Primate Antisaccade. II. Supplementary Eye Field Neuronal Activity Predicts Correct Performance

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Amador, Nelly, Madeleine Schlag-Rey, and John Schlag. Primate antisaccade. II. Supplementary eye field neuronal activity predicts correct performance. J Neurophysiol 91: 1672–1689, 2004. First published November 26, 2003; 10.1152/jn.00138.2003. Neuronal activities were recorded in the supplementary eye field (SEF) of 3 macaque monkeys trained to perform antisaccades pseudorandomly interleaved with prosaccades, as instructed by the shape of a central fixation point. The prosaccade goal was indicated by a peripheral stimulus flashed anywhere on the screen, whereas the antisaccade goal was an unmarked site diametrically opposite to the flashed stimulus. The visual cue was given immediately after the instruction cue disappeared in the immediate-saccade task, or during the instruction period in the delayed-saccade task. The instruction cue offset was the saccade go-signal. Here we focus on 92 task-related neurons: visual, eye-movement, and instruction/fixation neurons. We found that 73% of SEF eye-movement-related neurons fired significantly more before antisaccades than prosaccades. This finding was analyzed at 3 levels: population, single neuron, and individual trial. On individual antisaccade trials, 40 ms before saccade, the firing rate of eye-movement-related neurons was highly predictive of successful performance. A similar analysis of visual responses (40 ms astride the peak) gave less-coherent results. Fixation neurons, activated during the initial instruction period (i.e., after the instruction cue but before the stimulus) always fired more on antisaccade than on prosaccade trials. This trend, however, was statistically significant for only half of these neurons. We conclude that the SEF is critically involved in the production of antisaccades.

INTRODUCTION

Little is known, yet, about how the brain directs gaze to unmarked goals that are defined solely by instruction. The antisaccade task offers an experimental approach to this problem. Initially designed by Hallet (1978) to compare the mechanisms involved in programming reflexive and voluntary saccades, the antisaccade task requires a subject to generate a saccade to an unmarked site diametrically opposite to a flashed peripheral stimulus, without glancing at it. Untrained human subjects perform this task with a large percentage of errors (consisting of involuntary prosaccades, i.e., movements toward visual targets). When Guitton et al. (1985) submitted patients with frontal lobe ablations (performed to alleviate intractable epilepsy) to an antisaccade test, they found that the patients could not make prosaccades but could make normal prosaccades (saccades to a visual stimulus). The subjects reported that they knew where they wanted to move their eyes but they could not override the reflexive urge to look at the stimulus.

Subsequent studies have shown that patients with basal ganglia disorders (Dursun et al. 2000; Lasker et al. 1987; Tian et al. 1991) demonstrate similar impairments. The common deficit among these patients appears to lie in their inability to suppress reflexive glances to suddenly appearing visual stimuli. Given that patients with both discrete lesions and psychiatric disorders alike are impaired at performing antisaccades, the antisaccade paradigm has become an important diagnostic tool (for a review, see Everling and Fischer 1998).

In the 20 years since its inception, the classic antisaccade paradigm has undergone several modifications. One of the most important has been the introduction of a gap of the order of 200 ms between the offset of the fixation point and the onset of the peripheral cue. The presence of the gap had been previously shown to increase the number of express saccades (Fischer and Boch 1983). When a gap was introduced in antisaccade experiments, it increased the number of erroneous express prosaccades but it did not trigger express antisaccades (Fischer and Ramsperger 1984; Fischer and Weber 1992).

Because antisaccade latencies from stimulus onset are never in the range defining express saccades, Fischer and Weber (1992) postulated the existence of a reflexlike pathway from the retina to oculomotor centers in the brain stem that permits the release of express saccades if the reflex is disinhibited at the time of target presentation. Subsequent studies using a cued antisaccade task, or a gap task, have tended to focus on the problem of reflex inhibition rather than on the computational mechanism whereby a saccade can be made to an internally defined goal. However, blocking the visual grasp reflex does not suffice to ensure correct performance of antisaccades. To perform the task correctly, a subject must not only overcome an initial reflex but also initiate a voluntary eye movement that, even though the initial reflex has been overcome, still has to vanquish the powerful drive to look at the present or remembered stimulus. Correct performance critically depends on the subject’s ability to successfully execute 4 distinct operations: 1) decode the instruction (necessarily conveyed by a learned symbol in the case of a nonhuman primate), 2) inhibit the prepotent tendency to make a reflexive saccade, 3) calculate where to look, and 4) initiate a voluntary saccade to that computed location. Some of these operations are necessarily sequential.

Numerous experiments have been performed in monkeys to determine the neuronal basis of how voluntary saccades are prepared and generated to visual targets. Using various para-
Antisaccades: simple fixation, go/no-go, single/double/triple-step saccades to remembered locations, and so forth, as well as variations of these paradigms: shape/color of the fixation point, shape/color of stimulus, duration of fixation/stimulus, frame of reference, and so forth, all these experiments require gaze to be shifted from one place to another as cued by overt visual targets. On the other hand, the question of how voluntary saccades are made to computed targets or to locations in space that are devoid of visual landmarks is still largely unanswered. Only recently have several laboratories, including ours, made a concerted effort to address this question in subhuman primates through the use of the antisaccade task.

Funahashi et al. (1993) were the first to study the neuronal correlates of antisaccades in rhesus monkeys. Their study, using purely horizontal pro- and antisaccades, showed that the majority of neurons in the dorsolateral prefrontal cortex (DLPFC) code the location of the visual stimulus and hold the information “on-line,” which may allow it to be used at any time to compute the antisaccade. A smaller subset of neurons was found to code for the response direction regardless of whether a prosaccade or an antisaccade was made. The second study performed on nonhuman primates (Schlag-Rey et al. 1997) revealed that, in the supplementary eye field (SEF), a larger neuronal activation precedes antisaccades compared with prosaccades of the same dimensions. We suggested that this higher activation before antisaccades could serve to overcome the strength of competing saccades simultaneously programmed in the opposite hemisphere. A subsequent behavioral study (Amador et al. 1998) provided a comparison of monkey pro- and antisaccades in terms of accuracy, velocity, and latency of movement. It underscored the importance of randomizing the trials and training the monkey to perform antisaccades in all directions. Then, other cortical areas were studied. Gottlieb and Goldberg (1999) demonstrated that visual responses in parietal area LIP (lateral intraparietal) are larger on antisaccade than on prosaccade trials but these authors found very few neurons activated before antisaccades. Zhang and Barash (2000), also recording from LIP, reported that one-third of their visual neurons, on antisaccade trials, were activated by a stimulus presented at the destination site of the required movement (i.e., opposite the receptive field of the neuron). Hence, they called this response “paradoxical.” Yet, this activity was time-locked to the stimulus, although with a longer latency. This finding suggests that the necessary visual-to-motor transformation may already occur at the time of the visual response. In the superior colliculus (SC), using a gap paradigm, Everling et al. (1999) observed an increased activity of fixation-related neurons and a decreased activity of stimulus-related and saccade-related neurons before antisaccades compared with prosaccades. In the frontal eye field (FEF), Everling and Munoz (2000) found, likewise, that saccade-related neurons had lower prestimulus, stimulus, and saccade-related activity before antisaccades. Many of these saccade-related neurons were, in fact, corticocortical neurons identified by antidromic FEF stimulation. Thus before the appearance of a visual stimulus, the FEF and SC could prevent a potential express saccade to it by promoting fixation-related activity. Once the visual stimulus has appeared, however, competing pro- and antisaccade commands develop in parallel, as evidenced by “turn-around” saccades (Amador et al. 1998). Thus in terms of conflicting signals, what was initially a competition between a “go” (flex) and a “no-go” (reflex suppression) becomes a competition between 2 “go” signals: “go to this site or go to the opposite site.” At that point, the weaker activity of the FEF and the SC before antisaccades compared with prosaccades can ill account for an antisaccade command overriding a prosaccade command. What is needed, at the final stage of the decision process, is a stronger signal favoring the initiation of antisaccades. Because our previous study in the SEF (Schlag-Rey et al. 1997) had revealed that SEF neurons discharge more vigorously before antisaccades than before prosaccades, a further investigation of this finding was warranted.

The objective of the present study was to carry out a thorough investigation of SEF neuronal activity in all phases of antisaccade generation. For this endeavor, we used, as before, a task that randomly interleaves pro- and antisaccades in the preferred and null direction of the sampled neuron. We expanded the scope of our first study by computing the probability that the monkey will choose to make a required antisaccade on a given trial, as a function of the firing rate displayed by the SEF movement-related neurons studied on that trial, just before the onset of the saccade. [Some preliminary results previously appeared in abstract form (Amador et al. 1996, 1997, 2001).]

Methods

Subjects

Three female macaque monkeys (MKA, MKD, MKI, ranging from 8 to 10 kg) served as subjects. The surgical procedures, training, and care of the monkeys followed the guidelines of the National Institute of Health’s Guide for the Care and Use of Laboratory Animals and the Instructions of the UCLA Animal Research Committee.

Surgical procedures

A search coil was implanted under the conjunctiva of one eye (Judge et al. 1980). Wire leads from the eye coil were secured to a dental cement cap that was anchored by stainless-steel screws to the monkey’s skull. In the cap were embedded nuts by which the head was secured to the head restraint apparatus during all training and experimental sessions. After preliminary training sessions, a craniotomy was performed, followed by injection of buprenorphine, repeated as needed. At least 1 wk elapsed between surgery and further training. After the experiments were completed the monkeys were euthanized and perfused with 10% formalin. Relevant brain sections (60 µ) stained with thionin were examined for histological reconstruction of microelectrode tracks.

Equipment

During training sessions, the monkey sat in a primate chair, facing a tangent screen 61° wide and 50° high placed at a distance of 132 cm in front of her eyes (to minimize ocular convergence). Low-intensity (25 mcd/°²) luminous dots (0.23° diameter) in the form of circles or squares (<3°) were back-projected onto a tangent screen by a Tektronix 608 oscilloscope through a wide-angle projection lens. Visual stimuli could be positioned anywhere on the screen by joysticks, in any direction and eccentricity ≤25°. Training and recording sessions were carried out in dim red light (150 mcd/m² of luminance on the screen) to prevent dark adaptation. An infrared camera allowed con-
tinuous monitoring of the monkey’s facial movements. The eye position signal was calibrated in each session while the monkey maintained steady fixation on a stimulus. Eye position was sampled at 1 kHz and continuously monitored. Saccades were automatically detected.

A computer system, with MacProbe software, controlled the behavioral paradigms. It rewarded the monkey and stored all stimuli and behavioral events for off-line analysis.

Microelectrodes were lowered stereotaxically through the intact dura. Before penetrating the dura, the microelectrode traveled through a 20-mm stainless-steel guide tube to ensure a straight trajectory. When used to identify the SEF, electrical microstimulation was applied through the recording electrode. Trains of stimuli were delivered from a constant-current Haer stimulator. Eye position, visual stimuli, and unit activity (or electrical pulses) were displayed on-line on a computer screen, 2 Tektronix monitor oscilloscopes (one displaying eye and stimuli in xy coordinates, the other monitoring action potentials and the output of a window discriminator), and on a running polygraph. All trial events were stored for off-line analysis.

**Tasks and experimental procedures**

At the beginning of each trial, the instruction to make a pro- or an antisaccade was conveyed by the shape of the initial fixation point: a small square or a circle. The meaning of these stimuli was reversed between monkeys but remained consistent for each one (for convenience, in all illustrations, the square always specifies an antisaccade).

In the **immediate-saccade task**, a peripheral stimulus (a dot) was briefly flashed (~100 ms) when the instruction cue disappeared, thus prompting the monkey to make the instructed saccade (Fig. 1A). An electronic window centered on the peripheral stimulus (for prosaccades) or diametrically opposite (for antisaccades) determined whether the pro- or antisaccades met the criterion accuracy (usually within 6°). When a prosaccade or antisaccade terminated in and stayed within the window (minimum of 250–300 ms), a drop of 50% diluted apple juice, sweetened with aspartame, was delivered simultaneously with a brief flash at the exact location of the saccade goal. No reward was given if a saccade did not end within the window. Moreover, “turn-around saccades” (a saccade in the wrong direction followed by a saccade in the correct direction) were not rewarded.

In the **delayed-saccade task** (Fig. 1B), the peripheral stimulus (~200 ms) was flashed about 200 ms after the monkey started to fixate the instruction cue. This delay was increased ~400 ms when the neuron appeared to be active with fixation of the instruction cue. The monkey was required to maintain gaze on the instruction cue for its whole duration (variable ≤1,600 ms). Delays between the flashed stimulus and the offset of the fixation cue were varied to discourage anticipatory saccades and to separate visual responses from oculomotor responses. While recording from a neuron, delayed and immediate-saccade tasks were intermixed.

**Test trials used during recording sessions**

When a neuron was isolated, first, its visual responsiveness was probed by flashing peripheral dot stimuli (~3°). The flashed stimulus could appear anywhere on the screen. Centers of visual receptive fields were determined by finding successively the preferred angle and the preferred eccentricity at that angle, tested in a pseudorandom order, while the monkey maintained fixation. Centers of movement field were determined in the same way except that the monkey was required to make a saccade to the peripheral stimulus when the fixation point disappeared. The purpose of these tests was merely to find the location of the stimuli and/or the goal of the saccades that elicited the strongest response, to select the optimal placement of stimuli for subsequent antisaccade testing.

When pro- and antisaccade testing began, peripheral stimuli were presented only at the location eliciting the strongest response or at the 180° opposite site. The combination of 2 stimulus locations and 2 saccade directions (mandated by instruction) generated 4 types of trials. Because the latter were intermixed in pseudorandom order and because the proportions of errors fluctuated, the total number of trials per neuron varied. However, this number always included a minimum of 5 valid trials of each type.

In the trial labels of Fig. 1C, the 1st “Y” or “N” refers to the location of the peripheral stimulus: in or opposite the receptive field. The 2nd “Y” or “N” refers to the instructed saccade goal: in or opposite the response field. The capital letters Y and N define a type of trial (i.e., what the monkey is instructed to do). Therefore the same letters (YY, NN) specify prosaccade trials, whereas different letters (YN, NY) specify antisaccades trials. Eventually, a 3rd letter (lower-case y or n) indicates the direction of the saccade actually made. Thus in a 3-letter label, the match or mismatch of the last 2 letters indicates whether the performance was correct (YYy, NNNn, YYyN, NNNy) or incorrect (YYn, NNy, NNY, NNN). The rare cases in which saccades began in the proper direction but diverged from the reward window were not included in the analyses.

Repeated microelectrode penetrations were made in the SEF, as originally defined by Schlag and Schlag-Rey (1987), corresponding to area F7 of Luppino et al. (1993). To locate this region devoid of surface landmarks, for each monkey we first determined the putative

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**FIG. 1.** Prosaccade and antisaccade tasks. A: immediate-saccade task. B: delayed-saccade task. A and B: time course of stimuli and saccades. From top to bottom the traces represent: the central fixation point conveying the Pro-instruction cue (circle) or Anti-instruction cue (square), the peripheral stimulus (dot), the correct saccade (continuous line), and incorrect saccade (dashed line). Disappearance of the fixation point was the go-signal for the saccade. C: spatial displays of the stimuli and saccades in 4 types of trials. Instruction cue (circle or square) appeared at the center; the peripheral stimulus appeared in the neuron’s receptive field (large circle) or on the opposite side. Arrow represents the required saccade. Four types of trials are designated by the combination of the 2 letters Y and N. The 1st letter specifies whether the peripheral stimulus was in the neuron’s response field (Y) or not (N). The 2nd letter specifies whether the required saccade was in this field (Y) or not (N). Same letters (YY, NN) mean prosaccade trials; different letters (YN, NY) mean antisaccade trials.
location of the SEF by evoking saccades with low-current microstimulation (Schlag and Schlag-Rey 1987). The standard parameters of the trains were: 10–30 diphasic pulses of 0.2-ms duration, with a 10- to 40-μA current. The impedance of the electrode was continuously monitored. In the present study, microstimulation was used sparingly, to avoid tissue damage. Because of the parametric constraints of the task, explorations of the SEF were confined mostly to a region where the eccentricity of the centers of response fields ranged from >5 to <20°.

Data analysis

Rasters of unit activity were displayed on-line but final analyses were made off-line. First, pro- and antisaccade trajectories were plotted in xy coordinates and saccade metrics were quantitatively analyzed. Antisaccade trials were screened to exclude the least-accurate and the slowest trajectories (see Amador et al. 1998). Then, for each neuron, a subset of antisaccades was selected such that it would best match the subset of prosaccades in terms of saccade direction, amplitude, and velocity (e.g., Fig. 4B). Commonly, when the firing of movement cells varies with saccade velocity, it increases as this velocity increases. Because antisaccades are often slower than prosaccades (see Amador et al. 1998), antisaccades could be at a disadvantage in a comparison of firing rate, simply because of metrical differences. Our matching procedure helped reduce the imbalance in velocity, but it never reversed the trend. Third, each subset of saccades was ranked in order of latency from stimulus onset. For each neuron and each type of trial, 2 rasters of spike activity were made: one aligned on stimulus onset, the other on saccade onset. In each one, the time of occurrence of the other nonaligned event was shown by tick marks. These paired rasters and their corresponding spike density profiles (constructed from Gaussians with σ = 20 ms) allowed us to distinguish “Visual,” “EM,” and “Visual and EM” neurons (examples appear in Fig. 3B). Our primary goal, however, was not to classify neurons but to dissociate saccade-related signals from visual signals. Comparisons of pro- and antisaccade activities were made at 3 levels. At the population level, the trials obtained for each neuron were pooled and averaged to generate compound spike density profiles, reflecting the output of the region studied. At the single-neuron level, the quantitative comparisons between pro- and antisaccade trials focused on the peak visual response (~20 to +20 ms astride the peak) and the last 40 ms preceding saccade onset. The statistical significance of the differences observed between pro- and antisaccade trials was tested by paired t-test for the population means, and by unpaired t-test for the neuronal means (Glantz 2001). At the trial level, we attempted to determine whether the firing rate obtained during the critical visual and motor epochs defined above could predict the monkey’s behavioral response on a given trial. For each neuron, this was done by counting, on each trial, the number of spikes in the critical epoch considered, ranking these firing rates in ascending order, and computing the percentage of correct versus incorrect saccades corresponding to each firing rate. The rationale underlying this procedure is given in the relevant results sections.

Results

Location of the SEF and types of neurons

The cortical territory explored was found restricted to the SEF in monkeys MKA and MKD (MKI is still participating in current experiments). This territory overlapped with the SEF region known to send direct projections to the SC and to the oculomotor region of the brain stem, including the nucleus raphe interpositus (RIP), containing the omnipause cells—physiologically described by Keller (1974)—that gate descending signals to the saccade generator (Huerta and Kaas 1990; Shook et al. 1988, 1990).

The topographical distribution of recording sites that yielded data included in this study is shown for monkey MKD (Fig. 2). Our choice of microelectrode penetrations, aided by initial microstimulation (see METHODS), was designed to maximize the encounter of neurons potentially involved in saccade initiation. It did not aim to provide a systematic survey of larger dorso-medial areas explored by other authors (Huerta and Kaas 1990; Russo and Bruce 2000; Schall 1991b; Tehovnik 1993) nor to determine precise boundaries of the SEF (for a review of the respective locations of SEF, SMA, and pre-SMA, see Tanji 1994).

We recorded from 502 SEF neurons while the monkeys performed both the immediate and the delayed pro- and antisaccade tasks illustrated in Fig. 1. The oculomotor behavior of MKA and MKD in these tasks was previously described (Amador et al. 1998). On the basis of prosaccade trials, 305 neurons were classified into the conventional categories of fixation, visual, and saccade-related neurons observed in all eye fields when simple visual targeting tasks are used, and a broad category of reinforcement-related neurons, found to exist in the SEF (Amador et al. 2000; Coe et al. 2002; Roesch and Olson 2003; Stuphorn et al. 2000) as well as in the anterior cingulate cortex (Shima and Tanji 1998), posterior parietal cortex (Platt and Glimcher 1999), prefrontal cortex (Rosenkilde et al. 1981; Watanabe 1996), and orbital cortex (Tremblay and Schultz 1999). Neurons that signal different events at different times were distinguished from those that carried a single signal. The proportions of neurons found belonging in these categories are depicted in Fig. 3A. These proportions are naturally constrained by the set acquired by the monkeys in performing the pro/antisaccade task and our criteria for deciding whether the same neuron carried single or multiple types of signals (exemplified in Fig. 3B). Figure 3A reveals that about two thirds of the neurons recorded had activities related to visual events and motor planning preceding saccade onset, one third to reward events after the saccade. Figure 3B describes the main neuronal types by a sample of rasters aligned with particular events.

Neurons with fixation-related activity (Bon and Luchetti 1990; Lee and Tehovnik 1995; Schlag et al. 1992) were characterized by a tonic increase in firing rate, maintained throughout the fixation of the instruction cue, stopping shortly before the initiation of a saccade and reappearing whenever fixation was resumed (not shown). Neurons exhibiting responses time-locked to the appearance of a visual stimulus varied from phasic to sustained. What distinguished them from the next category, illustrated below, was the lack of consistent relationship between the cessation of their activity and the beginning of a targeting saccade. This was easily demonstrated by using the delayed-saccade paradigm. In contrast with these purely visual neurons, Visual (Vis.) and Eye-Movement (EM) neurons had 2 separate bursts of activity, one in response to the peripheral stimulus and a later one, starting after the first one had subsided and peaking at the time of saccade onset. To verify the temporal independence of the 2 bursts, the intervals between stimulus and saccade were varied on-line by changing the duration of the fixation cue in the delayed-saccade task. Presaccadic movement-related neurons displayed a characteristic increase in firing frequency before the movement onset. Postsaccadic neurons displayed no change in activity before saccades but their firing rate increased after the onset of the movement (not illustrated). In this report, only presaccadic
neurons are referred to as Movement-related neurons because only these neurons discharge early enough to contribute to saccade initiation. Some of these Movement-related neurons had a separate visual activity. When they had one, the centers of the visual and motor fields were at the same location, as previously found by Russo and Bruce (2000). The characteristics of Reinforcement neurons, which either predict or detect the occurrence of the reward, were described previously (Amador et al. 2000).

Here we focus on 92 SEF neurons (22 Fixation neurons, 21 Visual-only neurons, 14 Visual-and-eye-movement neurons, and 35 Movement-only neurons), affording quantitative comparisons of their firing rates during prosaccade and antisaccade trials.

**Movement-related activity**

SEF Movement-related neurons were more active before correct antisaccades than before correct prosaccades. Two examples are illustrated in Fig. 4, with correct trials only: a Visual-and-eye-movement neuron in A studied in the delayed-saccade task to separate in time the movement from the visual activity, and a Movement-only neuron in B studied in the immediate-saccade task. On prosaccade trials (YYy), the neuron in A first gave a transient response to the visual stimulus (not seen because it occurred before the epoch shown) and then it progressively started to increase its presaccadic activity. On antisaccade trials (NYy), it did not fire in response to the appearance of the peripheral stimulus (because the latter was not in the receptive field) but it started to increase its firing rate about 200 ms before saccade onset. Its peak firing rate was significantly higher for NYy trials than for YYy trials ($t$-test, $P < 0.02$). The neuron in B demonstrated an even larger difference in activation before antisaccades (NYy) compared with prosaccades (YYy) ($t$-test, $P < 0.01$). Yet, as shown at the right, the saccade trajectories corresponding to the raster in B had a typically larger dispersion of endpoints and a lower
velocity for antisaccades compared with prosaccades (as reported by Amador et al. 1998).

We start with the description of movement-related activity (35 + 14 neurons) because it was immediately relevant to observed saccades. Then, we describe the responses to the antecedent events of the trial.

The following questions were addressed by comparing different types of trials.

1) Were the Movement neurons more active before correct antisaccades than before correct prosaccades having the same amplitude and direction? The trials to compare are NYy and YYy.
Were the Movement neurons more active before correct antisaccades than before forbidden prosaccades having the same amplitude but opposite directions? When an antisaccade instruction is given, 2 outcomes are possible: a correct antisaccade or an erroneous prosaccade. The same type of SEF movement-related neurons, located in opposite hemispheres, contributes to these opposite movements. If the activity of such neurons depends only on saccade metrics, the firing level should be the same before either movement. If it is not the same, the difference may help predict whether a correct antisaccade or an erroneous prosaccade will be made. We can ask whether such a difference appears in the population sampled, and if so, whether it is consistently shown by most SEF Movement neurons; we can even ask if the activity of individual neurons, on single antisaccade trials, predicts whether the monkey will make the correct eye movement.

Comparison of movement-related activities at the population level

Figure 5A shows compound spike density profiles based on 49 neurons: 35 Movement-only +14 Visual-and-movement. All 3 profiles, aligned on saccade onset, include only saccades made to the movement field (as indicated by the last letter “y” in the 3-letter label). These profiles correspond to subsets of trials consisting, respectively, of correct prosaccades (YYy), correct antisaccades (NYy), and erroneous prosaccades made on mandated antisaccade trials (YNy). (Let us recall that mandated antisaccades are indicated by a mismatch of the 1st 2 letters, and incorrect saccades, by a mismatch of the last 2 letters; see Fig. 1.)

For the population of neurons represented in Fig. 5A, the buildup of activity before correct antisaccades (NYy) was unquestionably larger than that observed before correct prosaccades having the same vector (YYy). The difference between the 2 means, just before saccade onset (-40 to 0 ms), was highly significant (paired t-test, P < 0.0001). The mean firing rate associated with erroneous prosaccades (YNy)—that is, made instead of the mandated antisaccade—was lower than the mean of correct antisaccades (NYy), although the same instruction was given (paired t-test, P < 0.0001). However, the mean firing rate for erroneous prosaccades (YNy) was higher than the mean of correct prosaccades, although the saccade vectors were the same (paired t-test, P < 0.0001). This suggests that, when the movement was directed to their response field, SEF Movement neurons were always selectively more activated in any antisaccade condition (YN or NY) than in the most optimal prosaccade condition (YY).

Based on the 49 neurons included in Fig. 5A, Fig. 5B shows the percentage of neurons exhibiting a significantly higher activity for correct antisaccades versus prosaccades in successive 40-ms bins (backward from 0 to 280 ms before saccade onset). This percentage increased moderately until about 40 ms before saccade onset, at which time it climbed from <40% to...
more than 70% (black dots). As shown by the individual neuron results, displayed in gray, the decision to make a correct antisaccade could be reached and sustained by some neurons much earlier than 40 ms from saccade onset.

**Comparison of movement-related activities at the single-neuron level**

Figure 6A plots the mean firing rate of each neuron before correct antisaccades (NYy) against the mean firing rate before correct prosaccades (YYy), both in the preferred direction. Remarkably, all neurons fired more before antisaccades. Filled circles identify neurons for which the difference was statistically significant (t-test, P < 0.05); empty circles represent neurons for which this difference was not significant (t-test, P > 0.05). The ratio of firing between pro- and antisaccades was relatively constant for all neurons, as shown by the tight clustering of data points along the best-fit line (r^2 = 0.94).

Figure 6B plots the mean firing rate of each neuron before erroneous prosaccades (YNy) against the mean rate before correct prosaccades (YYy). Inaccurate antisaccades were excluded from this plot. All but one neuron showed a slight tendency to fire more before an erroneous prosaccade than before a correct one, but none of the differences reached statistical significance (t-test, P > 0.05).

**Comparison of movement-related activities at the trial level**

The results described, thus far, strongly suggest that a relationship exists between the intensity of firing of SEF neurons and the probability that a correct antisaccade will be made (Fig. 5A). To specify further this relationship we attempted to determine this probability as a function of the number of spikes discharged by a given neuron, on each trial, just before the onset of the mandated antisaccade or the forbidden prosaccade. A fundamental assumption underlies the analysis presented below. Beyond the early part of antisaccade trials in which express prosaccades are prevented by preset inhibition, 2 sac- cade goals are simultaneously represented in the brain: one is the lingering trace of a peripheral stimulus, the other is the computed antisaccade goal derived from it.

In the example provided in Fig. 7, we assume (in A) that a stimulus is presented on the left side of the fixation point. Therefore a Movement neuron in the left hemisphere becomes active if a rightward antisaccade in its field is imminent (NYy), whereas a Movement neuron in the right hemisphere (B) becomes active if a leftward prosaccade is about to occur (YNy). The 2 types of trials depicted in A and B are identical in terms of instruction and stimulus location. They differ only by the actual saccade direction. Note that C represents the same neuron as pictured in A (in the left hemisphere) when it finds...
itself in the condition YNy illustrated in B. Therefore, in the absence of data collected in the right hemisphere, it is reasonable to substitute C for B to compare with A. For our purpose, there is an advantage in taking the same (e.g., left) neuron as the image of its own (e.g., right) counterpart because this avoids the risk of unbalanced sampling of neurons from the 2 hemispheres.

We analyzed 17 Movement neurons satisfying a double-criteria selection: a raw minimum of 5 erroneous prosaccades and a minimum percentage of 25% of erroneous prosaccades in the data set of YN trials. Under the assumption specified above and illustrated in Fig. 7, the 17 Movement neurons can be taken as representatives of 17 contralateral Movement neurons, even though the different roles of the observed neurons were actually played on different trials (NYy vs. YNy). Using these data, we determined how the probability of performing a correct antisaccade increases as a function of the number of spikes in the 40-ms bin before saccade onset. For such an analysis to be meaningful, we had first to establish for each neuron that the 2 subsets of trials, correct (NYy) and incorrect (YNy), were not samples from the same population. This null hypothesis was rejected for 12 of the 17 neurons (Mann–Whitney rank-order test, \( P < 0.05 \)). Then, the 12 probability curves shown in Fig. 8 were obtained by plotting the proportion of correct antisaccades (NYy) to erroneous prosaccades (YNy) associated with each level of firing rate (0, 1, 2, \( n \)). Thus \( P = 1.0 \) means that a correct antisaccade always occurred when the neuron fired at least \( n \) spikes in the 40 ms preceding saccade onset. As the 12 neurons shown in Fig. 8, the 5 excluded neurons also had a smoothly increasing slope and a threshold level of firing at

![FIG. 7. Schematic representation of the roles played by supplementary eye field (SEF) Movement neurons in the correct and incorrect performance of antisaccades. A: trial in which a left SEF neuron is activated before a correct antisaccade to the right (red arrow) in the neuron’s movement field (colored area), after the appearance of an antisaccade instruction (white square) at the center of the screen and a visual stimulus at left (yellow circle). B: trial in which a right SEF neuron is activated before a wrong prosaccade to the left (black arrow) in the neuron’s movement field (colored area). Note that, in B, the instruction and the stimulus location are the same as in A. C: trial in which the same left SEF neuron is activated before a wrong prosaccade in the neuron’s movement field. Note that in C, the left SEF neuron finds itself in the same YNy condition as the neuron in B.

![FIG. 8. Trial-by-trial analysis of the firing rate of 12 Movement-related neurons. Each colored line shows, for a particular neuron, the relation between the probability that an antisaccade in the response field (NYy) will be made and the number of spikes fired by the neuron in individual trials (40 ms preceding saccade onset). Probability value corresponding to each number of spikes was calculated as the proportion of correct antisaccades NYy to erroneous prosaccades YNy associated with each level of firing rate (0, 1, 2, \( n \)). Thus \( P = 1.0 \) means that a correct antisaccade always occurred when the neuron fired at least \( n \) spikes in the 40 ms preceding saccade onset. As the 12 neurons shown in Fig. 8, the 5 excluded neurons also had a smoothly increasing slope and a threshold level of firing at...
which the occurrence of correct antisaccades had a probability \( P = 1.0 \).

Errors on antisaccade trials were not the only types of errors observed during performance of the task. Errors on prosaccade trials (i.e., antisaccades made instead of mandated prosaccades) also occurred, but so rarely that a trial-by-trial analysis of their associated firing rates could not be performed.

**Visual activity: responses to the peripheral stimulus**

Figure 9 illustrates the broad tuning of a visually responsive neuron representative of our sample. For this neuron, a stimulus elicited the highest frequency burst when it appeared at 135° (with an eccentricity of 15°). The responses decreased as the stimulus position deviated from this angle and vanished when the stimulus appeared at 315°.

To find whether visually responsive neurons responded differentially to a same stimulus, depending on whether it was used to make a prosaccade (YY trials) or an antisaccade (YN trials), we compared firing rates obtained during peak visual responses, in a 40-ms bin astride the peak. Figure 10A illustrates the responses of a phasic Visual neuron that gave a larger burst of spikes when the visual stimulus appearing in the receptive field was used to make an antisaccade (YNn) compared with a prosaccade (YYy) (t-test, \( P < 0.05 \)). Another neuron in Fig. 10B exhibited the opposite pattern of responses: that is, its response was stronger on prosaccade trials (YYy) than on antisaccade trials (YNn) (t-test, \( P < 0.05 \)). Both neurons remained silent when the stimulus was placed outside their receptive fields (NYy and NNn trials).

Like Movement-related neurons previously described, the Visual neurons were analyzed at 3 levels: population, single-neuron, and trial-by-trial. Based on 35 visually responsive neurons, Fig. 11A shows 3 compound spike density profiles, corresponding respectively to trials in which the monkeys made correct antisaccades (YNn), erroneous prosaccades (YNy), and correct prosaccades (YYy). In all cases, the visual stimulus appeared at the center of the receptive field. Despite the heterogeneity of the responses of individual neurons, the same hierarchy in the intensities of visual responses was found as in the case of movement-related activity (see Fig. 5A); that is, the firing rate on correct antisaccade trials (YNn) was higher than the firing rate on erroneous prosaccade trials (YNy), which was itself higher than that on correct prosaccade trials (YYy). In all cases, the differences were statistically significant (paired t-test): \( P < 0.01 \) for YNn versus YNy, \( P < 0.001 \) for YNy versus YYy, and \( P < 0.0001 \) for YNn versus YYy.

Figure 11B plots mean firing rates during the peak visual response on correct antisaccade trials (YNn) against the comparable means on correct prosaccade trials (YYy). Comparing these mean firing rates during the visual response epoch (40 ms astride the peak) reveals that 17 out of 35 neurons (49%) had a significantly higher firing rate on antisaccade trials (YNn) (t-test, \( P < 0.05 \)), whereas 2 had a significantly higher firing rate on prosaccade trials. As in Fig. 6A—which compares

![Directional tuning of a typical Visual-only neuron.](https://www.jn.org)

**Fig. 9.** Directional tuning of a typical Visual-only neuron. Spike density profiles (\( s = 20 \) ms) of visual responses obtained during the preliminary receptive field mapping. Stimulus eccentricity: 15°. Maximum response was elicited by stimuli at 135° and the smallest one, at 315°. Abscissa: time in ms from the stimulus. Ordinate: firing frequency (spikes/s).
movement-related activities of single neurons—in Fig. 11B, filled circles represent neurons showing a significantly different response on the 2 types of trial (t-test, \( P < 0.05 \)). Note that the data points are much more scattered in Fig. 11B than in Fig. 6A.

**Comparison of visual responses at the trial level**

A trial-by-trial analysis was performed for 18 visual neurons to determine whether the prediction of correct performance that we observed in the activity of Movement-related neurons (Fig. 8) could already be made at the time of the visual response. The relevant comparison, now, is between the YNn and YNy trials (see Fig. 12). For each individual neuron, the mean rate in the peak visual response when the stimulus was presented in the receptive field was used for this analysis.

\[ P = 1.0 \]

corresponds to the condition in which the monkey always made the instructed antisaccade (YNn) and \( P = 0.0 \) corresponds to the condition in which the monkey always made an erroneous prosaccade (YNy). Five neurons showed that the probability of performing a correct antisaccade increased with the intensity of the visual responses (Fig. 12A). The difference between the 2 subsets of trials (i.e., correct and incorrect) was significant (Mann-Whitney test, \( P < 0.05 \)). Four neurons (not illustrated) did not show a significant difference but, nevertheless, showed the trend seen in Fig. 12A. Nine neurons showed no consistent relation at all (Fig. 12B).
Instruction-related activity

A subset of neurons in the SEF responded tonically from the presentation of the instruction cue to the end of the fixation period. These cells were clearly different from purely visual cells because their activity was sustained even when the fixated visual stimulus had disappeared but gaze remained fixated. Figure 13 illustrates the activity of a Fixation neuron that discriminated between a prosaccade and antisaccade instruction given at the beginning of the trial (t-test, \( P < 0.05 \)). This neuron displayed a higher firing rate during fixation of the antisaccade cue (NY and YN trials) than during fixation of the prosaccade cue (YY and NN trials). The 2 types of antisaccade trials (NY and YN) and the 2 types of prosaccade trials (YY and NN) were pooled in the 2 average spike density profiles shown at the bottom of Fig. 13 because the monkey did not know yet in which direction the saccade would have to be made. Differences in firing rate were assessed in 40-ms bins, running backward from the subsequent visual stimulus onset to the start of fixation (not the appearance of the instruction cue). This analysis—performed on 22 Fixation neurons—revealed that all of the neurons fired more when the monkeys fixated the antisaccade cue compared with the prosaccade cue, but the difference reached statistical significance for only half of the neurons (11/22). Nevertheless, it is remarkable that not a single neuron discharged more while fixating the prosaccade cue. The sign of the differential rate was the same, although the symbols encoding the instruction differed among monkeys. This suggests that the physical characteristics of the instruction cue were irrelevant. More analysis of SEF instruction-related activity in antisaccade tasks is in progress, with a paradigm that dissociates activity related to the information conveyed by the cue from fixation activity per se (Amador et al. 2002).

Figure 14 illustrates 2 other neurons showing a typical instruction-related firing pattern. Both appeared to discriminate the antisaccade from the prosaccade instruction, long before stimulus onset (300 ms in Fig. 14A and 200 ms in Fig. 14B). One of them (A) had strong visual responses, the other (B) only weak ones. Thus the increased fixation activity observed in response to the antisaccade instruction did not necessarily translate into an increased visual response. For the 22 Fixation neurons reported here, there was no significant relation between displaying (or not) a significant differential activity during the instruction period and giving (or not) significantly different responses to the subsequent visual stimulus (\( \chi^2 = 3.62, \text{df} = 1, P > 0.05 \)). There was, however, a significant relation between showing a significant differential activity during the fixation period and showing a significant difference between presaccadic activation (\( \chi^2 = 5.37, \text{df} = 1, P < 0.05 \)). In other words, the activation elicited by an antisaccade instruction did not affect the next neuronal event (visual response) but it apparently affected the subsequent one (presaccadic activation, in turn, predictive of performance). An example of this pattern of activity appears in Fig. 15. Finally, the fact that, on antisaccade trials, there was no significantly stronger visual response (\( \chi^2 = 2.89, \text{df} = 1, P > 0.05 \)), intercalated between significantly increased instruction-related and increased movement-related activations, argues against the possibility that a nonspecific arousal enhanced all neuronal activities throughout the trial.

Comparison of movement, visual, and fixation-related responses

The movement-related, visual, and fixation-related activities of 92 neurons are compared in Fig. 16 with respect to the \( P \) value of differential rates of firing observed on antisaccade and prosaccade trials. From this viewpoint, the movement-related

**FIG. 12.** Trial-by-trial analysis of 14 Visual neurons. Each colored line shows, for a single neuron, the function relating the probability that a mandated antisaccade will be made (YNn) instead of an erroneous prosaccade (YNy), as a function of the number of spikes emitted by the neuron, during the peak visual response to a stimulus appearing at the center of the receptive field. For neurons in A (\( n = 5 \)), the function described above grew progressively from 0.0 to 1.0; for neurons in B (\( n = 9 \)), it did not.
and the visual responses appeared to be respectively the least and the most variable.

DISCUSSION

Contribution of SEF Movement-related neurons to the initiation of antisaccades

In this study the vast majority of SEF Movement-related neurons fired significantly more before antisaccades than before prosaccades. For most neurons, this difference became statistically significant during the last 40 ms preceding saccade onset, i.e., at a time compatible with the putative transfer of a saccadic command to the brain stem saccade generator (Scudder et al. 2002). The differential activity for pro- and antisaccades was demonstrated for the population studied as well as for individual neurons (Fig. 6A). Importantly, the level of firing of single SEF Movement neurons was found to predict the probability of correct performance of antisaccades on individual trials. The firing rate just before saccade onset reflected the outcome of a decision process between making a saccade to a sensory target or to an internally generated goal, both being concurrently programmed. Remarkably, within a range of 0 to 12 spikes, each additional spike produced by a given neuron appeared to contribute to tip the balance. This attests to the reliability and relevance of the signals conveyed by the SEF Movement-related neurons.

In contrast to the present results, a lower firing rate before antisaccades compared with prosaccades was found characteristic of FEF presaccadic neurons identified by antidromic stimulation as projecting directly to the SC (Everling and Munoz 2000). As proposed by Everling et al. (1999), who found that saccade-related SC neurons have a lower level of presaccadic activity before antisaccades, additional movement signals that bypass the SC are needed for the generation of antisaccades. These signals may be provided by the SEF because it appears to be the only structure, thus far, where Movement-related neurons are found to fire more before antisaccades than before prosaccades. The larger activity of SEF Movement neurons in NYy and YNy trials compared with YYy trials (Fig. 5) suggests that SEF neurons are specifically engaged when the mechanism deciding the direction of a saccade relies on the symbolic meaning of an abstract instruction rather than on the location of a physical target.

Ambiguity of the visual responses

The population response of visually responsive neurons was much larger on correct antisaccade trials than on correct prosaccade trials (Fig. 11A). This finding may seem paradoxical given that this enhanced response occurs precisely when the visual stimulus should not trigger the saccade. We previously pointed out the ambiguous nature of this stimulus, which acts both as a landmark for—and a distractor from—the goal of the required movement (Schlag-Rey et al. 1997). Individual neurons pooled in the population average seem to reflect this ambiguity. Those neurons that responded with a larger burst on antisaccade trials may have summoned more attention to a stimulus whose precise location must be kept in working memory until the antisaccade goal has been computed. This might be the mirror image of the classical enhancement of visual responses observed when saccades are directed to a visual target, for example, in the SC (Wurtz and Goldberg 1972), in the FEF (Bruce et al. 1985; Goldberg and Bushnell 1981), in the LIP (Robinson et al. 1978), and in the central thalamus (Schlag-Rey and Schlag 1989). Slightly more than 50% of the visual neurons, however, did not respond more on antisaccade trials than on prosaccade trials, including 2 neurons that responded significantly less. Whereas some Visual neurons showed a relation between the number of spikes in the burst and the probability of making a correct antisaccade, the majority did not. Why was there such a disparity among Visual neurons on antisaccade trials? Although some neurons may reflect an increased attention, as mentioned above, others might reflect the top-down inhibition necessary to prevent reflexive targeting.

Clearly, the modulations of visual activity in SEF differed from the “paradoxical activity” observed in LIP (Zhang and Barash 2000) because the latter occurred on the side opposite the receptive field. Obviously, more research is needed to...
elucidate the contribution of SEF visual responses to the determination of an antisaccade goal to explain its prevalence on the physical goal provided by the stimulus.

**Differential activity induced by the instruction cue**

The existence of Fixation neurons in the SEF has long been known (Bon and Lucchetti 1990, 1992; Lee and Tehovnik 1995; Schlag et al. 1992), although such neurons were sparsely represented in this study. According to Tehovnik and Lee (1993), SEF fixation neurons tend to be found more caudally than movement-related neurons on which the present study was focused. Nonetheless, the Fixation neurons described in this study appeared to discriminate between the prosaccade and antisaccade instructions: half of them fired signifi cantly more during the fixation of the antisaccade instruction cue and none fired less (Fig. 16). This result cannot be attributed to the visual characteristics of the anti-cue (e.g., square vs. circle) because interchanging the meaning of the cues between monkeys did not affect the results. Nor can it be linked to the preparation or the inhibition of a specific saccade because during the fixation of the instruction cue, the location at which a stimulus will appear was still unknown. Thus the increased activity induced by the fixation of an antisaccade instruction cue may refl ect a general preparatory set to block a refl exive prosaccade that might be triggered by the appearance of a peripheral target.

In contrast to the SEF, the FEF has a higher level of prestimulus activity associated with the generation of erroneous express prosaccades that are promoted by a gap paradigm (Everling and Munoz 2000). However, as in the SEF, increased fixation-related activity on antisaccade trials has been found in

![Figure 14](image1.png)

**FIG. 14.** Two Fixation neurons showing contrasting responses to the visual stimulus after similar instruction-related activities. Neurons in A and B were both more active during fixation of the antisaccade instruction (red trace) compared with the prosaccade instruction (black trace) ($t$-test, $P < 0.05$ for the difference of rate during 400 ms from stimulus onset for A, and during 200 ms for B). Neuron A strongly responded to the subsequent visual stimulus; neuron B did not. Spike density profiles are aligned on the instruction cue in left panels, and on the peripheral stimulus in right panels. Three arrows indicate the approximate time of the other event: peripheral stimulus in left panels and instruction cue in right panels.

![Figure 15](image2.png)

**FIG. 15.** Neuron significantly more active ($t$-test, $P < 0.05$) during the fixation of the antisaccade instruction (red trace, in A) compared with the prosaccade instruction (black trace, in A) as well as during the last 40 ms preceding saccade onset (in B). Difference between visual responses (in A) was not significant ($P > 0.05$).
Possible mechanisms involved in antisaccade generation

Several mechanisms could account for the ability of voluntary antisaccade commands to prevail on the natural tendency to look at the visual stimulus.

1) Receptive field shift. Could a shift in the receptive field of involved neurons suffice to account for a successful performance and is there evidence that the instruction to make an antisaccade causes the receptive fields to shift from one hemisphere to the other (as required for horizontal and most of the oblique saccades)? If this were the case, the Visual neurons— and the appropriate Movement-related neurons that they would activate after the shift—would reside in the same hemisphere. According to Zhang and Barash (2000) one-third of the visual neurons in LIP provide evidence of switching a discharge time-locked to the stimulus from the visual to the motor direction of antisaccade trials. This observation may help understand how the brain determines the goal of an antisaccade, a problem that still eludes us. We looked for a similar shift in the SEF but we never saw any sign of it.

2) Winner-take-all. In the behavior of our monkeys, there was evidence of competition between an unwanted prosaccade (generated in the hemisphere contralateral to the stimulus) and a voluntary antisaccade (generated in the hemisphere ipsilateral to the stimulus). Indeed, the competition gave rise occasionally to “turn-around” or “back-to-back” saccades revealing their concurrent programming (Amador et al. 1998). In our first study (Schlag-Rey et al. 1997), we hypothesized that the onset of the single peripheral stimulus (following an anti-instruction cue) sets in motion 2 streams of signals eventually leading to the initiation of the correct antisaccade with the help of a winner-take-all mechanism (Amari and Arbib 1977; Yuille and Geiger 1995; for a neurophysiological application in a different context, see Britten et al. 1992; Salzman and Newsome 1994).

The winner-take-all principle, applied to the conflict between 2 motor programs (pro- and anti-), simply means that whichever develops the largest signal (i.e., highest firing rate) wins the competition at a downstream junction. Antagonism between Movement neurons in opposite hemispheres, as evidenced by mutual inhibition, has been found, for instance, in the 2 FEFs (Schlag et al. 1998). SEF neurons voting for a correct antisaccade could compensate for their weak numerical importance by firing more intensely than the vast number of movement-related neurons voting elsewhere for a prosaccade.

3) Plasticity of stimulus-response associations. Chen and Wise (1995) demonstrated that SEF neurons can change their firing patterns as the monkey learns arbitrary associations through operant conditioning. This is one possible mechanism through which antisaccades could be generated and it was probably in use at the early stage of training. However, it is unlikely to have been used much longer in our experiments once trials were randomized instead of being run in blocks and once training was extended to saccade vectors in all directions and varying amplitudes.

4) Pre- and poststimulus inhibition. Errors are most often generated when the subject fails to suppress the prepotent tendency to look at the peripheral stimulus. Although inhibiting a wrong saccade does not suffice to produce the correct one, inhibitory mechanisms have undoubtedly a major role to play in preventing a disallowed glance even before it could be triggered by a visual stimulus. In addition to its essential function in working memory (Funahashi et al. 1989,1993; Fuster 1973 1997; Takeda and Funahashi 2001), the prefrontal cortex provides a preparatory set activity that may be instrumental in blocking an unwanted visual reflex. The inhibitory function of the prefrontal cortex has also been documented by the effect of cortical lesions in humans (Pierrot-Deseilligny et al. 2002). In the SEF, the increased activity of Fixation neurons during the antisaccade instruction period could also contribute to inhibit the visual orientation reflex before it is set in motion. Once the visual stimulus has appeared, other mechanisms may come into play. In humans, a deficit in working memory capacity (Engle 2002) or an increase in working memory load (Roberts et al. 1994; but see Kristiansson et al. 2001) has been suggested as a source of antisaccade errors. In monkey, prevention of errors may also depend on inhibitory interactions between certain types of neurons located in different oculomotor centers, such as the SEF and FEF (Sadeghpour et al. 1998). One could even suspect that there are inhibitory interactions between the SEFs similar to those existing between the FEFs (Schlag et al. 1998).

Comparison between the SEF and the FEF

The difference between FEF and SEF revealed by current antisaccade studies should not be surprising. It seems to be linked to their respective involvement in visually guided (FEF) and internally guided (SEF) eye movements. When the SEF was identified as a second eye field in the frontal cortex, the initial unit recording studies demonstrated that a large number of SEF neurons are active before spontaneous exploratory saccades, in the absence of a visual target (Schlag and Schlag-Rey 1985, 1987). In this case, the progressive increase in
presaccadic activity may occur as early as 500 ms before the movement (Schlag and Schlag-Rey 1985, 1987). These observations stand in contrast with the little (if any) FEF activity displayed before spontaneous saccades (Bruce and Goldberg 1985). The pattern of anatomical connections of the SEF suggests that it may not necessarily depend on its projections to the FEF to send commands downstream. The SEF has direct anatomical connections to the brain stem oculomotor structures (Huerta and Kaas 1990; Shook et al. 1998, 1990). Support for the relative independence of these pathways comes from the fact that saccades can still be elicited by electrical stimulation of the SEF after lesions of the SC or FEF (Tehovnik et al. 1990). On the other hand, the dominant role of the FEF in the production of visually guided saccades (Bruce and Goldberg 1985; Goldberg and Segraves 1989; Hanes and Schall 1998; Thompson et al. 1996) has been reemphasized by the contrast displayed before spontaneous saccades (Bruce and Goldberg 1985; Goldberg and Segraves 1989; Hanes and Schall 1998; Thompson et al. 1996) has been reemphasized by the contrast between the effects produced by lesions respectively in the FEF and SEF of monkeys (Schiller and Chou 1998).

**Role of the SEF in human and subhuman saccade generation**

A larger presaccadic firing rate on antisaccade compared with prosaccade trials is consistent with cortical potential recordings, positron emission tomography (PET) studies, and magnetic resonance imaging studies performed on humans. First, cortical potential studies conducted by Everling et al. (1997) demonstrated a larger negativity before antisaccades than before prosaccades in the SEF. Everling et al. (1998) later demonstrated a shift in negativity from contralateral to the ipsilateral hemisphere during the performance of antisaccades. This may reflect a change of plan: from a saccade to the stimulus to a saccade to the opposite side. Second, PET studies by O’Driscoll et al. (1995) and Sweeney et al. (1996) reported a larger amount of cortical activation before antisaccades than prosaccades in the region of the SEF. Deiber et al. (1991) found a larger activation in tasks with internal cues when the subjects could prepare their movements before the trigger stimulus. Finally, using magnetic resonance imaging, Müri et al. (1998) found a significant increase in activity in the region of the SEF during the performance of antisaccades. According to Müri et al. (1998), this increased activity probably reflects the role of the SEF in planning and initiating internally guided behavior. More recently, Curtis and D’Esposito (2003) used fMRI during the performance of an antisaccade task that provided a substantial preparatory delay (6,000 ms) between the appearance of the antisaccade (vs. prosaccade) instruction cue and the saccade stimulus onset. In this condition, the pre-SMA and SEF—compared with the FEF and intraparietal sulcus (IPS)—showed the largest activation during the preparatory period, whereas the FEF and IPS were most activated after the stimulus appeared. Thus human studies suggest that the SEF is directly involved in generating the motor signals necessary for antisaccades.

In nonhuman primates, a number of physiological studies, using tasks involving visual target acquisition, have confirmed the basic oculomotor properties of the SEF (Mann et al. 1988; Olson et al. 1995; Russo and Bruce 1993, 1996, 2000; Schall 1991a; Schiller and Chou 1998; Tehovnik and Lee 1993; Tehovnik et al. 1994), fixation (Bon and Lucchetti 1990, 1992; Lee and Tehovnik 1995) and pursuit (Heinen 1995; Heinen and Liu 1997; Missal and Heinen 2001). New hypotheses on the role of the SEF have emerged from recent works purporting to detect differences between the SEF and FEF, or simply to examine the role of the SEF in the context of different tasks. These hypotheses include a role for SEF neurons in the acquisition of conditional oculomotor associations (Chen and Wise 1995), in the object-centered localization (Olson and Gettner 1995, 1999), in the prediction and detection of reward (Amador et al. 2000), in the monitoring of performance (Stuphorn et al. 2000), in the control of the initial gain of smooth pursuit (Missal and Heinen 2001), in the coding of a decision to catch or not to catch a moving target (Kim and Heinen 2001), and in the production of sequences of eye movements (Isoda and Tanji 2002; Lu et al. 2002). Likewise, in humans, a role for the SEF in the programming of sequences of saccades is suggested by the interference of transcranial magnetic stimulation with the order of saccades (Heide et al. 2001; Tobler and Müri 2002). The location of the human SEF has been revealed by several fMRI studies using prosaccade and antisaccade tasks (O’Driscoll et al. 1995; Sweeney et al. 1996) and, interestingly, self-paced eye movements (Grobras et al. 1999). The common link between the various hypotheses proposed about the SEF function in human and monkey may be the production of eye movements in tasks requiring a high degree of endogenous control such as the antisaccade task, or else, involving a conflict of cues (Olson and Gettner 2002). Such tasks preclude reliance on a simple visual reflex. Thus on a general level, the present study reinforces the hypothesis of a role, for the SEF, in the initiation, planning, and execution of voluntary saccades to internally defined goals.

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**References**


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