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Effects of Stimulus-Response Compatibility on Neural Selection in Frontal Eye Field

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Summary

We investigated the neural basis of visual and saccade selection in the frontal eye field of macaque monkeys using a singleton search task with prosaccade or antisaccade responses. Two types of neurons were distinguished. The first initially selected the singleton even in antisaccade trials, although most subsequently selected the endpoint of the saccade. The time the singleton was located was not affected by stimulus-response compatibility and did not vary with reaction time across trials. The second type of neuron selected only the endpoint of the saccade. The time of endpoint selection by these neurons accounted for most of the effect of stimulus-response compatibility on reaction time. These results indicate that visual selection and saccade selection are different processes.

Introduction

Measures of reaction time (RT) provide insights into the dynamics and architecture of human cognition. Many models assume that tasks are performed by a sequence of more or less distinct processes such as stimulus encoding, memory retrieval, and response preparation (reviewed in Meyer et al., 1988). Several studies developed means to manipulate and identify these processes (reviewed in Sternberg, 2001), but ultimately the structure of covert processes cannot be deduced solely from the timing of overt responses. Event-related potentials have provided additional insights about the covert processes (e.g., McCarthy and Donchin, 1981; Coles et al., 1988). However, without knowledge of their neural generators, conclusions drawn from these studies are limited. More spatial and temporal resolution is available by recording the activity of single neurons.

These issues can be investigated usefully in the FEF because it is located at the interface between processing an image and preparing an orienting response (Thompson et al., 2001; Schall, 2002). A visual search task requires at least two processes: the analysis of the visual array and the preparation of an orienting response (Hooge and Erkelens, 1996). In monkeys performing visual search, visually responsive neurons in FEF select the target for the saccade (Schall and Hanes, 1993; reviewed in Schall, 2002). The initial activity of visually responsive cells does not discriminate whether the target or distractors fall in the receptive field, but the late phase of the activity reliably differentiates the target from distractors. We have hypothesized that the time when FEF neurons select the target from distractors marks the outcome and conclusion of stimulus encoding and selection (Thompson et al., 1996).

Supporting this hypothesis, we have shown that although search efficiency and response interference both affect RT, only search efficiency affects the time when neurons select the target (Sato et al., 2001). While persuasive, these findings do not completely exclude the possibility that the target selection by FEF neurons corresponds to saccade preparation. More conclusive evidence requires manipulation of stimulus-response mapping to explicitly decouple stimulus encoding and response preparation (Kornblum et al., 1990).

For this study, monkeys were trained to produce a prosaccade or an antisaccade in response to an elongated color singleton in a visual search array (Figure 1A). If the selection of the target in a search array by FEF neurons corresponds to the selection of the location of the singleton, then the singleton should be selected regardless of the direction of the gaze shift at a time that should not be influenced by stimulus-response compatibility (Figure 1B, left). On the other hand, if target selection by FEF neurons corresponds to preparation of the saccade, then only the endpoint of the saccade should be selected regardless of the position of the singleton at a time that should vary with RT according to stimulus-response compatibility (Figure 1B, right). We found both types of neurons in FEF. This suggests that visual selection and saccade selection are distinguishable processes.

A preliminary report of some of these data has appeared (T. Sato et al., 2002, Soc. Neurosci., abstract).

Results

Behavioral Data

Table 1 presents the mean RT for three monkeys in prosaccade and antisaccade trials. RT was significantly longer in antisaccade trials than in prosaccade trials. Because the error rate was higher in antisaccade trials compared to prosaccade trials (L: 3.6% for pro-, 13.4% for antisaccade; M: 5.3% for pro-, 9.6% for antisaccade; P: 1.8% for pro-, 6.1% for antisaccade), the difference in RT cannot be due to a speed/accuracy tradeoff. Thus, RT was manipulated by stimulus-response compatibility.

Importantly, stimulus-response compatibility did not affect the metrics or dynamics of the saccades. The average ratio of the amplitude of antisaccades to that of prosaccades for each monkey was 1.01 (L), 0.98 (M), and 0.99 (P). The average ratio of the peak velocity for antisaccades relative to prosaccades was 1.01 (L), 0.98 (M), and 1.00 (P).

Overview of the Physiological Data

This study had three goals. The first was to examine whether FEF neurons select the singleton among dis-

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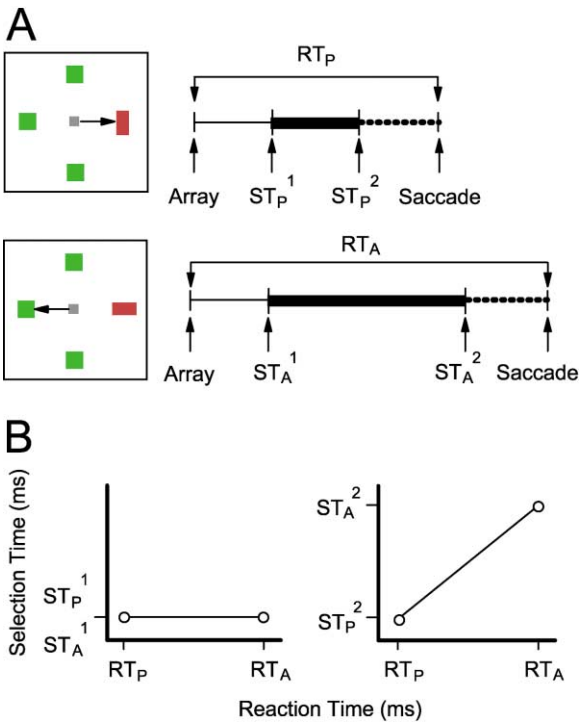

Figure 1. A Visual Search with Explicit Stimulus-Response Mapping

(A) A vertical singleton instructed a prosaccade. A horizontal singleton instructed an antisaccade. RT is subdivided into an encoding stage (thin line), stimulus-response mapping stage (thick line), and response preparation stage (dotted line).

(B) Alternative hypotheses about how the stimulus selection time (ST) of FEF neurons and reaction time (RT) vary with stimulus-response compatibility. If the selection time is not affected by stimulus-response compatibility, then the fraction of the change in RT accounted for by the change in the selection time $[(ST_A - ST_P)/(RT_A - RT_P)]$ should be close to 0% (left). If the selection time corresponds to or follows the stimulus-response mapping process, then the fraction of the change in RT accounted for by the change in ST should be close to 100% (right).

tractors even when monkeys shift gaze away from it. The second was to examine the effect of stimulus-response compatibility on the selection times of FEF neurons. The third was to examine the relationship between the variability of RT across trials and the variability in the time when FEF neurons select a stimulus.

We recorded 77 neurons that changed discharge rate between the presentation of the search array and the initiation of the saccade. The present study focused on neurons that selected the singleton in prosaccade trials. The difference was calculated between the spike density function from trials in which the singleton was in the receptive field ($SDF_{s\text{-}in}$) and that from trials in which the singleton was located opposite the receptive field ($SDF_{s\text{-}out}$). If, after the search array appeared, this difference reached the mean plus 5 standard deviations of the difference in activity measured before the search array appeared and remained above the mean plus 2 standard deviation level for more than 15 ms, the neuron was regarded to have selected the singleton. Using this criterion, 65 neurons discriminated the singleton from distractors in prosaccade trials.

Do FEF Neurons Select the Singleton before Antisaccades?

The first goal of this study was to determine whether FEF neurons select the singleton among distractors even when monkeys shift gaze away from it. Using equivalent measurement criteria, 44 neurons selected the singleton in antisaccade trials and 21 neurons did not.

The activation of a representative FEF neuron that selected the singleton in antisaccade trials is shown in Figure 2A (left). The presence of visually evoked activity and saccade-related activity was tested with memory-guided saccades to a stimulus flashed in the receptive field. This neuron was visually responsive with minimal activity during the delay period and little modulation associated with the memory-guided saccade (Figure 2B). Regardless of the ultimate gaze shift, the singleton was selected around 100 ms after the array appeared. In prosaccade trials, the singleton continued to be selected until the saccade. In antisaccade trials, the singleton was initially selected, but subsequently a dramatic transition occurred whereby the endpoint of the antisaccade was selected. This transition was observed in 38 of 44 neurons that selected the singleton in antisaccade trials. The remaining six neurons selected the singleton throughout pro- and antisaccade trials. We will define the neurons that selected the singleton in antisaccade trials as Type I.

The pattern of activation of a representative FEF neuron that did not select the singleton in antisaccade trials is shown in Figure 3A (left). Immediately after presentation of the array, this neuron exhibited a pre-excitatory pause (Sato and Schall, 2001). The neuron selected the endpoint of the saccade regardless of the location of the singleton. During a memory-guided saccade task, this neuron exhibited a visual response followed by elevated activity during the delay period and pronounced saccade-related activity (Figure 3B). We will define the 21 neurons that selected only the endpoint of saccade in antisaccade trials as Type II.

The measure of singleton selection used to distinguish Type I from Type II neurons was used in previous studies (Hanes et al., 1998; Bichot and Schall, 1999). As is the case with any biological measurement, the distribution

Table 1. Mean ± SD Reaction Times in Prosaccade Trials and Antisaccade Trials with Difference of Means and Results of T Test

Monkey	Prosaccade[a]	Antisaccade	Difference of Means	Statistical Test
L	235 ± 48 (n = 1706)	299 ± 81 (n = 1707)	64	$p < 0.001$
M	198 ± 44 (n = 2057)	258 ± 119 (n = 2060)	60	$p < 0.001$
P	221 ± 62 (n = 7719)	253 ± 75 (n = 7721)	32	$p < 0.001$

[a] Reaction times are in milliseconds.

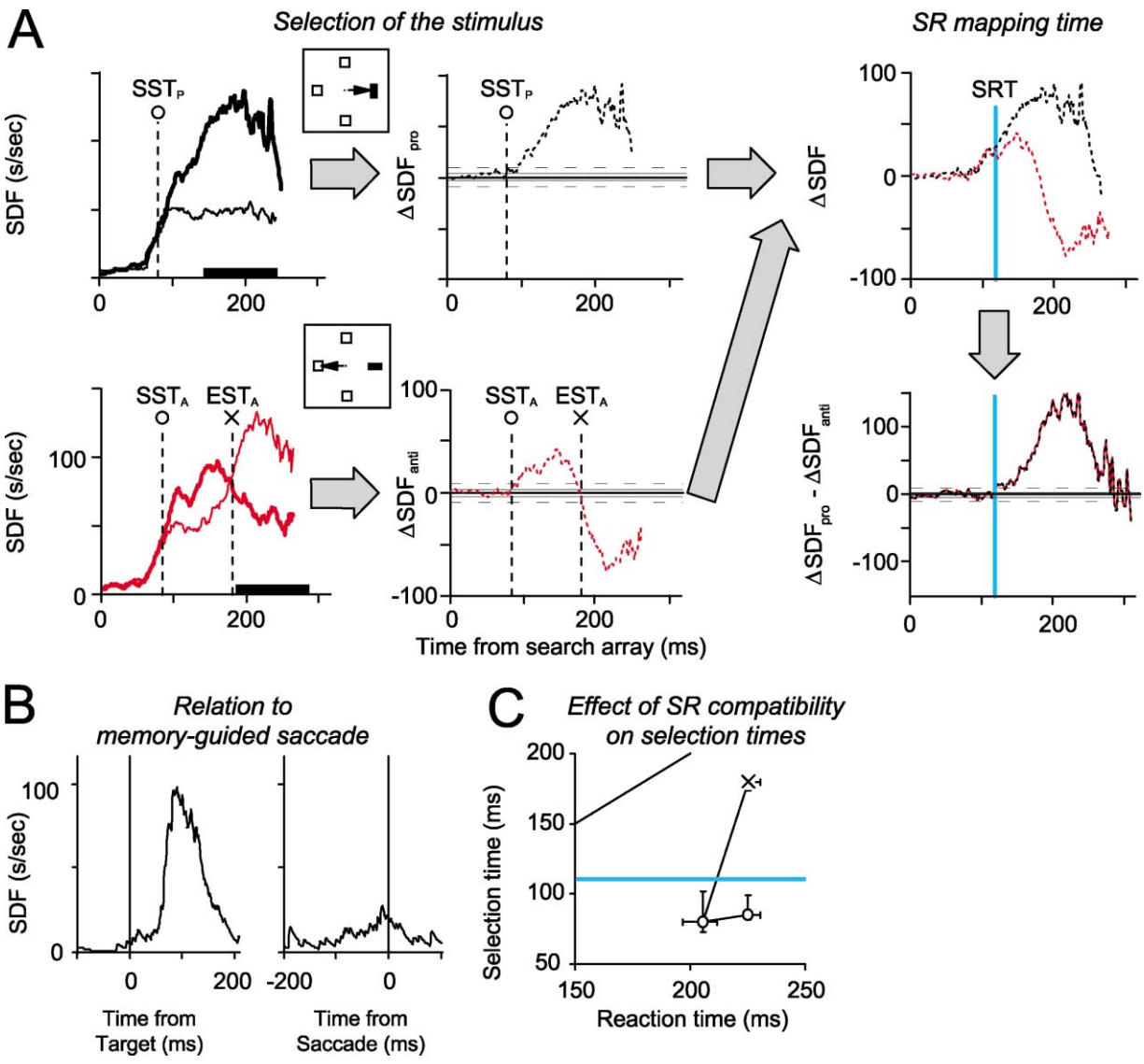

Figure 2. Effect of Stimulus-Response Compatibility during Visual Search on a Type I Neuron

(A) Left-most panels plot average discharge rate when the singleton fell in the neuron's receptive field (thick line) and when the singleton was located opposite the receptive field (thin line) in prosaccade (top) and antisaccade (bottom) trials. Solid bar on abscissa marks range of RT. Vertical dashed lines show singleton selection time (SST_P and SST_A) and endpoint selection time (EST_A). Middle panels plot the difference between the SDF for trials with the singleton in the receptive field and that for trials with the singleton opposite the receptive field (ΔSDF). Thick horizontal lines show 0 spikes/second difference. Thin horizontal lines show ±2 standard deviations, and dashed horizontal show ±5 standard deviations of the prestimulus difference of activity. Right-most panels show calculation of stimulus-response mapping time (SRT) the instant when the response dictated by singleton shape was first evident in the activity of the neuron. Top right shows superposition of ΔSDF from pro- and antisaccade trials. Bottom right plots the difference between the difference functions ($\Delta SDF_{pro} - \Delta SDF_{anti}$). Blue vertical line indicates the time when the ΔSDF for prosaccade trials and ΔSDF for antisaccade trials became different.

(B) Activity during memory-guided saccade trials aligned on stimulus presentation (left) and on saccade initiation (right). This neuron was visually responsive with little movement-related modulation.

(C) Selection times versus median RT for pro- and antisaccade trials. Circles plot SST_P (left) and SST_A (right). Cross plots EST_A. Error bars show 95% confidence intervals derived from repeated random subsampling of the trials. Blue line plots stimulus-response mapping time (SRT). Oblique line shows unity relation.

of the maximum difference of the activity (ΔSDF) in antisaccade trials was a continuum (Figure 3D), and we defined Type I and II neurons based on the criteria described above. For two neurons, ΔSDF reached 5 standard deviations but did not maintain above 2 standard deviations for 15 ms. These two neurons were defined as Type II, although the population results were identical if we exclude them from the analysis. The validity of these criteria is supported by another measure of the magnitude of singleton selection during antisaccade trials (antisaccade singleton selection index, ASSI). First, the difference between $SDF_{s\text{-}in}$ and $SDF_{s\text{-}out}$ was integrated in the interval from array presentation to the moment each neuron selected the endpoint of saccade

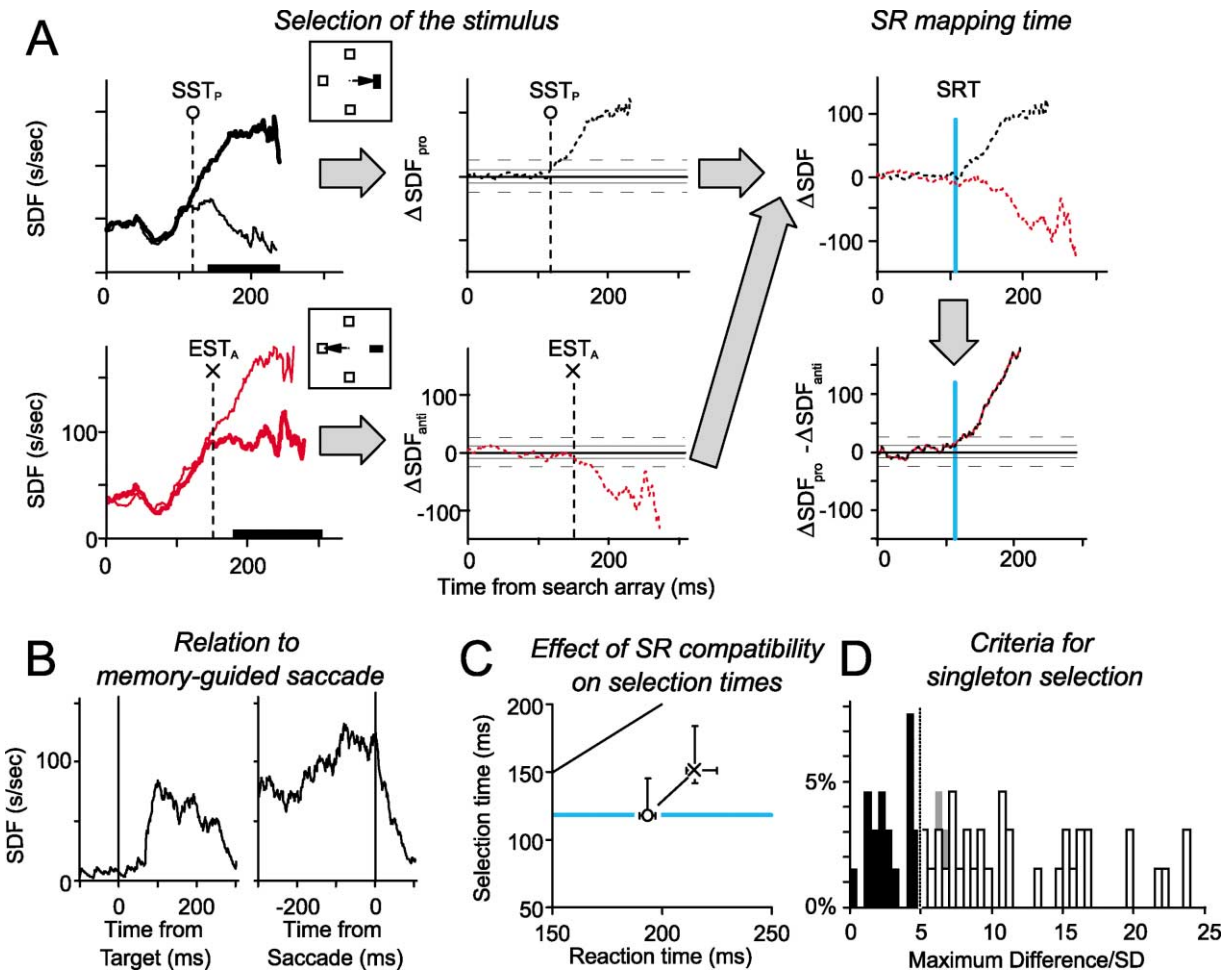

Figure 3. Effect of Stimulus-Response Compatibility on a Type II Neuron during Visual Search

(A–C) Conventions as in Figures 2A–2C.

(D) Distribution of the maximum ΔSDF after array presentation divided by the standard deviation of ΔSDF before array presentation in antisaccade trials. Type I neurons indicated by open bars. Type II neurons indicated by closed bars. Two Type II neurons indicated by gray bars exhibited ΔSDF reaching the 5 standard deviation criterion, but the difference was not maintained for the necessary 15 ms.

(EST) and then divided by the standard deviation of ΔSDF before array presentation. The distribution of ASSI of Type II neurons were centered at 0 (mean ± standard error = 3 ± 26), which is consistent with the definition of Type II neurons.

To determine whether the distinction between Type I and II neurons simply mapped onto the visual-movement axis, 62 neurons (42 Type I, 20 Type II) were tested during memory-guided saccades. The magnitude of the activity during the delay period was not different between Type I and II neurons (Type I, 19.9 spikes/sec; Type II, 25.9 spikes/sec; $t_{60} = 1.03$). To quantify the relative magnitude of visually evoked and saccade-related activity, a visual-movement index (VMI) was calculated as the difference divided by the sum of stimulus-evoked activity and saccade-related activity. A visually responsive neuron with no movement-related activity has a VMI of 1.0. An exclusively saccade-related neuron has a VMI of −1.0. The mean (± SEM) of the VMI for Type I neurons was 0.25 ± 0.08 (25th percentile = −0.19, 75th percentile = 0.72) and that for Type II neurons was −0.06 ± 0.14 (25th percentile = −0.49, 75th percentile = 0.53). Although Type I neurons tended to have larger VMI values, the difference between the VMI values for the two types of neurons was not significant ($t_{60} = 1.34$). These results indicate that the nature of the target selection process exhibited by FEF neurons does not relate directly to the strength of visually evoked or saccade-related modulation.

How Does Stimulus-Response Compatibility Affect the Selection Times of FEF Neurons?

We found that the difference of selection times in pro- and antisaccade trials of Type II but not Type I neurons could account for the effect of stimulus-response compatibility on RT. For antisaccade trials, we calculated the time the neuron selected the singleton location (singleton selection time, SST_A) and the time the neuron selected the endpoint of the saccade (endpoint selection time, EST_A). In prosaccade trials, EST could not be distinguished from SST because the singleton and the

endpoint of the saccade occupy the same location; the selection time in prosaccade trials is identified as SST_P.

While recording the neuron shown in Figure 2, the median RT in prosaccade trials was 206 ms, and that in antisaccade trials was 225 ms. SST_P of this neuron was 80 ms, and SST_A was 85 ms, amounting to a difference of 5 ms. This accounted for only 26% of the difference in RT between pro- and antisaccade trials (Figure 2C).

Next, we examined whether the difference between SST_P and EST_A of this neuron could account for the difference in RT between pro- and antisaccade trials. EST_A of this neuron was 180 ms. The difference between EST_A and SST_P was 100 ms, which was substantially larger than the 19 ms difference in RT. The ratio of the difference between EST_A and SST_P to the difference in the median RT of antisaccades and prosaccades was 526%. Obviously, the difference between SST_P and EST_A exceeded the difference of RT between pro- and antisaccades.

Across the population, Type I neurons selected the singleton at a time unaffected by stimulus-response compatibility. As shown in Figure 4A, the average percentage of the difference in RT accounted for by the difference between SST_P and SST_A was 12% $\pm$ 15%, which was significantly different from 100% ($t_{43} = 5.75$, $p < 0.001$) but not from 0% ($t_{43} = 0.81$).

The difference between EST_A and SST_P also could not account for the difference in RT between pro- and antisaccade trials (Figure 4B). The average percentage of the difference between SST_P and EST_A to the difference in RT was 337% $\pm$ 37%, which was significantly different from both 0% ($t_{37} = 9.18$, $p < 0.001$) and 100% ($t_{37} = 6.46$, $p < 0.001$). Obviously, the delay of EST_A relative to SST_P overestimates the difference in RT.

To examine whether these results are biased by measurement errors, a Monte Carlo analysis was performed. Neurons with at least 30 trials in each condition were used; 20 trials were selected randomly without replacement 1000 times for each neuron. From each sample, the ratio was calculated of the difference in the selection times to the difference in the RT between pro- and antisaccade trials. This Monte Carlo analysis resulted in 1000 values of each ratio for each neuron. The confidence intervals from this analysis are plotted in Figures 2C and 3C; the entire distribution of ratios derived from this analysis is illustrated in Figure 4. Clearly, the measurements from individual neurons corresponded precisely to the respective random subsample distributions, demonstrating that the results are not an artifact of measurement bias.

The relationship between SST_P, EST_A, and RT in pro- and antisaccade trials was notably different for Type II neurons. While recording the neuron shown in Figure 3, the median RT in prosaccade trials was 192 ms and that in antisaccade trials was 215 ms. SST_P of this neuron was 118 ms and EST_A was 151 ms. Recall that by definition Type II neurons have no SST_A. The change in RT accounted for by the difference in the EST_A and SST_P, 143%, was close to 100% (Figure 3C). Across the population of Type II neurons, the average ratio of the difference between EST_A and SST_P to the difference in RT was 146% $\pm$ 39%, which was significantly different from 0% ($t_{20} = 3.76$, $p < 0.005$) but not from 100% ($t_{20} = 1.19$) (Figure 4C).

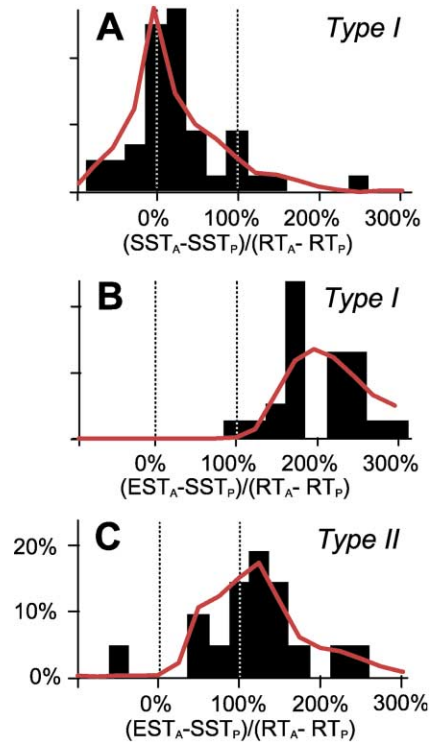

Figure 4. Effect of Stimulus-Response Compatibility on Selection Times

Distributions of the percentage of the change in RT accounted for by the change in the indicated selection times for single FEF neurons.

(A) Ratios for the difference between SST_P and SST_A of Type I neurons divided by the difference in RT.

(B) Ratios for the difference between SST_P and EST_A of Type I neurons divided by the RT difference.

(C) Ratios for the difference between SST_P and EST_A of Type II neurons divided by the RT difference. SST of Type I neurons was the same in pro- and antisaccade trials, whereas the delay of EST_A relative to SST_P of Type I neurons was substantially larger than the difference in RT between pro- and antisaccade trials. The difference between SST_P and EST_A of Type II neurons was directly proportional to the change in RT across pro- and antisaccade trials. Red lines superimposed in each panel show results from a repeated random subsampling of the data to estimate measurement error; the trends remain.

Comparing the selection times of Type I and Type II neurons reveals other differences between these two types of neurons. The mean SST_P of Type I neurons (91 $\pm$ 3 ms) was significantly earlier than that of Type II neurons (115 $\pm$ 6 ms) ($t_{63} = 3.78$, $p < 0.001$). On the other hand, the mean EST_A of Type I neurons (179 $\pm$ 4 ms) was significantly later than that of Type II neurons (159 $\pm$ 8 ms) ($t_{57} = 2.76$, $p < 0.01$). This difference of EST_A between Type I and II neurons does not arise from extra time taken to counteract the initial selection of the singleton; EST_A was not correlated with the magnitude of the singleton selection across the population of Type I neurons ($r^2 = 0.007$).

The values of SST_P and EST_A exhibited no correlation with magnitude of visually evoked or movement-related activity. For Type I neurons, the coefficient of determination for SST_P regressed on VMI was 0.01, and that for EST_A was 0.05. For Type II neurons, the coefficient of

determination for SST_P regressed on VMI was 0.20 and that for EST_A was 0.09.

Stimulus-Response Mapping Time

EST measures when the neural activation for the endpoint of the saccade first exceeds significantly the neural activation for the singleton. This transition must have a starting time, which corresponds to the instant when neural activity first distinguishes between an antisaccade trial and a prosaccade trial. We measured the earliest time when neural activity distinguished between prosaccade and antisaccade trials cued by the shape of the singleton. This will be identified as stimulus-response mapping time (SRT). Two comparisons of the activity in prosaccade and antisaccade trials were possible—one between trials with the singleton in the receptive field, and the other between trials with the singleton opposite the receptive field. To incorporate both comparisons, a two-step analysis was performed. First, the difference was calculated between the spike density function from trials when the singleton was in the receptive field ($SDF_{s\text{-}in}$) and that from trials when the singleton was opposite the receptive field ($SDF_{s\text{-}out}$) for prosaccade (ΔSDF_{pro}) and antisaccade trials (ΔSDF_{anti}) separately (Figures 2A and 3A, right top). Then, the difference between ΔSDF_{pro} and ΔSDF_{anti} was calculated (Figures 2A and 3A, right bottom). The stimulus-response mapping time (SRT) was the time when $\Delta SDF_{pro} - \Delta SDF_{anti}$ became significantly different from 0.

For the Type I neuron shown in Figure 2, SRT was 118 ms. Out of the 44 Type I neurons, 42 were differentially activated in antisaccade trials versus prosaccade trials. The mean SRT (120 $\pm$ 4 ms) was significantly later than the mean SST_P (92 $\pm$ 3 ms) or SST_A (100 $\pm$ 5 ms) ($t_{41} = 7.71$, $p < 0.001$; $t_{41} = 3.10$, $p < 0.005$, respectively). In other words, Type I neurons encoded the location of the singleton before they discriminated the shape of the singleton. Thirty-seven out of forty-two Type I neurons also selected the endpoint of the saccade before saccade initiation. Not surprisingly, the mean SRT was significantly earlier than the mean EST_A of these neurons in antisaccade trials (179 $\pm$ 4 ms) ($t_{36} = 15.0$, $p < 0.001$). Thus, Type I neurons distinguished between pro- and antisaccade trials before the endpoint of the antisaccade is selected.

For the Type II neuron shown in Figure 3, SRT was 114 ms. Characteristically, all Type II neurons discriminated prosaccade trials from antisaccade trials. The mean SRT (112 $\pm$ 7 ms) was not significantly different from the mean SST_P (115 $\pm$ 6 ms) ($t_{20} = 0.64$). The mean SRT of Type I neurons and of Type II neurons were not significantly different ($t_{61} = 1.01$). Both the mean SRT of Type II neurons and the mean SRT of Type I neurons were earlier than the mean EST_A of Type II neurons (159 $\pm$ 8 ms) ($t_{20} = 4.68$, $p < 0.001$; $t_{61} = 4.67$, $p < 0.001$, respectively). Thus, Type II neurons located the singleton and discriminated its shape at the same time, following localization of the singleton by Type I neurons.

How Does the Variability of RT across Trials Relate to the Variability in Singleton and Endpoint Selection Time?

Trials were partitioned into the short and the long half of the RT distribution after excluding the upper and lower 10% of the distributions. SST_P, SST_A, and EST_A were determined for each RT group. If the variability in the time *after* SST_P, SST_A, and EST_A accounts for all of the RT variability, then SST_P, SST_A, and EST_A should not vary with RT. On the other hand, if the variability in the time *before* the SST_P, SST_A, and EST_A accounts for all the RT variability, then SST_P, SST_A, and EST_A should increase as RT increases. To obtain SST_P, SST_A, or EST_A from the same data set, we restricted this analysis to neurons for which the selection time could be measured in both short and long RT groups for both prosaccade and antisaccade trials. As a result, 29 Type I neurons and 17 Type II neurons contributed to this analysis.

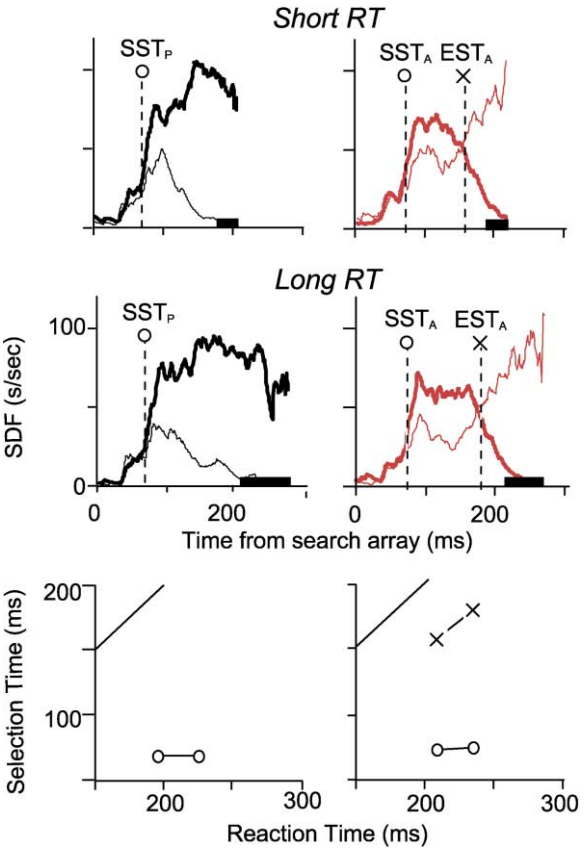

Figure 5. Selection Times of a Type I Neuron in Short and Long RT Groups for Pro- and Antisaccade Trials

Conventions as in Figure 2. Top, short RT; bottom, long RT; left, prosaccade trials; right, antisaccade trials.

The activity of a representative Type I neuron in short and long RT trials is shown in Figure 5. In prosaccade trials, from the short RT to long RT groups, median RT increased from 195 ms to 225 ms, whereas SST_P did not change at all (69 ms in both). Consequently, the ratio of the change in SST_P to the change in RT was 0%. In antisaccade trials, RT increased from 209 ms to 235 ms from the short to long RT group. SST_A was 73 ms for the short RT group and 74 ms in the long RT group. In contrast, EST_A increased from 158 ms to 180 ms across the RT groups. The variation in RT accounted for by the variation of SST_A was 4%, but that accounted for by the variation of EST_A was 85%.

Across the population of Type I neurons that provided

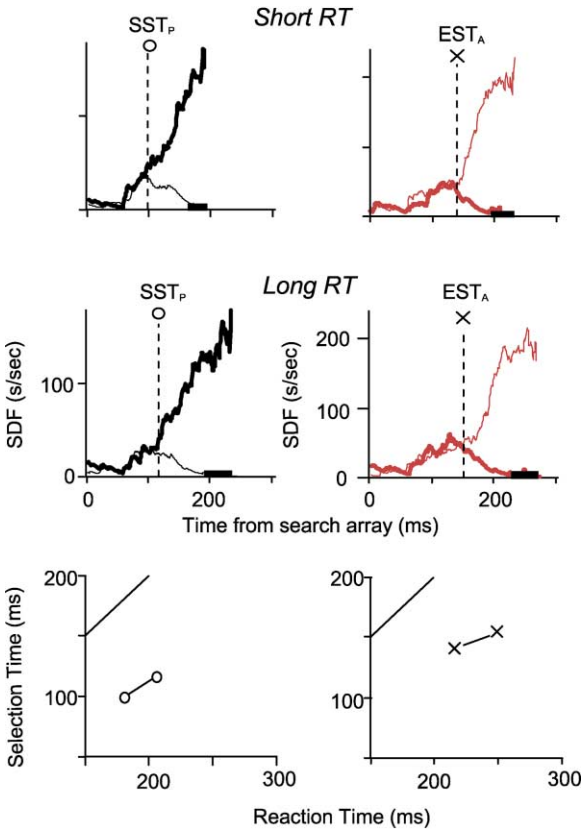

Figure 6. Selection Times of a Type II Neuron in Short and Long RT Groups for Pro- and Antisaccade Trials

Conventions as in Figure 5.

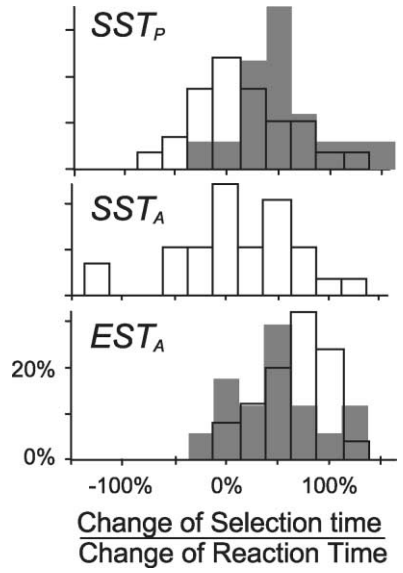

Figure 7. Variability of Selection Times and Variability of RT

Distributions of the percentage of the change in RT accounted for by the change in selection time for single FEF neurons. Top, SST$_P$; middle, SST$_A$; bottom, EST$_A$. Open bars represent data from Type I neurons, solid bars from Type II neurons.

sufficient data for this analysis, SST$_P$ and SST$_A$ were synchronized on the presentation of the search array. As shown in Figure 7, for prosaccade trials, the percentage of the change in RT accounted for by the change in SST$_P$ was 8% $\pm$ 11%, which was significantly different from 100% ($t_{28} = 8.03$, $p < 0.001$), but not different from 0% ($t_{28} = 0.67$). For antisaccade trials, the percentage of the increase in RT accounted for by the change in SST$_A$ was 12% $\pm$ 11%, which was significantly different from 100% ($t_{28} = 7.98$, $p < 0.001$) but not different from 0% ($t_{28} = 1.05$). The Monte Carlo analysis was not performed because too few trials were available.

Out of the 29 Type I neurons, 25 selected the endpoint of the saccade in antisaccade trials in both the short and long RT group. The percentage of increase in RT accounted for by the change in EST$_A$ was 66% $\pm$ 7%, which was significantly greater than 0% ($t_{24} = 9.87$, $p < 0.001$) but less than 100% ($t_{24} = 5.07$, $p < 0.001$). Thus, although EST$_A$ in antisaccade trials increased when the RT increased, it was not entirely synchronized with saccade initiation.

The selection times of Type II neurons showed a different relationship to RT as shown in Figure 6. In prosaccade trials, from the short to long RT group, the median RT increased from 181 ms to 206 ms (25 ms), and SST$_P$ increased from 99 ms to 115 ms (16 ms). The increase in RT accounted for by the increase in SST$_P$ was 64%. In antisaccade trials, RT increased from 217 ms to 249 ms (32 ms), and EST$_A$ increased from 141 ms to 153 ms (12 ms) across the two RT groups. The change in RT accounted for by the change in EST$_A$ was 38%.

Across 17 Type II neurons with sufficient data, both SST$_P$ in prosaccade trials and EST$_A$ in antisaccade trials increased with RT, but the variability of the SST$_P$ and EST$_A$ could not account for all of the variability in RT. As shown in Figure 7, for prosaccade trials, the percentage of the change in RT accounted for by the change in SST$_P$ was 52% $\pm$ 10%, which was greater than 0% ($t_{16} = 5.35$, $p < 0.005$) but less than 100% ($t_{16} = 4.86$, $p < 0.001$). For antisaccade trials, the percentage of the change in RT accounted for by the change in EST$_A$ was 56% $\pm$ 12%, which was significantly greater than 0% ($t_{16} = 4.57$, $p < 0.001$) but less than 100% ($t_{16} = 3.63$, $p < 0.005$).

Discussion

It is well known that stimulus-response compatibility affects RT (Kornblum et al., 1990). The present study addressed three questions by manipulating stimulus-response compatibility in a visual search task. First, do FEF neurons select the singleton even when gaze is shifted away from it? Second, how does stimulus-response compatibility affect the selection process in FEF? Third, how does the variability of reaction time across trials relate to the variability of the selection times of FEF neurons?

We found that about two-thirds of FEF neurons selected the singleton regardless of the direction of the saccade (Type I neurons). In antisaccade trials, nearly all of these neurons exhibited a clear transition of discharge rate such that the location of the endpoint of the saccade was selected before saccade initiation. On the other

hand, about one-third of neurons encountered in FEF selected only the endpoint of the saccade regardless of the position of the singleton (Type II neurons). In a memory-guided saccade task, Type I neurons exhibited somewhat more visual- than saccade-related activity and Type II neurons were somewhat more saccade related, but several Type II neurons exhibited only visual responses with no saccade-related activity.

Classification and Measurement Issues

Numerous studies have reported functional differences among neurons sufficient to categorize different types (e.g., Hubel and Wiesel, 1962). The distinction of Type I and II neurons in FEF parallels observations in two recent studies of target selection in the superior colliculus. The first study, using a motion discrimination task, reported two types of prelude neurons; the first exhibited direction selectivity and were modulated by the strength of the motion stimulus, and the other showed strong saccade-related activity independent of motion strength (Horwitz and Newsome, 2001a, 2001b). The second study, using a color singleton search task, reported that the time of target selection by some neurons in the superior colliculus did not vary with saccade latency, but other neurons selected the target at a time that was correlated with saccade latency (McPeek and Keller, 2002). We believe the former correspond to Type I and the latter to Type II neurons identified in this study.

It is necessary to consider the criteria for the distinction between Type I and II neurons. The distribution of selection magnitudes was a continuum, as are most biological measurements. Thus, we used particular criteria that were refined in previous studies (Hanes et al., 1998; Bichot and Schall, 1999). The validity of the criteria is supported by another measure. The integral of the difference between $SDF_{s\text{-}in}$ and $SDF_{s\text{-}out}$ from array presentation to EST scaled by the standard deviation of ΔSDF before array presentation measures the magnitude of the difference in discharge rate between the two sets of trials. For Type II neurons, this measure was centered at 0, which is consistent with the characteristic of having no particular difference in activity for the singleton versus distractor in the response field. The functional difference between Type I and II neurons is supported further by the finding that the selection times of Type I and II neurons and their relationship to RT were different even though these neurons were defined entirely by the activity pattern in antisaccade trials. These data provide converging evidence for the hypothesis that distinguishable functional classes can be observed in FEF and that the activity of Type I neurons corresponds to the encoding of the singleton location, whereas that of Type II neurons corresponds to the selection of the saccade endpoint.

Given the intrinsic variability of cortical neuron discharges (Softky and Koch, 1993; Shadlen and Newsome, 1998), it is well known that conclusions drawn from single neurons are not necessarily reliable; therefore, our conclusions are based on the central tendencies of populations of neurons. Moreover, a Monte Carlo analysis demonstrated that measurement errors did not bias the selection times or their relationship to RT.

Relation to Previous Studies

A number of studies have examined the neural correlate of stimulus-response translation (e.g., Crammond and Kalaska, 1994; Riehle et al., 1997; Shen and Alexander, 1997; Connolly et al., 2002), and neural activity associated with antisaccades has been examined in various cortical areas including the dorsolateral prefrontal cortex (Funahashi et al., 1993), supplementary eye field (Schlag-Rey et al., 1997; Olson and Gettner, 2002), FEF (Everling and Munoz, 2000), and the lateral intraparietal area (Gottlieb and Goldberg, 1999; Zhang and Barash, 2000) as well as the superior colliculus (Everling et al., 1999). These studies consistently showed that early neural activity depended on the location of the visual stimulus, but that before saccade initiation, the activity depended on the location of the saccade endpoint (but see Gottlieb and Goldberg, 1999).

Although several studies have addressed the neural basis of RT (Lecas et al., 1986; Hanes and Schall, 1996; Dorris and Munoz, 1998; Krauzlis and Dill, 2002; Cook and Maunsell, 2002; Roitman and Shadlen, 2002), only one study has examined the neural correlates of stimulus-response mapping in an RT paradigm (Mouret and Hasbroucq, 2000). That study showed that neurons in primary motor cortex with firing rate modulated by the selected response were affected by stimulus-response compatibility, whereas neurons with firing rate modulated by the sensory stimulus were not. This is entirely consistent with our findings.

The pattern of modulation of Type I neurons resembled the data in these earlier studies with one significant difference. In the previous studies, only one stimulus was presented with no stimulus at the location to which the antisaccades were directed. In the present study, the singleton was presented with distractors, so selection of the stimulus guiding the response from distractors was required. This afforded the examination of a modulation of sensory activity rather than the mere presence of sensory activity. Moreover, the presence of a stimulus at the endpoint of the antisaccades allowed them to be of normal amplitude and velocity, unlike antisaccades to a blank area (Amador et al., 1998; Bell et al., 2000).

Neural and Mental Chronometry

Human cognition has been viewed in terms of component processes performing distinct functions requiring a certain amount of time (Meyer et al., 1988; Sternberg, 2001). We have proposed that the time when FEF visual and visual-movement neurons select the target from distractors marks the end of the process of stimulus encoding and selection. The time of target selection by most but not all FEF visually responsive neurons during efficient pop-out search was synchronized on stimulus presentation rather than saccade initiation (Thompson et al., 1996). Also, the time of target selection was affected by target-distractor similarity but not by response interference (Sato et al., 2001). The present study extends this line of research by introducing explicit stimulus-response mapping between stimulus selection and response preparation. This allowed us to dissociate the time of selection of the singleton location (SST) from the time of encoding the stimulus-response rule (SRT) and the time of selection of the endpoint of the saccade

(EST). The presence and timing of these different kinds of selection distinguished Type I and Type II neurons. These results suggest certain plausible relationships between these selection times and the covert processes occurring during this task (Figure 8).

The SST of Type I neurons was not affected by stimulus-response compatibility and did not vary with RT in either prosaccade or antisaccade trials. This is consistent with the hypothesis that SST of Type I neurons corresponds to the time the singleton was located. SST in pro- or antisaccade trials was earlier than SRT that marks the time when neurons first distinguish between pro- and antisaccade trials. This finding indicates that the singleton was located before its shape was encoded to signal prosaccade versus antisaccade. The delay of SRT relative to SST may be due to the fact that locating the singleton was easier than discriminating its shape. Further research will explore the effects of search efficiency and cue discriminability on the patterns of activity of neurons in FEF.

At SRT when the stimulus-response rule was first expressed in the neural activity, the representation by Type I neurons of the singleton location exceeded that of the endpoint of the saccade. At EST, the representation of the endpoint first exceeded that of the singleton location. In other words, until EST neurons postsynaptic to Type I neurons were influenced more by the singleton location, but after EST they were influenced more by the endpoint of the saccade. However, the delay of EST in antisaccade trials relative to SST in prosaccade trials exceeded the difference in RT between anti- and prosaccade trials. This demonstrates that the modulation of Type I neurons cannot account for the effect of stimulus-response compatibility on RT.

Characteristically, for Type II neurons, SRT was identical to SST in prosaccade trials. Interestingly, SRT was about the same in Type I and II neurons, which suggests that the entire FEF was influenced by the identification of the shape of the singleton instructing the stimulus-response rule.

The timing of endpoint selection by Type II neurons was consistent with the hypothesis that the time at which Type II neurons select a stimulus corresponds to the time when the endpoint of the saccade was selected. First, the difference between the time when Type II neurons selected the endpoint of the saccade in prosaccade trials and that in antisaccade trials corresponded to the difference in RT between these two conditions. SST in prosaccade trials was earlier in Type I neurons than in Type II neurons. This indicates that selection of the endpoint of the saccade follows selection of the singleton even in prosaccade trials. This probably occurs because stimulus-response mapping follows localization and discrimination of the singleton, but it will be important to explore the relative effects of search efficiency and cue discriminability. Second, the time of saccade endpoint selection by Type II neurons varied with RT across trials in both pro- and antisaccade trials. However, not all of the variability of RT could be accounted for by variability in the endpoint selection time of Type II neurons. We believe that the remaining delay and variability of RT will be accounted for by variability in the activity of neurons ultimately initiating the saccade (Hanes and Schall, 1996).

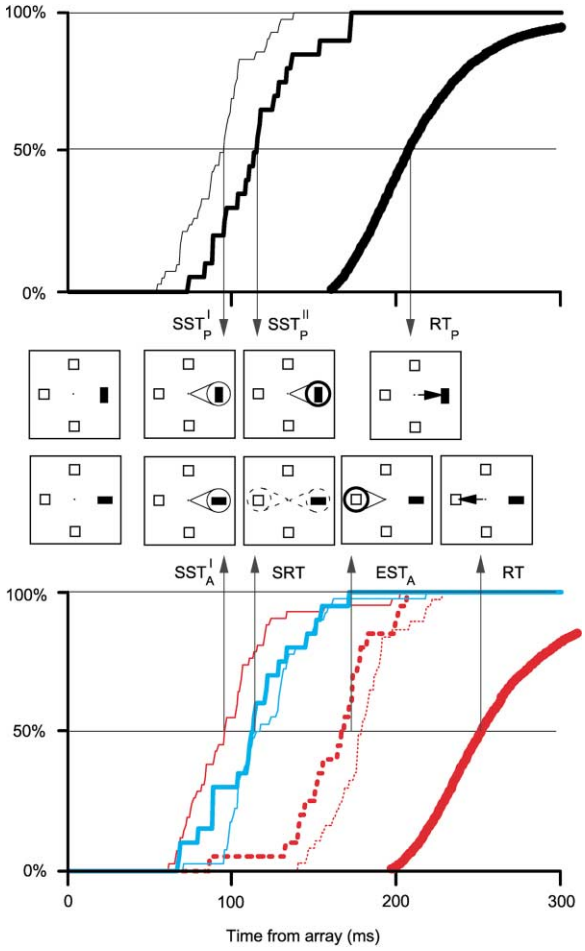

Figure 8. Cumulative Distributions of Modulation Times in Prosaccade and Antisaccade Trials for Type I and Type II Neurons with Corresponding RT

Top, prosaccade; bottom, antisaccade; Type I, thin lines; Type II, thicker lines; corresponding RT, thickest lines. The inset arrays indicate hypothesized functional correlates. After presentation of the array, selection of the singleton location occurs at the SST of Type I neurons (indicated by the spotlight on the singleton); this occurs at the same time in pro- and antisaccade trials and does not predict RT. In prosaccade trials, Type II neurons select the singleton at a later time, which accounts for some of the variability of RT. A comparison of activation in pro- and antisaccade trials reveals the time at which the shape of the singleton is encoded to specify the correct saccade direction; this follows singleton selection and coincides for Type I (thin blue) and Type II (thicker blue) neurons. At this time in antisaccade trials, the representation of the singleton decreases, and the representation of the endpoint of the antisaccade increases (indicated by the weaker spotlight on the singleton and growing spotlight on the saccade endpoint). At this same time in prosaccade trials, the representation of the saccade endpoint is enhanced by the selection that occurs in the Type II neurons (indicated by the highlighted spotlight on the singleton). Subsequently, in antisaccade trials the endpoint of the saccade becomes selected more than the location of the singleton by Type I (thin red dashed line) and Type II (thicker red, dashed) neurons (indicated by the highlighted spotlight on the antisaccade endpoint). The time taken to select the endpoint of the saccade predicts the delay and much of the variability of RT.

Relation to Covert and Overt Orienting

There is no doubt that FEF is involved in overt orienting through saccade production (Bruce and Goldberg, 1985; Hanes et al., 1998), but the role of FEF in covert orienting has been less clear. An original study of FEF visual activity reported that visual responses were enhanced when monkeys shifted gaze to a visual stimulus, but not when they responded manually without shifting gaze (Goldberg and Bushnell, 1981). However, subsequent studies have presented several lines of evidence indicating that selection of the singleton by FEF neurons could correspond to covert orienting dissociated from saccade execution (Thompson et al., 1997; Bichot and Schall, 1999; Murthy et al., 2001; Sato et al., 2001, 2003; see also Kodaka et al., 1997). In fact, electrical stimulation of FEF can facilitate perceptual processing in a task requiring selective spatial attention (Moore and Fallah, 2001).

The present results indicate a more involved role of FEF in covert and overt orienting. While we did not measure the allocation of attention directly, the findings of other studies indicate that attention was allocated first to the location of the singleton (because it was conspicuous and because its shape needed to be discriminated) and then to the endpoint of the saccade (e.g., Kowler et al., 1995; Deubel and Schneider, 1996; Theeuwes and Godljn, 2002). It is tempting to identify the selection of the singleton by Type I neurons with the stimulus-driven shift of attention and to identify the dramatic modulation leading to selection of the endpoint of the saccade to the endogenous allocation of attention preceding the saccade. The diversity of neurons observed in this study may provide the substrate for stimulus-driven and endogenous control of attention guiding saccades.

Experimental Procedures

Subjects and Surgery

Data were collected from three macaque monkeys (F, M, L, *Macaca radiata*) weighing 4–10 kg. The animals were cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the guidelines of the Vanderbilt Animal Care Committee. The surgical procedures have been described previously (Schall et al., 1995).

Behavioral Training

Monkeys were trained to perform a color singleton visual search task with reward contingent on producing a prosaccade or an antisaccade cued by the shape of the singleton. After fixation of a central spot for 400–700 ms, four stimuli were presented at isoeccentric locations equally spaced around the central fixation spot (Figure 1A). One of the four stimuli was a color singleton target, which was distinguished from iso-luminant distractors (i.e., red target among green distractors or green target among red distractors). The green was CIE $x = 284$, $y = 608$, red was CIE $x = 631$, $y = 328$ with a luminance of 11.4 cd/m^2 on a black background. The color of the singleton and distractors remained the same during each recording session and varied pseudorandomly across sessions. The four stimuli were arranged so that one of the stimuli was located in the center of the receptive field of the recorded neuron. The singleton could be a vertical or a horizontal rectangle. The vertical singleton required a prosaccade to its location within 1500 ms. The horizontal singleton required an antisaccade to the location of the distractor diametrically opposite the singleton within 1500 ms. Pro- and antisaccade trials were randomly interleaved. In both types of trials, after the correct saccade, all the stimuli but the one that served as the endpoint of saccade disappeared. The monkeys were required to fixate the correct saccade target for 500 ms to obtain reward. In some of the recording sessions, trials were interleaved in which the singleton was square, which required monkeys to maintain fixation on the central spot for 2000 ms. Pro- and antisaccade trials were the focus of this report. The distractors were always squares that scaled from 0.6° of visual angle at 6° eccentricity to 1° at 10° eccentricity. The aspect ratio of the rectangle singleton remained the same within each recording session, and was between 1.4 and 2.0. The area of the rectangle was equal to that of the distractors.

Monkeys were also trained to produce memory-guided saccades to distinguish visual from saccade-related activity (Hikosaka and Wurtz, 1983; Bruce and Goldberg, 1985). A single target was flashed for 80 ms, but the monkeys were required to maintain fixation on the central spot for another interval of random duration ranging from 400 to 1000 ms. When the fixation spot disappeared, the monkeys were rewarded for shifting gaze to the remembered location of the target. Once gaze shifted, the target reappeared to provide feedback and a fixation target for the monkeys.

Data Collection and Analysis

Single units were recorded with tungsten electrodes (FHC). The electrode was introduced through a guide tube positioned in a 1 mm spaced grid (Crist et al., 1988) and was positioned with a hydraulic drive (FHC). Action potentials were amplified, filtered, and discriminated using an analog time-amplitude window discriminator (BAK). FEF recordings were done in the rostral bank of the arcuate sulcus, which was confirmed with the magnetic resonance imaging.

Measurements of neural activity were derived from spike density functions generated by convolving action potentials with a function that resembled a postsynaptic potential: Activation(t) = $(1 - \exp(-t/\tau_g)) \times (\exp(-t/\tau_d))$. Physiological data from excitatory synapses estimate the growth constant τ_g at 1 ms and the decay constant τ_d at 20 ms (e.g., Sayer et al., 1990). The rationale for this approach, which has been described previously (Hanes and Schall, 1996; Thompson et al., 1996), was to derive physiologically plausible spike density functions.

The time at which the neuron selects the singleton or the endpoint of saccade was determined by comparing two sets of trials in a neuron-antineuron analysis (Britten et al., 1992; Thompson et al., 1996). In earlier work, we measured the time when neurons select the target. However, in the antisaccade trials, the term "target" is ambiguous, for it might refer to the singleton or to the endpoint of saccade. Therefore, for antisaccade trials, we adopt more precise terminology by distinguishing singleton selection time (SST_A) and endpoint selection time (EST_A). SST and EST cannot be distinguished in prosaccade trials, and thus the selection time in prosaccade trials will be referred to as singleton selection time (SST_P). We also calculated stimulus-response mapping time (SRT), which is derived from comparison across pro- and antisaccade trials. These times are measured as follows. First, spike density functions were calculated for all the correct trials with the singleton in the receptive field ($SDF_{s\text{-}in}$) and for all the correct trials with the singleton diametrically opposite the receptive field ($SDF_{s\text{-}out}$). The difference between these two spike density functions was calculated:

$$\Delta SDF = SDF_{s-in} - SDF_{s-out}.$$

This function represents the discrimination process of the neuron and was closely correlated with the ROC area used in our previous work (Thompson et al., 1996; Sato et al., 2001). The mean and standard deviation of the baseline of ΔSDF was calculated in the interval of 50 ms before to 50 ms after array presentation across pro- and antisaccade trials. The time at which the difference function crossed the mean baseline difference plus 2 standard deviations was selected as SST_P (prosaccade trials) or SST_A (antisaccade trials), only if the difference function reached the baseline plus 5 standard deviations and remained above the mean plus 2 standard deviation level for more than 15 ms.

In antisaccade trials, the singleton and the endpoint of the saccade occupied opposite locations. Therefore, the trials with the singleton in the receptive field were the trials in which the endpoint of the saccade was opposite the receptive field, and the trials with the singleton opposite the receptive field were the trials in which the endpoint of the saccade was in the receptive field. Therefore,

in antisaccade trials, $SDF_{s\text{-}in}$ describes activity for trials in which the endpoint of the saccade was opposite the receptive field, and $SDF_{s\text{-}out}$ is the activity for trials in which the endpoint of the saccade was in the receptive field. Therefore, the time at which the neuron selected the endpoint of the antisaccade (EST_A) was defined using the same criteria as for SST_A but with the opposite sign. We also measured the earliest time that FEF neurons discriminate between pro- and antisaccade trials. SRT was calculated from the difference between ΔSDF for prosaccade trials and ΔSDF for antisaccade trials ($\Delta SDF_{pro} - \Delta SDF_{anti}$) using the same criteria used to determine SST_P, SST_A, and EST_A. SRT is the earliest time pro- and antisaccade trials can be distinguished based on the discrimination process (ΔSDF) calculated from a neuron-antineuron analysis.

To quantify the relative magnitude of visual and movement activity in the memory-guided saccade task, visual-movement index (VMI) was calculated for each neuron. Visual activity (VA) was defined as the highest activity of a 50 ms window that moved by 1 ms from 0 ms to 200 ms after stimulus onset. Movement activity (MA) was defined as the mean firing rate of a time window 50 ms to 0 ms before saccade onset. VMI was calculated as

$$VMI = (VA - MA)/(VA + MA).$$

Delay activity was defined as the mean firing rate of a time window 400 ms to 300 ms before saccade onset.

To quantify the singleton selection process in antisaccade trials, an antisaccade singleton selection index (ASSI) was calculated for both Type I and II neurons. First, ΔSDF in antisaccade trials was integrated from the time of array presentation to EST_A for each neuron. For neurons that did not select the endpoint of saccade in antisaccade trials, the interval between the array presentation and the median RT was used. This value was then divided by the standard deviation of ΔSDF before the array appeared.

To determine how SST_P, SST_A, and EST_A varied with RT in prosaccade trials and antisaccade trials, trials were grouped according to RT. To minimize the effect of outliers, trials in the lower and the upper 10% of the RT distribution were excluded. The trials were divided into the early and the late half of the remaining RT distribution. Then, SST_P, SST_A, EST_A, and the median RT were calculated for each group. It was impossible to divide the total trials into more RT groups to obtain finer resolution due to limited number of trials. For this analysis, the neurons included contained on average 18 trials for each spike density function in each RT group.

To estimate the effect of measurement errors, a Monte Carlo analysis was performed. Neurons with more than 30 trials for each condition were selected, and 20 trials were randomly sampled without replacement 1000 times for each neuron. From each such sample, SST and EST for prosaccade and antisaccade trials and the associated RT were calculated. The ratio of the difference in the selection times to the difference in the RT between pro- and antisaccade trials was calculated as described above. Then the distribution of the ratios was examined for (1) $(SST_A - SST_P)/(RT_A - RT_P)$ for Type I neurons (n = 21), (2) $(EST_A - SST_P)/(RT_A - RT_P)$ for Type I neurons (n = 18), and (3) $(EST_A - SST_P)/(RT_A - RT_P)$ for Type II neurons (n = 12). The neurons in this analysis contained on average 52 trials for each condition.

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