltage} \cdot H_{Voltage}$$

where $H_{Degrees}$ and $V_{Degrees}$ are the visual field coordinates in degrees , and $H_{Voltage}$ and $V_{Voltage}$ are digitized voltages. These coefficients were used to fit the eye movement data from the rest of the session. Importantly, this also included optimizing the axes and eccentricity of the search array subsequent to finding the stimulation site. The median endpoint of the saccades towards each singleton location was computed. If a saccade ended in a region ± 4 degrees of this median, it was counted as correct.

Trials were grouped after they were collected according to whether they were prosaccade or antisaccade trials and according to stimulation latency times. In most sessions, to our surprise, the direction of saccades evoked at the earliest microstimulation time was different than the direction of the saccades evoked in the dark. Thus, saccade deviations following later stimulation times were measured relative to the average direction of the saccades evoked at the earliest stimulation time. Note, though, that the overall conclusions did not change if this adjustment was not done. Evoked saccades that ended in the correct location were not included in the computation of the mean direction. If there was only one saccade that ended in an incorrect location and that was evoked at the earliest microstimulation time, then saccade deviations were measured relative to the angle of the saccades evoked in the dark. Deviations were only analyzed for saccades evoked at the last two microstimulation times. Stimulation trials in which the stimulated and subsequent voluntary saccade did not fall within the correct regions were excluded. Stimulation trials in which the evoked saccade latency relative to the time of stimulation was greater than 60 ms or less than 0 ms were excluded.

Measurement of Deviation

Microstimulation-evoked endpoints deviating toward the singleton were denoted as positive, and microstimulation-evoked endpoints deviating opposite the singleton (i.e., toward the antisaccade endpoint) were negative. The analysis of deviation was limited by the geometry of the saccades in the array.

Microstimulation-evoked endpoints in the quadrant opposite the average angle of the saccades evoked at the earliest microstimulation time had no clear angular definition relative to the singleton. Therefore, all microstimulation-evoked endpoints falling in the 90º quadrant directly opposite the baseline direction were not counted in subsequent analyses.

Classification of Type I and Type II Neurons

Type I were distinguished from Type II neurons through an algorithm slightly different from that of Sato and Schall (2003). The neuron types were distinguished by whether and when they selected the singleton or the endpoint in antisaccade trials. The measurement was derived simply from the difference in activity in trials with the singleton in the response field and activity in trials with the singleton opposite the response field (endpoint on antisaccade in response field). A baseline criterion was determined from the activity before the visually evoked response, and the presence and times of singleton selection and endpoint selection were determined by whether and when the time-varying difference in activity exceeded this criterion. The baseline criterion used by Sato and Schall (2003) was just the mean plus or minus two standard deviations of the difference in activity preceding the visual response. We found that this criterion was overly sensitive to the modulation of movement neurons that had very low baseline discharge rates. Therefore, a different measure of baseline criterion variability was calculated as follows: (1) The standard deviation of the time-varying difference between the mean activity from trials in which the singleton

was in the response field and the mean activity from trials when the singleton was opposite the response field (making the endpoint of the antisaccade in the response field) was computed in the 100 ms interval beginning 50 ms before array presentation. (2) The logarithm of 1 plus this standard deviation was taken; the addition of 1 prevented large negative logarithm values. (3) If this baseline criterion variability was less than 0.05, then 0.5 was added to it; this compensated for the very low firing rates in movement neurons. The time after array presentation at which the time-varying difference between activity in trials with the singleton in the response field and activity in trials with the singleton opposite the response field (endpoint of antisaccade in response field) first exceeded the mean plus or minus the baseline criterion variability for at least 30 ms was measured. To ensure that this difference in activity was reliable, an additional criterion was applied that was derived from the area under the activity difference plot. The area under the difference plot was integrated from the instant of first exceeding the baseline criterion until the instant when the difference returned below the baseline criterion. If this integrated area exceeded an arbitrary threshold, then the modulation was taken as significant. The arbitrary threshold, determined through trial-and-error, was 370 times the maximum firing rate of the neuron across all trials divided by 57. If the difference resulted from significantly greater activity when the singleton was in the response field, this was counted as singleton selection time (SST). If the difference resulted from significantly greater activity when the endpoint of the antisaccade was in the response field, this was counted as endpoint selection

time (EST). The same criteria were applied to determine stimulus-response mapping time (SRT), the time at which the orientation of the singleton was first distinguished and the stimulus-response mapping rule encoded. For test-retest verification, we measured the difference between the new SST and EST values and those of Sato and Schall (2003); the mean absolute differences were 2.1 ms for prosaccade SST, 1.5 ms for antisaccade SST, and 0 ms for EST and SRT.

Errors

Thirty-five percent of monkey L's data and 50% of monkey P's data were excluded based on the criteria presented. Most of the exclusions were based on final saccades to the wrong location, although many trials from monkey P were excluded because the evoked saccade either had a negative latency relative to the time of stimulation or latency greater than 60 ms. Deviations in error trials went towards the singleton in prosaccade trials but also in antisaccade trials. Most of the rest of the exclusions were due to the trial being aborted from the effect of microstimulation but some were due to eye position calibration. Evidently, the high fraction of stimulation trials disrupted performance. When physiological recordings were done, these monkeys performed at high rate (average of 7% incorrect).

CHAPTER III

RESULTS

Saccade Latency

Figure 3 compares the saccade latencies in non-stimulated trials measured in this study with those obtained in the original single-unit physiology study (Sato and Schall 2003) and with those obtained in the previous microstimulation search experiment (Juan and others 2004). In the single-unit study in which the singleton appeared with equal probability at the four locations antisaccade latencies were significantly longer than prosaccade latencies. In the previous microstimulation experiment with the singleton appearing at only two locations, this difference was minimal in one monkey and absent in the other. However, in the current study, when the singleton could appear with equal probability at each of the four locations in the array, the difference between antisaccade and prosaccade latencies in non-stimulated trials was clear (monkey L: prosaccades: mean = 198.5 ms, st. dev. = 39.4, antisaccades: mean = 211.7 ms, st. dev. = 39.8, $t(890) = 5.99$, $p < 0.001$; monkey P: prosaccades: mean = 173.8 ms, st. dev. = 31.4, antisaccades: mean = 191.8 ms, st. dev. = 35.2, $t(329) = 9.76$, $p < 0.001$). To verify the effect of singleton location uncertainty on saccade latency, monkey P was tested in some sessions in which the singleton was presented at only two locations. The latencies of prosaccades and antisaccades were much shorter but were still significantly different although

more similar (prosaccades: mean = 140.6 ms, st. dev. = 82.4, antisaccades: mean = 149.0, st. dev. = 55.8, $t(811) = 4.79$, $p < 0.001$), in contrast to the findings of Juan and others (2004). Clearly, monkeys can adjust saccade latency in this task because two of the monkeys in this study were also tested in Juan and others (2004).

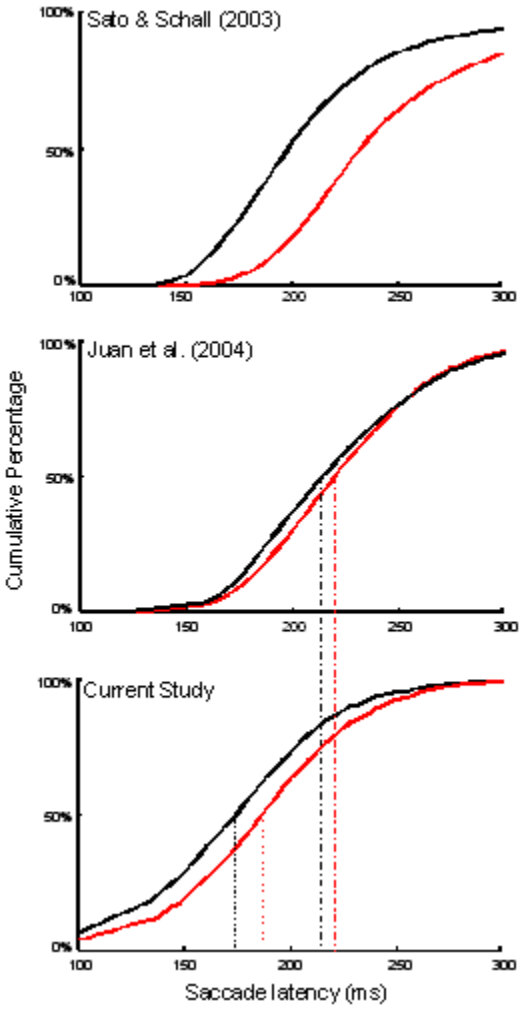

Figure 3. Prosaccade and antisaccade latencies from the current study and two previous studies.

Cumulative distributions of latencies of saccades in non-stimulated trials from this study, Juan et al. (2004), and Sato and Schall (2003). There was a significant latency cost for antisaccades in this study and in Sato and Schall (2003). The overall cost was not significant in Juan et al. (2004) when the singleton appeared at only two of the four array locations. Vertical lines mark median latencies.

Properties of Evoked Saccades

Each site was characterized by the threshold and angle of the dark-evoked saccades. Stimulation at 39 of 48 sites evoked saccades into the upper quadrant. The latencies of the evoked saccades decreased with increasing delay of microstimulation (monkey L: $t(7327) = -47.01$, $p < 0.001$; monkey P, 2 singleton locations: $t(331) = -2.27$, $p < 0.05$; monkey P, 4 singleton locations: $t(124) = -7.02$, $p < 0.001$) (Figure 4A). This decreasing latency supports the claim that the deviation measurement used in this study samples the moment-by-moment state of saccade preparation. We were surprised to find that commonly the angle of the endpoints of microstimulation-evoked saccades at the earliest microstimulation time differed from the angle of the endpoints of microstimulation-evoked saccades in the dark (Figure 4B), most commonly being rotated slightly counter-clockwise. Sites at which microstimulation-evoked endpoints in the dark were in the lower quadrant typically had microstimulation-evoked endpoints at the earliest microstimulation time in the upper quadrant (Figure 4C). A Watson-Williams test (Batschelet 1981) was performed on the angles of the microstimulation-evoked endpoints at the earliest microstimulation time to determine if the angle changed as a function of the location of the singleton. The angle of the microstimulation-evoked endpoints at the earliest microstimulation time did not differ significantly as a function of the location of the singleton in 47 of 48 sessions. Thus, this rotation was not a function of the direction of the saccade produced to perform the visual search task. To reduce noise in the main analysis, the deviations of the microstimulation-evoked

endpoints at the later microstimulation times in the visual search task were measured relative to the average angle of the microstimulation-evoked endpoints at the earliest microstimulation time of each session. However, the main observations were qualitatively identical to deviations measured relative to the microstimulation-evoked endpoints in the dark.

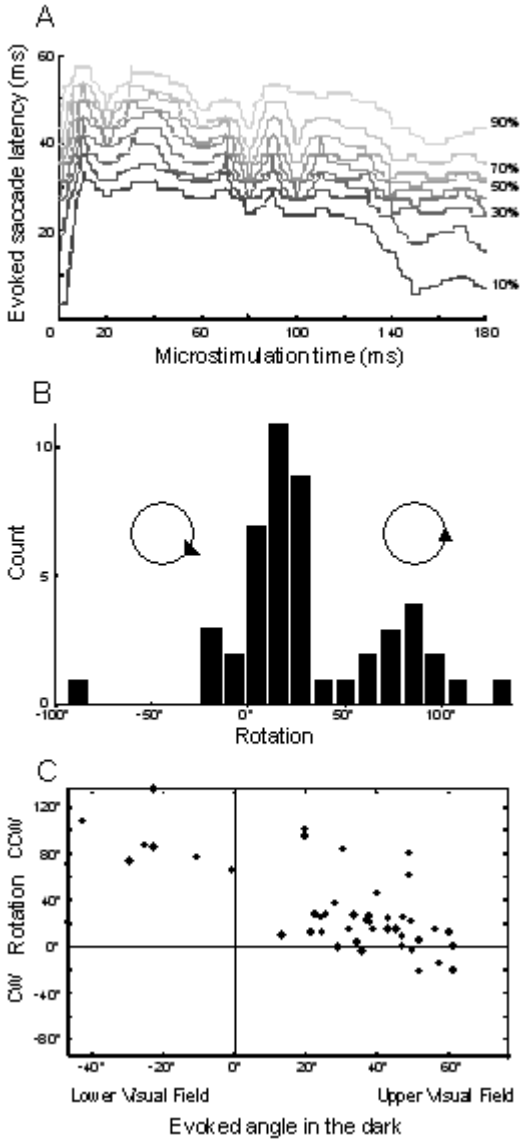

Figure 4. Microstimulation-evoked saccade latency by microstimulation time, histogram of rotation of direction of saccades evoked at the earliest microstimulation time from saccades evoked in the dark, and rotation of saccade direction as a function of the direction of saccades evoked in the dark.

Properties of saccades evoked by microstimulation. *A*: Quantile plot of the distributions of latencies of evoked saccades as a function of the time at which microstimulation was applied. Latency of evoked saccades tended to decrease with increasing microstimulation delay. *B*: Histogram of the rotation of direction of microstimulation-evoked saccade endpoints in the dark relative to those evoked at the earliest microstimulation time. *C*: Rotation of direction of saccades evoked at the earliest microstimulation time relative to the direction of saccades evoked in the dark plotted as a function of the direction of saccades evoked in the dark. Most saccades evoked in the dark were in the upper quadrant, and most rotated slightly counter-clockwise (CCW; CW is clockwise). All sessions in which the saccades evoked in the dark were in the lower quadrant rotated counter-clockwise.

Analysis of Deviation: Main Result

Figure 5A plots the microstimulation-evoked endpoints at the earliest microstimulation time from a representative site in FEF. Figure 5B plots the eye position traces of all stimulated trials for the last two stimulation times after which the monkey shifted gaze to the correct location to earn reinforcement and Figure 5C plots only the endpoints. Some microstimulation-evoked endpoints at the later microstimulation times fell towards the singleton location and others fell towards the location opposite the singleton. Figure 5D plots the deviation of the microstimulation-evoked endpoints as a function of microstimulation time for this session. Microstimulation-evoked endpoints on prosaccade trials deviated towards the singleton, and microstimulation-evoked endpoints on antisaccade trials deviated towards the correct endpoint but not the singleton. The deviation increased with increasing microstimulation latency, demonstrating the progression of saccade preparation.

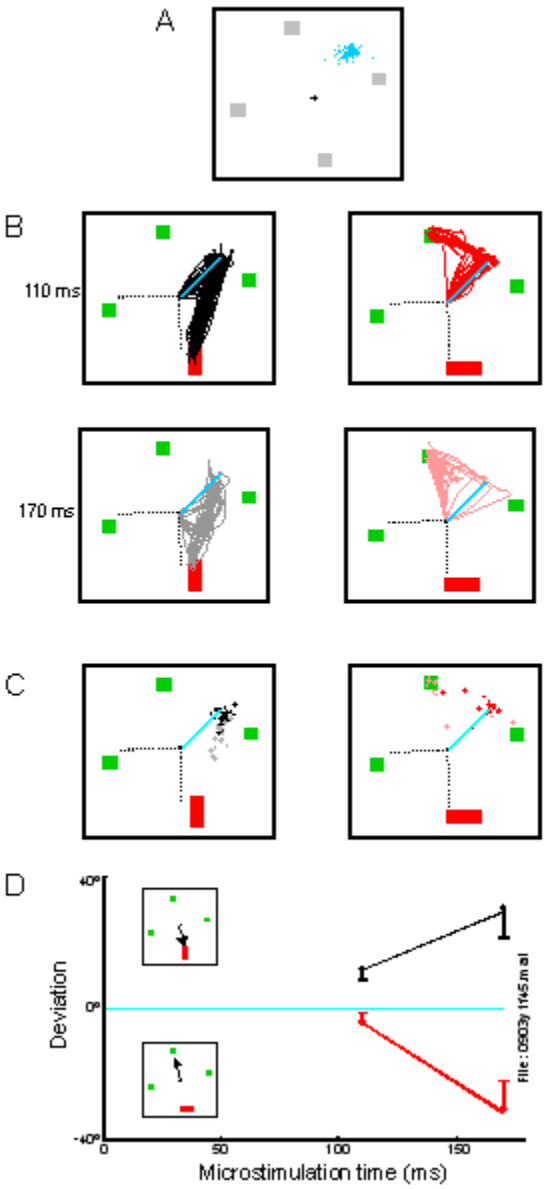

Figure 5. Microstimulation-evoked and voluntary saccade trajectories from an example session and the mean deviation of prosaccades and antisaccades.

Data from representative session. *A*: Endpoints of saccades evoked at the earliest microstimulation time are plotted as cyan dots. Gray squares represent the locations at which stimuli were presented. *B*: The cyan line represents the average direction and amplitude of the saccade endpoints in A. Trials in which a saccade was evoked 110 ms (top) or 170 ms (bottom) after the presentation of the array and the subsequent self-generated saccade was correct are plotted for prosaccades (left) and antisaccades (right). If an evoked saccade fell within the area marked by the two dotted black lines, the trial was excluded from analysis. Search array not drawn to scale. *C*: Endpoints of the evoked saccades in *B* are plotted with the color corresponding to the time of microstimulation. The display is not drawn to scale. *D*: Deviation of the endpoints of the evoked saccades is plotted with positive values signifying deviation towards the singleton and negative, deviation away from the singleton. Deviation in prosaccade trials is plotted in black, and deviation in antisaccade trials is plotted in red. Deviation increases towards the correct endpoint with increasing microstimulation latency, and in antisaccade trials evoked saccades did not deviate toward the singleton. Error bar is 95% confidence interval.

Figure 6 plots the deviation of the microstimulation-evoked endpoints at all the last two microstimulation times saccades averaged across both monkeys. When the singleton was located 45-135º away from the angle of the microstimulation-evoked endpoints at the earliest microstimulation time (Figure 6A), deviations of microstimulation-evoked endpoints at the later microstimulation times in prosaccade trials were always towards the singleton and deviations of microstimulation-evoked endpoints at the later microstimulation times in antisaccade trials were always towards the antisaccade endpoint. The magnitude of the deviation increased with the delay of the electrical stimulation for both monkeys in prosaccade trials and antisaccade trials (Table 1). The same trend was present but not significant for antisaccade trials of monkey P when 4 singleton locations were used. When the singleton was located within 45º of the angle of the microstimulation-evoked endpoints at the earliest microstimulation time (Figure 6B), the deviations measured in prosaccade and antisaccade trials followed the same trend (Table 1); for monkey P, however, not enough prosaccade trials were present to conduct a test due to the configuration of the stimuli relative to the angle of the saccades evoked in the dark. When deviations were measured relative to the angle of the microstimulation-evoked endpoints in the dark, the results were qualitatively identical for both monkeys. Therefore, the pattern of results was not contingent on measuring deviation relative to the angle of microstimulation-evoked endpoints at the earliest microstimulation time. This reinforces the validity and reliability of our general conclusions. Thus, in monkeys exhibiting significantly longer antisaccade than

prosaccade latencies the pattern of deviation revealing the state of saccade preparation reported by Juan and others (2004) was replicated.

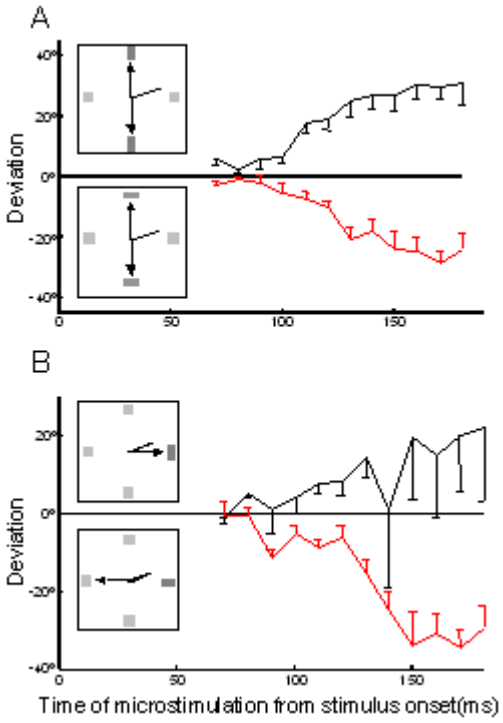

Figure 6. Deviation of prosaccade and antisaccades in sessions in which the singleton was either 45°-135° or 0°-45° away from the direction of the saccades evoked at the earliest microstimulation time.

Summary data. *A*: Deviation of evoked saccades across all sessions plotted as a function of microstimulation time. Deviation towards the singleton is plotted as positive. Data are only shown for trials in which the singleton location was 45°-135° away from the direction of the saccades evoked at the earliest microstimulation time. *B*: Deviation of evoked saccades when the singleton was 0°-45° away from the direction of the saccades evoked at the earliest microstimulation time. Error bar marks 95% confidence interval.

	Prosaccades		Antisaccades	
Monkey	45º-135º	0º-45º	45º-135º	0º-45º
L	$t(3293)=17.9^{**}$	$t(1088)=12.3^{**}$	$t(3464)=-18.3^{**}$	$t(1076)=-6.2^{**}$
P, 4 Locations	$t(45)=6.1^{**}$	N/A	$t(47)=-1.9$ $p=0.06$	$t(15)=-2.9^{**}$
P, 2 Locations	$t(144)=3.2^{**}$	N/A	$t(197)=-4.8^{**}$	$t(23)=-8.1^{**}$

Table 1. T values from linear contrasts on deviation of microstimulation-evoked saccades as a function of microstimulation time

t values are shown for linear contrasts on deviation of microstimulation-evoked saccades as a function of microstimulation time. Significant values indicate an increase in deviation with increasing microstimulation time. * indicates significance at the $p = 0.05$ level and ** indicates significance at the $p = 0.01$ level. 4 locations indicate the sessions in which the singleton was presented at all 4 locations; 2 locations, the sessions in which it was presented at only 2 locations.

Analysis of Deviation: Timecourse

One potential problem with the results presented so far is that the microstimulation may not have sampled the crucial interval after the singleton was selected but before the endpoint was selected in antisaccade trials. If the stimulation occurred only after the endpoint of the antisaccade (or prosaccade) was selected, then it is not unexpected to find deviations only towards the endpoint of the saccade that was about to be produced. We performed an analysis to address this concern. The analysis measured the frequency with which microstimulation was delivered in the period after the singleton was selected but before the endpoint was selected. Specifically, we calculated the probability that microstimulation was delivered between singleton selection time (SST) and endpoint selection time (EST) for each session. SST and EST were defined in the original physiology study of Sato and Schall (2003). The earliest SST occurred ~100 ms after array presentation; specifically, this value is the SST of Type I neurons in FEF (see Figure 2 of Sato and Schall 2003). SST of Type I neurons is equivalent on prosaccade and antisaccade trials and does not vary with saccade latency. In contrast to SST, EST varies with saccade latency, so a single value could not be used. The results of Sato and Schall (2003) show that under the conditions of this experiment EST was achieved approximately halfway between SST and saccade initiation. Thus, from the saccade latency for each trial we can derive a distribution of estimated ESTs for each session. It is simple to determine whether the start of microstimulation falls within this time window. However, the beginning of microstimulation is not necessarily the beginning of an

influence on the brain. Therefore, to estimate an upper bound on when the microstimulation could influence saccade preparation, we used the 50th percentile saccade latency for each microstimulation time from Figure 4A. Figure 7 plots the results of this analysis. The probability that microstimulation-evoked antisaccade latencies fell within this interval approached 100% when the microstimulation was applied from 70-100 ms after array presentation. Sessions in which a higher proportion of microstimulation-evoked antisaccade latencies were sampled between SST and the median EST are most likely, by the logic of our design, to show deviation towards the singleton in antisaccade trials. Figure 8 plots deviation as a function of microstimulation time separately for sessions in which the proportion of latencies of saccades evoked by microstimulation in antisaccade trials occurring between SST and EST was high or low. Consistent with the original finding, the endpoints of microstimulation-evoked saccades at the crucial times for “high” sessions never deviated toward the singleton in antisaccade trials.

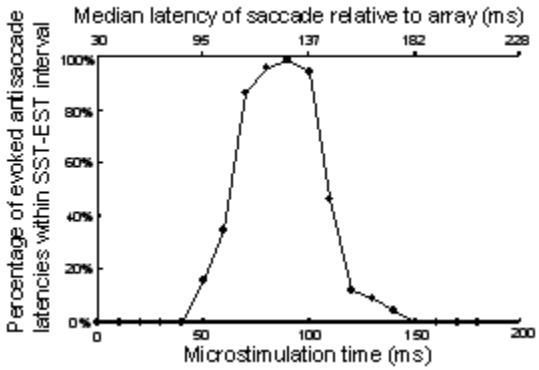

Figure 7. Proportion of antisaccade latencies with microstimulation within the interval between average singleton selection time (100 ms) and the median endpoint selection time estimated from the distribution of nonstimulated antisaccade latencies.

Proportion of antisaccade latencies with microstimulation occurring after singleton selection time and before endpoint selection time. Microstimulation applied 70-100 ms after presentation of the array was very likely to produce a saccade within this interval. Bottom axis plots microstimulation time. Top axis plots median latency of saccades evoked by microstimulation.

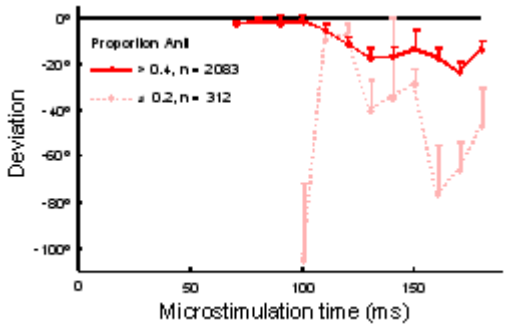

Figure 8. Saccadic deviation plotted as a function of microstimulation time.

Saccadic deviation plotted as a function of microstimulation time. Each line plots a subset of the data with a different proportion of stimulated antisaccade latencies within the interval between average singleton selection time (100 ms) and median endpoint selection time. There were only five sessions with a low proportion of antisaccade latencies within the crucial interval.

We explored whether other differences between “high incidence” and “low incidence” sessions might explain the difference in deviation between these sessions. We hypothesized that microstimulation-evoked antisaccade latencies in “low” sessions might occur more often after the estimated EST than “high” sessions. This would result in greater deviation for “low” sessions due to the interaction between the stimulated saccade and greater preparatory activity. The proportion of microstimulation-evoked antisaccades with latencies that occurred after the estimated EST out of the sample of microstimulation-evoked antisaccades with latencies that occurred either before or after the SST-EST interval was computed for “high” and “low” sessions. Microstimulation-evoked antisaccade latencies that occurred in the SST-EST interval were not included because doing so would make the proportion of antisaccade latencies after the SST-EST interval a function of the “low” and “high” categories. We applied an arcsine transformation to the proportions in order to perform a one-tailed paired t-test (Zubin, 1935), assuming unequal variances and using Satterthwaite's approximation for the degrees of freedom. There was a tendency for “low” sessions to have a higher proportion of microstimulation-evoked antisaccade latencies after the estimated EST than for “high” sessions (“high” sessions: mean = 0.57, st. dev. = 0.22, “low” sessions: mean = 0.77, st. dev. = 0.14; paired t-test: $t(8.1) = 2.2$, $p < 0.05$). When microstimulation-evoked antisaccade latencies within the SST-EST interval were included, this trend was stronger (“high” sessions: mean = 0.34, st. dev. = 0.14, “low” sessions: mean = 0.73, st. dev. = 0.16; paired t-test: $t(4.9) = 4.9$, $p < 0.01$).

This trend could be due to several factors: later microstimulation times for "low" sessions, later microstimulation-evoked antisaccade latencies in "low" sessions, or earlier EST's for "low" sessions, all of which would have resulted in more antisaccade latencies falling after the estimated EST. There was no significant difference in the times at which microstimulation was applied between "high" and "low" sessions ("high" sessions: mean = 96 ms, st. dev. = 55.1, "low" sessions: mean = 105 ms, st. dev. = 63.4; two-tailed paired t-test with unequal variances: $t(19.8) = 0.6$, $p = 0.6$). Thus, the greater deviation observed for "low" sessions was not caused by stimulating at later times in general. However, upon closer inspection, the proportion of "low" sessions with microstimulation times after 110 ms (the last time at which microstimulation, given an average saccade latency relative to stimulation of 30-40 ms, would produce a saccade within the average SST-EST interval) was higher than the corresponding proportion in "high" sessions (52% vs. 39%). Thus, "low" sessions were more likely to have microstimulation times after the interval in which saccades could be produced within the SST-EST interval. Moreover, for "low" sessions the latencies relative to stimulation of microstimulation-evoked antisaccades were slightly longer ("high" sessions: mean = 36.1 ms, st. dev. = 10.8, "low" sessions: mean = 38.4, st. dev. = 14.2; one-tailed paired t-test with unequal variances: $t(491) = 3.3$, $p < 0.001$). Finally, "low" sessions had a slightly earlier distribution of estimated EST's ("high" sessions: mean = 152 ms, st. dev. = 22.2, "low" sessions: mean = 148 ms, st. dev. = 21.4; one-tailed paired t-test with unequal variances: $t(1427.7) = -5.4$, $p < 0.001$). The strongest of these three effects is the greater proportion

of microstimulation times in “low” sessions that occurred after the EST. This, combined with slightly later stimulated antisaccade latencies and earlier EST’s, is consistent with more microstimulation-evoked antisaccades being produced in “low” sessions when preparatory saccade activity was greater, leading to larger deviation. Thus, the trend of “low” sessions to have a higher proportion of microstimulation-evoked antisaccade latencies after the estimated EST than for “high” sessions is incidental.

Analysis of Deviation: Relation to Final Endpoint

The location of the correct endpoint relative to the direction of the microstimulation-evoked endpoints at the earliest microstimulation time possibly could have an effect on saccade dynamics and latency. When analyzed as a function of the correct endpoint location, the pattern of evoked saccade deviation did not differ in any consistent way.

We analyzed saccade latencies as a function of the correct endpoint. Figure 9 plots latencies of evoked and non-evoked saccades separated by the location of the correct endpoint relative to the angle of the microstimulation-evoked endpoints at the earliest microstimulation time. When the angle of the microstimulation-evoked endpoints at the earliest microstimulation time and the correct endpoint were within 90º, saccades tended to be evoked more quickly than when they were more than 90º apart in prosaccade and antisaccade trials, although this trend was not always significant (Table 2). Moreover, the latency of self-generated saccades in non-stimulated trials was significantly shorter when

they landed close to the microstimulation-evoked endpoints at the earliest microstimulation time for monkey L and for monkey P when the singleton was presented at 2 locations (Table 2). When the singleton was presented at 4 locations for monkey P, the latencies of self-generated saccades in non-stimulated trials did not vary with direction relative to the microstimulation-evoked endpoints at the earliest microstimulation time. Thus, the latency of voluntary saccades can be affected by the direction of saccades evoked over the course of a session.

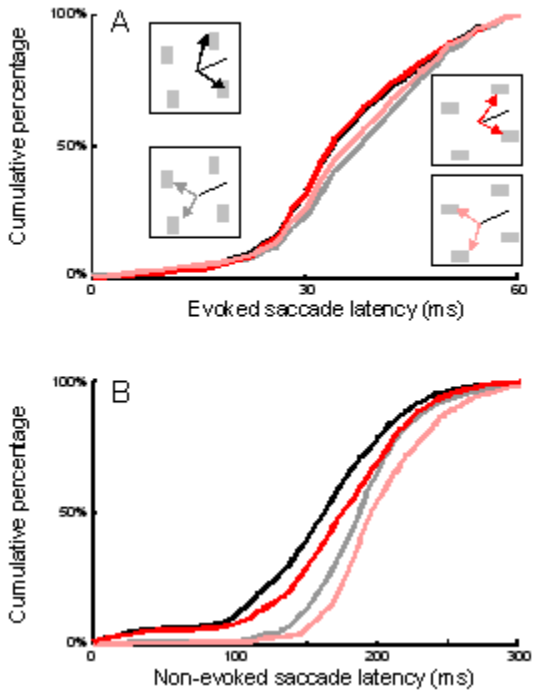

Figure 9. Cumulative distributions of latencies relative to the time of microstimulation of evoked saccades and cumulative latencies of self-generated saccades in non-stimulated trials.

A: Cumulative distributions of latencies relative to the time of microstimulation of evoked saccades. The black and red lines plot data from prosaccade and antisaccade trials, respectively, in which the endpoint was 0°-90° from the direction of saccades evoked at the earliest microstimulation time, plotted as a black line in the insets. The gray and pink lines plot data from prosaccade and antisaccade trials, respectively, in which the endpoint was 90°-135° away from the direction of saccades evoked at the earliest microstimulation time. *B*: Cumulative distributions of latencies of self-generated saccades in non-stimulated trials. Saccades latencies were shorter when the correct endpoint was closer to the direction of microstimulation-evoked saccade endpoints at the earliest microstimulation time.

	Prosaccades		Antisaccades	
Monkey	Stimulated	Non-stimulated	Stimulated	Non-stimulated
L	t(3781)=-8.5**	t(2923)=-4.0**	t(1048)=-11.1**	t(783)=-12.1**
P, 4 Locations	t(53)=-1.4	t(47)=-0.6	t(303)=1.5	t(146)=0.5
P, 2 Locations	t(130)=-0.7	t(153)=-2.1 p=0.06	t(305)=-10.4**	t(281)=-11.4**

Table 2. T values for comparison of latencies of saccades with correct endpoints 0°-90° or 90°-135° away from the direction of microstimulation-evoked endpoints at the earliest microstimulation time.

t values for comparison of latencies of saccades with correct endpoints 0°-90° or 90°-135° away from the direction of microstimulation-evoked endpoints at the earliest microstimulation time. Conventions as Table 1.

Analysis of Deviation: Latency and Curvature

In Figure 5, it is apparent that some evoked saccades were directed towards the correct endpoint, but then curved towards the direction of the microstimulation-evoked endpoints at the earliest microstimulation time. To determine whether the deviation of the microstimulation-evoked endpoints at the later microstimulation times was a function of the curvature of the saccade, we measured deviation as a function of curvature for trials in which the singleton was 45°-135° away from the direction of the microstimulation-evoked endpoints at the earliest microstimulation time. Curvature was measured as the absolute difference between the direction of saccades 12 ms after saccade initiation and the endpoint direction. Regression lines were fit to the data and slopes tested for significance. In both monkeys, there was a slight trend towards decreasing deviation with increasing curvature, although these slopes were very small. Thus, the curvature of the microstimulation-evoked saccades did not greatly affect the measurement of deviation.

Deviation could also be influenced by the latency of the self-generated saccade, measured either from the end of the microstimulation-evoked saccade, from microstimulation, or from the start of the trial. Regression lines were fit to deviations by latency of the self-generated saccade up to 500 ms. When measured from the time of microstimulation or from the end of the microstimulation-evoked saccades, monkey P showed a small but significant trend towards less deviation with increasing latency of the self-generated saccade for trials in which the singleton was 45°-135° away from the direction of

the microstimulation-evoked endpoints at the earliest microstimulation time (Table 3). Monkey L did not show any trends. When latency was measured from array presentation, no trends emerged either.

Monkey	Prosaccades		
	Start	Stimulation	End of Evoked
L	$ß_1$=0.008 $F(1,2037)=1.5$	$ß_1$=-0.005 $F(1,2399)=0.8$	$ß_1$=0.02 $F(1,2412)=12.4$**
P, 4 Locations	$ß_1$=-0.08 $F(1,71)=1.1$	$ß_1$=-0.1 $F(1,71)=1.8$	$ß_1$=-0.09 $F(1,71)=1.5$
P, 2 Locations	$ß_1$=-0.2 $F(1,154)=11.6$*	$ß_1$=-0.2 $F(1,160)=18.1$**	$ß_1$=-0.2 $F(1,161)=14.5$**
Monkey	Antisaccades		
	Start	Stimulation	End of Evoked
L	$ß_1$=-0.012 $F(1,2305)=3.8$	$ß_1$=0.02 $F(1,2491)=14.1$**	$ß_1$=0.01 $F(1,2491)=3.7$
P, 4 Locations	$ß_1$=-0.003 $F(1,58)=0.001$	$ß_1$=0.06 $F(1,60)=0.6$	$ß_1$=0.03 $F(1,61)=0.2$
P, 2 Locations	$ß_1$=-0.1 $F(1,212)=3.8$	$ß_1$=0.2 $F(1,215)=16.7$**	$ß_1$=0.2 $F(1,215)=8.9$**

Table 3. $ß_1$ and significance values for regression of deviation by latency of second saccade from the beginning of the trial, from the end of the first saccade, and from time of microstimulation.

$ß_1$ and significance values for regression of deviation by latency of second saccade from the beginning of the trial, from the end of the first saccade, and from time of microstimulation. $ß_1$'s represent the slopes of the regression lines. Conventions as Table 1.

Some self-generated saccades had latencies of 0 ms when measured relative to the end of the microstimulation-evoked saccade for trials in which the singleton was 45°-135° away from the direction of the microstimulation-evoked endpoints at the earliest microstimulation time (monkey L: 7%; monkey P: 11%). These short latency saccades could be the result of the self-generated saccade being prepared concurrently with the microstimulation-evoked saccade (Schlag and Schlag-Rey 1990; Dassonville and others 1992; McPeek and others 2000; McPeek and Keller 2001; Sheliga and others 2002; Godijn and Theeuwes 2002; Murthy and others, 2005). If so, one might expect the curvature of microstimulation-evoked saccades to be larger when the subsequent self-generated saccade latencies were shorter latency as a result of greater preparatory activity for the self-generated saccade interacting with the microstimulation-evoked saccade (Aizawa and Wurtz 1998; McPeek and others 2003; Port and Wurtz 2003). Curvature was regressed onto latency of self-generated saccades relative to the end of the microstimulation-evoked saccades for latencies up to 500 ms. Monkey L showed a significant increase in curvature with increasing latency for prosaccade trials ($ß_1$ =0.033, $F(1,2412) = 13.5$, $p < 0.001$). Monkey P showed a significant increase in curvature with increasing latency for antisaccade trials ($ß_1$ =0.067, $F(1,285) = 6.2$, $p < 0.05$) (Table 4). All other slopes were not significant. Considering the small size of these slopes and the fact that they run opposite of the prediction above, it seems that the curvature present in this experiment did not depend on the degree to which the self-generated saccade had been prepared as measured by its latency.

Monkey	Prosaccades	Antisaccades
L	$ß_1$=0.03 F(1,2412)=13.5**	$ß_1$=0.007 F(1,2491)=0.4
P, 4 Locations	$ß_1$=-0.0004 F(1,71)=5.7e-005	$ß_1$=0.05 F(1,215)=2.7
P, 2 Locations	$ß_1$=0.04 F(1,243)=2.4	$ß_1$=0.07 F(1,61)=3.1

Table 4. $ß_1$ and significance values for regression of curvature by latency of second saccade from the end of the first saccade.

$ß_1$ and significance values for regression of curvature by latency of second saccade from the end of the first saccade. Conventions as Table 1.

It is possible that the initial curvature of the microstimulation-evoked saccades runs in the direction opposite the final deviation of the entire saccade. To make sure that the above analyses were not the result of a mismatch in direction between the initial curvature and final direction, we computed the percentage of trials in which the direction of initial curvature and final deviation were either both towards the singleton or both towards the location directly opposite the singleton. We only included conditions in which there were five or more observations of evoked saccades. For monkey L, the median percentage that matched direction between the initial curvature and final deviation was 68% and for monkey P it was 85%. When the above analyses were conducted only with trials in which the initial curvature and final deviation matched, the results were qualitatively the same with only very small changes in significance or slope size.

Analysis of Deviation Toward Singleton in Antisaccade Trials

We also computed the proportion of microstimulated correct antisaccade trials in which the direction of the microstimulation-evoked saccade 12 ms after initiation was towards the singleton. Eighteen percent of microstimulated correct antisaccade trials matched this criterion. These trials were relatively evenly distributed across both monkeys and all sessions. The mean deviation at 12 ms of these trials was 106º (st. dev. = 86º). The microstimulation times were compared between sessions with a proportion greater than 0.2 of microstimulation-evoked saccades in antisaccade trials that curved towards the

singleton and those with a proportion less than 0.2. There was no significant difference between the microstimulation times for these two groups ($t(150) = -1.22$, $p = 0.11$). There was a tendency for trials with later microstimulation times to have a greater deviation at 12 ms towards the singleton (linear contrast: $t(1673) = 7.8$, $p < 0.001$) Of these trials, 46% had final deviations towards the singleton. Thus, only 9.8% (n=725) of all microstimulation-evoked saccades in correct antisaccade trials first curved towards the singleton and then towards the correct endpoint location.

Analysis of Deviation by Aspect Ratio

While we did not vary aspect ratio systematically, the latency data from sessions with different aspect ratios provides some evidence that attention to the singleton was required to perform the task correctly. For monkey P, saccade latencies in non-stimulated, correct trials became shorter the larger the aspect ratio (one-way ANOVA, prosaccades: $F(4,2899) = 26.3$, $p < 0.001$, by aspect ratio: 1.3 mean = 161 ms, st. error = 2.3, 1.6 mean = 146 ms, st. error = 2.6, 1.9 mean = 132, st. error = 3.0, 95% confidence interval for the difference between 1.3 and 1.6: 15.3 ± 9.9, for the difference between 1.6 and 1.9: 13.5 ± 11.2, antisaccades: $F(4,2548) = 47.85$, $p < 0.001$, by aspect ratio: 1.3 mean = 170 ms, st. error = 2.0, 1.6 mean = 150 ms, st. error = 2.2, 1.9 mean = 140, st. error = 2.5, 95% confidence interval for the difference between 1.3 and 1.6: 19.8 ± 8.4, for the difference between 1.6 and 1.9: 10.5 ± 9.3). The deviations between these different aspect ratio sessions were not significantly different. Moreover,

latencies of error saccades in non-stimulated trials were shortest for saccades that landed opposite the correct location and a little longer for saccades that landed at locations adjacent to the singleton. Correct saccades had the longest latencies (one-way ANOVA collapsed across both monkeys and prosaccade and antisaccade trials: $F(2,6370) = 357.7$, $p < 0.001$, correct mean = 178.5, st. error = 0.8, adjacent error mean = 150.4, st. error = 1.9, opposite error mean = 123.9, st. error = 2.1, all differences significant at the 0.05 level with Bonferroni correction). Thus, correct trials took the longest time to perform and the quickest error trials were ones in which the singleton was not discriminated correctly. This same trend occurred for monkey P in Juan and others (2004) but not monkey L. The trend did not occur for any monkey in Sato & Schall (2003) nor for monkey L in the present study.

Timing of Visual and Movement-Related Activity

Besides microstimulation, another clear measure of saccade preparation is the activity of movement neurons (e.g., Hanes and others 1998; Thompson and others 2005). Figure 10 contrasts the pattern of activity of visual and movement neurons in FEF. The top row shows the population activity for Type I neurons with only visual activity in memory-guided saccade trials. Although there was no movement-related activity in these neurons, they select the endpoint after selecting the singleton in antisaccade trials. Whereas the visual neurons initially select the singleton in antisaccade trials, movement neurons of the Type II class exhibited slightly elevated discharge rates after array presentation, but the

magnitude did not vary with singleton or location until after the endpoint was selected. If preparation means that one as opposed to any other saccade is represented, then the initial period of equivalent activity cannot be identified with preparation but may be described as readiness to produce any saccade. These data show clearly that unlike the Type I visual neurons in antisaccade trials, these Type II movement neurons were never preferentially active for the saccade to the singleton.

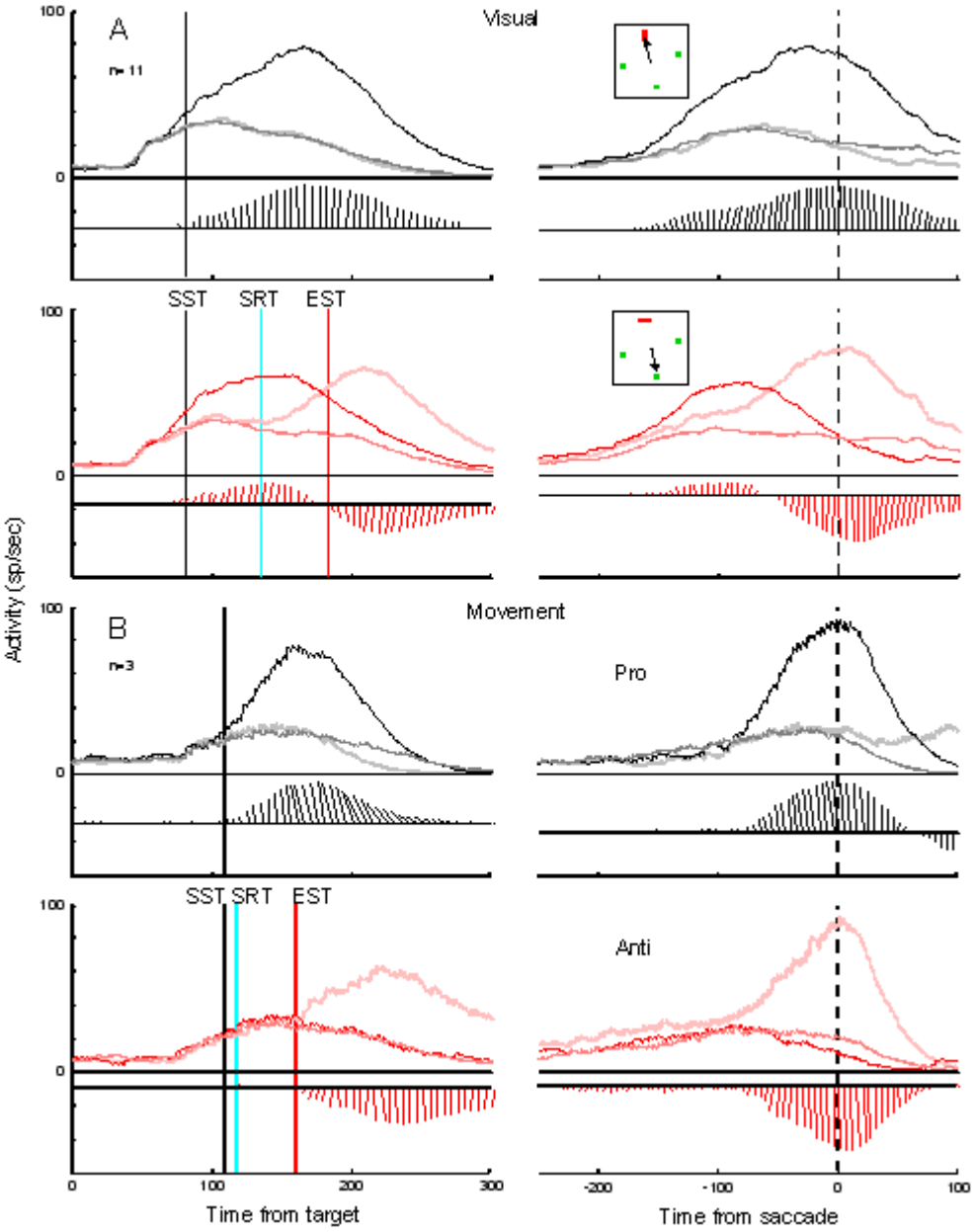

Figure 10. Spike-density functions (SDFs) of visual and movement neurons.

Weighted population average of visual (n = 11 Type I) (A) and movement (n = 3 Type II) (B) activity in prosaccade (black) and antisaccade (red) trials. Average spike-density functions (SDFs) aligned on array presentation (left) and saccade initiation (right) are drawn for trials with singleton in the response field (RF) (most saturated), for trials with singleton orthogonal to the RF (intermediate saturated), and for trials with singleton opposite the RF (antisaccade endpoint in RF) (least saturated). Vectors below each SDF plot indicate the vector average direction of activity around the array; upward is toward the singleton, downward is opposite the singleton. Average singleton selection time (SST) (black vertical), stimulus-response time (SRT) (cyan vertical) and endpoint selection time (EST) (red vertical) are shown. Note that in prosaccade trials the net vector of movement-related activity grows toward the endpoint following SST. In contrast, in antisaccade trials the net vector of movement-related activity grows toward the endpoint opposite the singleton only following EST, corresponding to the time with the activation of visual neurons for the singleton is waning and the activation for the endpoint of the antisaccade was growing.

CHAPTER IV

DISCUSSION

The goal of this experiment was to determine whether the allocation of attention necessarily requires saccade preparation. To dissociate the focus of attention from the endpoint of a saccade, macaque monkeys were trained to perform visual search for a uniquely colored rectangle and shift gaze either toward or opposite this color singleton according to its orientation. Antisaccade latencies were significantly longer than prosaccade latencies. Saccade preparation was probed by measuring the direction of saccades evoked by intracortical microstimulation of the frontal eye fields (FEF) at variable times following presentation of the search array. Eye movements evoked on prosaccade trials deviated progressively toward the singleton that was also the endpoint of the correct eye movement. However, eye movements evoked on antisaccade trials effectively never deviated toward the singleton but only progressively toward the location opposite the singleton. This result replicates a previous report by Juan, Shorter-Jacobi, and Schall (2004) that was obtained in a version of the task for which the latency cost of antisaccades relative to prosaccades was minimal or absent. Previous neurophysiological studies have demonstrated that on antisaccade trials most visually-responsive neurons in FEF initially select the singleton while attention is allocated to distinguish its shape and then select the endpoint at the opposite location in antisaccade trials (Sato and Schall 2003). The critical data are the deviations that occur in antisaccade

trials after the singleton is selected but before the endpoint is selected; the saccades evoked that sampled this interval effectively never deviated toward the singleton. In other words, during the interval when most neurons in FEF have selected the singleton while attention is allocated to it, no saccade planning toward the singleton was revealed by the deviations of evoked saccades. This result demonstrates that the mechanisms responsible for spatial attention and saccade planning are not identical because when attention was allocated, no covert saccade plan was evident. The absence of a saccade plan uniquely toward the singleton was confirmed in measurements of the activation of movement neurons in FEF. These results show that visual spatial attention and saccade planning are different in kind and not just degree.

Difference in direction of saccades evoked in the dark and during the display

Before addressing the broader theoretical implications of our work, we must consider an unexpected observation. We found that the vector of the saccades evoked in the dark was typically rotated relative to the vector of the saccades evoked during the visual search task at the earliest microstimulation time. This change in angle was unexpected because modulated activity in FEF (or elsewhere) had not occurred in the earliest microstimulation time interval (e.g., Schmolesky and others 1998). The degree of rotation was not a function of the location of the singleton, suggesting it was not affected by the preparation of a saccade. The rotation was typically upward and so may be related to the upward drift of memory-guided saccades made in the dark (Barton and Sparks

2001; White and others 1994) and also may be a particular expression of colliding saccades (Schlag and Schlag-Rey, 1990). Regardless of its basis, the pattern of deviation we observed did not depend on measuring the deviation of the evoked saccades relative to the direction of saccades evoked in the dark or relative to the direction of saccades evoked at the earliest time in the trials.

Was the singleton attended?

The relevance of our results as a test of the premotor theory of attention is predicated on the fact that monkeys shifted attention to the singleton and that this occurred during the interval between when visually responsive neurons in FEF selected the singleton and when they selected the endpoint of the antisaccade (Sato and Schall, 2003). We believe that it is very difficult to argue convincingly against the claim that the monkeys focused attention at least momentarily on the singleton for several reasons. First, a shift of covert attention is necessary to perform the antisaccade task (Olk and Kingstone 2003; Connolly and others 2000). Second, the discrimination of the orientation of the singleton required to perform the task was difficult, especially with an aspect ratio as low as 1.3. Regan and Hamstra (1992) found that the just-noticeable difference in aspect ratio for humans was 1.6 when the reference stimulus was a square at the fovea and that this judgement requires attention. Thus, given the fall off of peripheral acuity, our monkeys discriminated the orientation better than humans. Other studies have also demonstrated that discrimination tasks require attention (e.g., Sagi and Julesz, 1985; Nothdruft, 2002). Third, numerous studies have indicated

that attention is allocated even in pop-out search (Joseph and others, 1997; Nothdurft, 1999; Theeuwes and Godijn 2002; Theeuwes and others 2003; Muller-Plath and Pollman, 2003; VanRullen and others, 2004; de Fockert and others 2004). For example, Kim and Cave (1995) found that attention was allocated to targets even in easy search tasks, such as shape singleton detection. These results seriously challenge the dichotomy between preattentive and attentive mechanisms. Fourth, salient color singletons capture attention (e.g., Theeuwes 1991, 1992). Our monkeys were in singleton search mode, unlike conditions used to show that the capture of attention by singletons is not obligatory (Yantis and Egeth 1999). Moreover, the majority of evidence indicates that the amount of attention allocated to a singleton is proportional to its task-relevancy (Yantis and Egeth 1999; Bacon and Egeth 1994; Folk and others 1992), and the singleton in this experiment was entirely task-relevant. Also, salient stimuli can capture attention at locations other than the saccade endpoint before the endpoint is selected (Doré-Mazars and others 2004).

One could argue that we observed no effects of singleton selection on saccade deviations because the task was not difficult enough. For example, to test the allocation of attention, one might need to measure responses to probes at attended and unattended locations. Indeed, many studies cited in support of elements of the premotor theory have utilized dual-task paradigms (Shepherd and others 1986; Chelazzi and others 1995; Kowler, 1995; Hoffmann and Subramaniam 1995; Deubel and Schneider 1996; Peterson and others 2004). Other studies in which tasks were switched across trials provided evidence for

the independence of saccade production and attention allocation (Klein 1980; Klein and Pontefract 1994; Hunt and Kingstone 2003). Shepherd and others (1986), in contrast, argued that Klein's task (1980) might have been too difficult to observe a replicable affect. It is therefore important to consider what increasing the difficulty of the task might have done to the results and if there is a guaranteed method of increasing the difficulty without introducing other confounds. It must also be noted that introducing a secondary task to measure the allocation of attention affects the primary task of singleton detection (Joseph and others 1997; Theeuwes and others 1999; Logan and Gordon 2001; Kramer and others 2001; Levy and Pashler, 2001; Maki and Mebane, 2006). For example, Deubel and Schneider (1996) used a non-speeded two-alternative forced choice task in combination with the primary saccade task to avoid psychological-refractory period effects that would occur with saccadic and manual speeded responses (Wolf and others 1984; Pashler and others 1993). Such psychological-refractory period effects would have lengthened response times, although long reaction times have also been argued to weaken evidence against the premotor theory (Klein 1980; Shepherd and others 1986). Moreover, Deubel and Schneider's (1996) secondary task did delay saccade latency compared to the saccade task alone, consistent with subsequent data showing that non-speeded secondary tasks can influence response times on primary tasks (Arnell and Duncan 2002). Furthermore, Logan and Burkell (1986) found that much of the variance of dual-task interference could be accounted for by response competition. Given the pre-existing competition between prosaccade

and antisaccade processes in antisaccade trials, the response competition created by another task would have made interpretation of the results very difficult.

Finally, the attention needed to perform the task and the attention captured by the pop-out stimulus should be distinguished. VanRullen and others (2004) suggest that two attentional resources are used in dual-task visual search, so adding another task may not measure the allocation of visual spatial attention. It has been argued that some studies examining the relationship between attention and eye movements have failed to distinguish between attention captured by peripheral stimuli and attention required to program the eye movement (Shepherd and others 1986; Deubel and Schneider 1995). However, Theeuwes and others (2003) showed that color singletons induce both attentional and oculomotor capture, as measured at the end of the trial.

Therefore, we believe it is entirely plausible to conclude that monkeys allocated attention to the color singleton in antisaccade trials. Furthermore, our data can go beyond these human studies because ultimately they make inferences based on performance at the end of trials. In contrast, our study probes the evolving states and transitions of the system in real time. Certainly, the end state of the system must reflect the outcome of the evolution of the system, but this does not necessarily entail or guarantee that the system does not transition between states during a trial. Thus, we believe the task required and the single captured attention sufficient to test legitimately the premotor hypothesis. Further refinements in theories of visual attention (Schneider 1995;

Bundesen 2005) will help elucidate the conditions under which visual attention is deployed.

Neural correlate of attention allocation

If spatial attention is allocated to the singleton and then to the endpoint in antisaccade trials, and if Type I visual neurons in FEF initially select the singleton and then select the endpoint of the antisaccade, then it is plausible to entertain the linking proposition that the activity of these neurons (as well as counterparts in other relevant brain structures) instantiate the allocation of visuospatial attention. In other words, attention is allocated when and to the degree that the activity of these neurons in FEF (and concomitantly elsewhere in the relevant network) represents one as opposed to other locations in the image.

This linking proposition is consistent with several lines of evidence showing that FEF contribute to covert orienting as well as overt saccade production. First, visually responsive neurons in FEF select the location of a salient object in an array when monkeys maintain fixation or shift gaze away from that object (Thompson and others 1997; Murthy and others 2001). Furthermore, in a visual search task requiring a forelimb but not an eye movement operant response, visually responsive neurons selected the location of a color singleton but movement neurons were inhibited (Thompson and others 2005b). Second, microstimulation of FEF has been shown to influence attention allocation (Moore and Fallah 2001, 2004) possibly through modulation of activity in extrastriate area V4 (Moore and Armstrong 2003) via reciprocal connections (Schall and

others 1995). Other studies have provided parallel evidence for the the superior colliculus (Cavanaugh and Wurtz 2004; Muller and others 2005). Third, fMRI studies with humans have consistently identified activation in FEF with attention demanding tasks (Sweeney and others 1996; Corbetta and others 2002; Cornelissen and others 2002; Donner 2002; Lepsien and others 2002; Matsuda and others 2002; Shulman and others 2003; Koyama and others 2004; Makino and others 2004; reviewed by Corbetta and Shulman 2004), and activation in FEF is elevated relative to fixation even in low-load tasks (Pinsk and others, 2004). Fourth, transcranial magnetic stimulation over FEF in humans can influence visual detection (Grosbas and Paus 2002, 2003) and performance in a visual search task in which eye movements were not required (Muggleton and others 2003).

Possibility of weak saccade plan

One could argue that the activity in FEF selecting the singleton momentarily in antisaccade trials amounts to a weak motor plan towards the singleton. We believe this argument is not tenable for the following reasons. First, the interpretation that Type I visual neurons instantiate saccade planning is inconsistent with several converging lines of evidence. Many neurons in FEF that select the target during visual search are located in supragranular layers that do not project directly to oculomotor structures (Thompson and others 1996; Thompson and Schall 2000). Also, Sato and Schall (2003) showed that the timing of singleton or endpoint selection by these neurons bore no relation to the

time of saccade initiation. Furthermore, in a stop signal task, visual neurons in FEF and superior colliculus do not produce signals sufficient to contribute to the control of saccade generation (Hanes and others 1998; Paré and Hanes 2003).

Second, the concept of motor plan necessarily entails progressive commitment to an action. The Type I visual cell activity does not have this characteristic; visually responsive neurons in FEF select singletons if no saccade is made (Thompson and others 1997) and this was replicated in our pro-anti search task (Schall 2004). However, another population of neurons in FEF, the presaccadic movement-related neurons do produce activity sufficient to control saccade initiation (Hanes and others 1998). This distinction between visual selection and saccade planning signals has been observed in the superior colliculus too (Horwitz and Newsome 1999; Paré and Hanes 2003; Ignashchenkova and others 2004; McPeek and Keller, 2004).

Third, if a momentary plan to shift gaze to the singleton in antisaccade trials had occurred, then the saccades evoked by microstimulation should have deviated towards the singleton. However, a vanishingly small proportion of evoked saccades deviated towards the singleton at all in antisaccade trials despite the high proportion of samples from the interval after the singleton was selected but before the endpoint was selected in antisaccade trials (Figure 7). Such a small proportion could be dismissed as measurement noise or embraced as evidence for a weak plan.

Fourth, given the linking proposition identifing saccade planning with the activity of presaccadic movement neurons, a weak, momentary saccade plan

toward the singleton in antisaccade trials must correspond to greater activity of these movement neurons for the singleton until the endpoint is selected. However, we found that movement neurons do not show movement preparation uniquely toward the singleton in antisaccade trials (Figure 10). It was clear that movement neurons increased discharge rate before the endpoint was selected, but this increase was equivalent regardless of where the singleton was located. We believe such activity can be interpreted in two ways. Either it amounts to a motor plan to each location concurrently (e.g., Cisek and Kalaska 2005) or it corresponds to the more neutral process of readiness to produce any movement (e.g., Dorris and Munoz 1998). In either case, we obtained no indisputable evidence for a motor plan to the singleton in antisaccade trials.

Relation to previous studies of saccade deviation

Our results agree with but our interpretation differs somewhat from those of previous studies measuring deviations of imperative or artificially evoked saccades to probe ongoing processes. Sheliga and others (1994, 1995) cued attention in humans to one of two locations in opposite hemifields on the horizontal meridian. An imperative stimulus presented at either the cued or the uncued location instructed participants to make a vertical saccade. They found that the imperative saccade deviated opposite the location of the imperative stimulus, and this deviation was smaller but not reversed when the location was invalidly cued. Similarly, van der Stigchel and Theeuwes (2005) found that when subjects focused attention on two locations, their subsequent saccades deviated

away from the location to which they did not shift gaze (see also Godijn and Theeuwes 2002; Peterson and others 2004). The observation of saccade trajectory deviation opposite the focus of attention has been interpreted as the consequence of inhibition of a competing saccade plan toward the focus of attention. However, this inference can be evaluated only through invasive neurophysiological studies.

Such studies, like this one, are based on the fundamental observation that saccades evoked in one direction when monkeys are preparing a saccade to a stimulus in another direction exhibit a systematic deviation in the direction of the partially prepared saccade (Sparks and Mays 1983). Gold and Shadlen (2003) evoked saccades by stimulating FEF while monkeys performed a motion direction discrimination task in which opposite directions of motions were signaled by a saccade to one of two targets. In three separate experiments, the mapping of saccade response to the motion stimulus was varied. Monkeys made prosaccades (saccade to the target located in the direction of motion), antisaccades (reversed but predictable stimulus-response mapping), and saccades to colored spots that appeared at random locations around the motion stimulus (variable and unpredictable stimulus-response mapping). Saccades evoked by FEF stimulation deviated toward the monkey's directional choice, even when the monkey made an incorrect choice, in the prosaccade and antisaccade mapping conditions. However, no deviation of the evoked saccades was observed when the response targets were defined by color and their locations were unpredictable. No deviation occurred because in the arbitrary

color mapping condition monkeys could not prepare a saccade until the targets appeared after the motion stimulus extinguished. These authors concluded that the evoked deviations measure the accumulation of sensory evidence instantaneously transformed according to the mapping rule into the command to generate the response. This conclusion, if generally true, makes a prediction for our task. The singleton location and shape are the sensory evidence upon which the response must be based. The neurophysiological data demonstrate that singleton shape is encoded after its location is encoded (Sato and Schall 2003). If such evidence were immediately transformed into a saccade command, then saccades evoked after the singleton was selected but before the endpoint was selected (based on the shape of the singleton) in antisaccade trials, should deviate towards the singleton. The fact that they do not suggests that the results of Gold and Shadlen like ours are interpreted most sensibly as evidence that the experimentally evoked saccades are affected most proximally by the preparation of a saccade and only distally by the accumulation of sensory evidence. This general conclusion is also consistent with the observations of Barborica and Ferrera (2004) in a study requiring monkeys to make saccades to the extrapolated position of an invisible moving target. Saccades evoked immediately after the disappearance of the target deviated towards the initial position of the target, while saccades evoked later deviated towards the extrapolated position of the target. Thus, deviation followed the direction of the prepared saccade.

The relation between attention shifting and saccade programming

The results of the present study agree with several others demonstrating the contribution of the FEF (e.g., Murthy and others 2001; Moore and Fallah, 2001, 2004; Moore and Armstrong, 2003; Sato and Schall 2003; Juan and others 2004) and superior colliculus (Cavanaugh and Wurtz, 2004; Ignashchenkova and others 2004; Muller and others, 2005) to covert orienting of attention. Few would argue that covert orienting of attention and overt orienting of gaze are not guided by common selection mechanisms and coordinated in time (Klein 1980; Rizzolatti 1983; Shepherd and others 1986; Henderson 1992; Sheliga and others 1994, 1995; Hoffmann and Subramanian 1995; Kowler 1995; Deubel and Schneider 1996; Hunt and Kingstone 2003; Peterson and others 2004; Doré-Mazars and others 2004). The oculomotor readiness or premotor theory of attention has been suggested as an explanation for this relationship. However, this theory has been articulated and tested in various ways, some more direct and rigorous than others. Therefore, it is necessary to be clear just what the premotor theory of attention claims.

Klein stated, “Two forms of dependence between attention and eye movements are entailed in the oculomotor readiness mechanism… One is that a readiness to move the eyes to a certain locus produces an attentional bias toward that locus. The other is that attention to a location in space involves a readiness to move one’s eye to that locus” (Klein, 1980). Rizzolatti (1987) originally stated that “[i]t would seem highly plausible … that overt and covert orienting of attention are controlled by common mechanisms and that the

absence of eye movements in the case of covert orienting is a consequence of peripheral inhibition, which leaves unchanged the central programming". Also "According to the premotor theory of attention, the mechanisms responsible for spatial attention and…saccades are basically the same" (Sheliga and others 1994) and "in covert attention the motor program, albeit set, is not executed" (Sheliga and others 1994). Another statement said, "The premotor theory of attention ... proposes that spatial attention results from an activation of the same circuits that program eye movements as well as other motor activities. It maintains that spatial attention differs from movement execution in the degree of activation of the circuits coding the representation of action in space, rather than in the activation of dedicated systems" (Craighero and Rizzolatti 2005).

On the one hand, if "mechanisms" and "circuits" refer to particular populations of neurons instantiating a single process, then the results of this experiment contradict this claim. This conclusion is based on three premises -- if an attention shift is a covert plan and if our monkeys shifted attention to the singleton even in antisaccade trials and if a covert saccade plan is revealed by deviations of evoked saccades, then saccades evoked after the singleton was selected but before the endpoint was selected must deviate toward the singleton. We found no such deviation. Therefore, one of the antecedent premises must be incorrect. A literature has been based on the observation that deviations of evoked saccades measure growing saccade plans, and we believe we have demonstrated that the monkeys must have shifted attention to the singleton. Therefore, by a process of elimination, we reject the premise that an attention

shift is a covert saccade plan. The claim that shifting attention is accomplished by the same neurons that shift gaze is also contradicted by the results of Sato and Schall (2003), Murthy and others (2001), and Thompson and others (2005b) reviewed above. On the other hand, if "mechanisms" refers to entire brain structures or circuits comprised of heterogeneous populations of neurons performing different functions (like shifting attention by selecting stimuli and preparing saccades), then our results cannot challenge the theory. However, if the theory is formulated too general to map onto specific neural circuits, then it loses the force of falsifiability.

In conclusion, our results and analysis argue for a refinement of the premotor theory of attention. We believe that the premotor theory can be regarded as correct insofar as it posits a relationship between saccades and attention that occurs through some overlap between the brain circuits responsible for both. However, it seems clear that a premotor theory that posits an identity of saccade planning and attention shifting such that attention is an unexecuted saccade cannot be correct.

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