Dissociation of spatial attention and saccade preparation

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The goal of this experiment was to determine whether the allocation of attention necessarily requires saccade preparation. To dissociate the focus of attention from the endpoint of a saccade, macaque monkeys were trained to perform visual search for a uniquely colored rectangle and shift gaze either toward or opposite this color singleton according to its orientation. A vertical singleton cued a prosaccade, a horizontal singleton, an antisaccade. Saccade preparation was probed by measuring the direction of saccades evoked by intracortical microstimulation of the frontal eye fields at variable times after presentation of the search array. Eye movements evoked on prosaccade trials deviated progressively toward the singleton that was also the endpoint of the correct eye movement. However, eye movements evoked on antisaccade trials never deviated toward the singleton but only progressively toward the location opposite the singleton. This occurred even though previous work showed that on antisaccade trials most neurons in frontal eye fields initially select the singleton while attention is allocated to distinguish its shape. Thus, sensorimotor structures can covertly orient attention without preparing a saccade.

frontal eye fields | microstimulation | target selection

Humans can orient to an interesting object or region of the visual scene covertly by allocating attention and overtly by executing an eye movement. A longstanding issue has been whether the shift of attention and the shift of gaze are independent (1). The premotor theory of attention (2, 3) posits that the allocation of spatial attention is equivalent to planning but not executing a saccade. Evidence for this theory includes the coupling of spatial attention and saccade preparation (4–6), observations that neurons in sensorimotor structures such as frontal eye fields (FEF) are modulated when attention is allocated (7–11), that the trajectories of saccades can be influenced by the allocation of attention (12), and that electrical stimulation of FEF and superior colliculus can influence the allocation of attention (13, 14).

However, other evidence suggests a functional distinction between covert and overt orienting (15). It is possible to shift attention without shifting gaze (5, 6). Also, the selective activity of visually responsive neurons in sensorimotor structures corresponds to the allocation of attention distinct from saccade preparation (16–19). In particular, neurons in FEF select the location of a salient object in an array when monkeys maintain fixation or shift gaze away from that object (7, 20–23). Furthermore, in a stop signal task, visual neurons in FEF and superior colliculus do not produce signals sufficient to contribute to the control of saccade generation (24, 25).

The properties of neurons in the FEF of monkeys performing visual search requiring explicit stimulus–response mapping based on the shape of a color singleton provide an opportunity to investigate whether orienting to a visual stimulus necessarily requires preparing a saccade to that stimulus (20). Monkeys were trained to perform a color singleton visual search task with a prosaccade or antisaccade response cued by the orientation of the singleton (Fig. 1*A*). Single-unit recordings from FEF during this task showed that in prosaccade search trials, most neurons select the location of the singleton that was also the endpoint of the saccade (Fig. 1*B Left*), typically ≈100 ms after the presentation of the array (20). In antisaccade trials, most neurons initially select the singleton (also ≈100 ms) then undergo a dramatic modulation to select the endpoint of the saccade (≈200 ms; Fig. 1*B Right*). The period of selection of the singleton almost certainly corresponds to the allocation of attention (7).

Converging lines of evidence link visual attention with activity in the FEF. First, visual neurons in FEF signal the location of a singleton under conditions that have been shown to automatically attract attention (26, 27). This selection emerges even when gaze remains fixed or shifts to a location out of the response field (20–23). Second, weak electrical stimulation of macaque FEF has been shown to influence the allocation of attention and bias visual processing in extrastriate cortex in retinotopically matched sites (13). Third, functional imaging studies have shown that human FEF is active as attention is shifted, even when no eye movements are made (10, 28–30). Finally, transcranial magnetic stimulation delivered to the human FEF influences performance of visual search and visual attention tasks (31, 32).

Saccade preparation was probed in this experiment by using intracortical microstimulation. FEF stimulation evokes fixed-vector saccades in the absence of visual stimulation (33), but more recent studies have demonstrated that evoked saccades can be influenced by the preparation of a saccade to perform a task (14, 34, 35). The search array was arranged such that the saccades evoked by microstimulation of FEF in each experimental session were orthogonal to the axis of the stimuli guiding prosaccades or antisaccades. The evolution of saccade preparation was assessed by measuring the deviation of the saccades evoked by microstimulation at different times after search array presentation. In prosaccade trials, the deviations should increase progressively toward the singleton that is also the endpoint of the correct saccade (Fig. 1*C Left*). In antisaccade trials, the evoked saccades should deviate ultimately toward the endpoint of the saccade opposite the singleton. The key hypothesis of this experiment was evaluated by determining whether saccades evoked at intermediate times (when the singleton, but not yet the endpoint, was selected) deviated toward the singleton or the endpoint (Fig. 1*C Right*).

Eye movements evoked by stimulation during the task were quantified by the angular difference from the vector of the saccade evoked at the earliest stimulation time (0–60 ms) used during each session before any neural selection had occurred. Angular deviations toward the singleton were assigned positive values; deviations away from the singleton were assigned negative values (Fig. 1*D*). Accordingly, on prosaccade trials, the

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Abbreviation: FEF, frontal eye fields.

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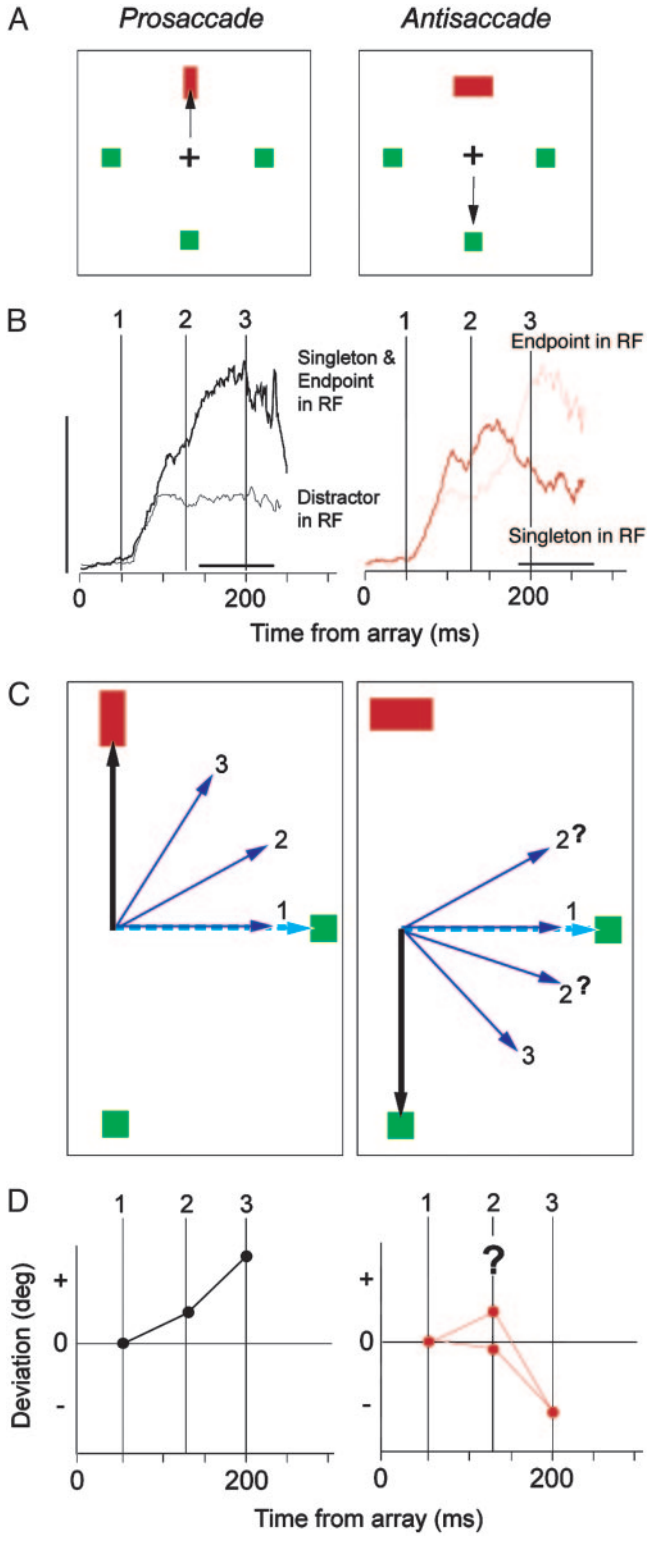

Fig. 1. Use of FEF microstimulation during visual search with prosaccade and antisaccade responses. (*A*) Prosaccade (*Left*) and antisaccade (*Right*) trials were cued by the orientation of the color singleton. (*B*) In prosaccade trials, most neurons in FEF selected the location of the singleton that was also the endpoint of the saccade (*Left*). In antisaccade trials, most neurons selected the singleton then selected the endpoint of the saccade (*Right*). Scale bar indicates 100 spikes per s. The black bar above the abscissa indicates the range of saccade latencies (adapted from ref. 20). (*C*) Expected results in prosaccade (*Left*) and antisaccade (*Right*) trials. The correct saccade in the illustrated prosaccade trial was toward the singleton (black arrow). The array was arranged so that the axis of the prosaccade (*Left*) or antisaccade (*Right*) guided by the singleton was orthogonal to the saccade evoked by microstimulation of a site in FEF (dashed blue arrow). Early microstimulation (time 1) should evoke a saccade with no deviation from the original vector because the brain has not yet encoded the search array. Later stimulation (times 2 and 3) should evoke saccades with directions that deviate progressively toward the singleton due to the preparation of the prosaccade to the singleton. During antisaccade trials (*Right*), early electrical stimulation should evoke a saccade with no deviation, and the latest stimulation when the endpoint of the antisaccade was selected (time 3) should evoke a saccade that deviates opposite the singleton, toward the endpoint of the antisaccade. The goal of this experiment was to determine whether saccades evoked by electrical stimulation at intermediate times (time 2), when the singleton of the search array had been selected but the endpoint of the antisaccade was not yet selected, deviated toward the singleton, toward the endpoint of the antisaccade, or not at all. (*D*) Plots of hypothesized deviations of evoked saccades as a function of time. Positive angles denote deviations toward the singleton, and negative angles denote deviations opposite the singleton.

deviation should always be positive. In antisaccade trials, if the neural selection of the singleton corresponds to preparation of a saccade, then at intermediate stimulation times evoked saccades should deviate toward the singleton (positive value) before reversing to deviate progressively toward the antisaccade endpoint (negative value). Alternatively, if selection of the singleton is distinct from preparation of a saccade, then the saccades evoked in antisaccade trials should only deviate toward the antisaccade endpoint opposite the singleton.

Methods

Two macaque monkeys (*Macaca radiata* and *Macaca mulatta*) were prepared for cortical microstimulation by using aseptic procedures under isofluorane anesthesia as described previously (36) according to guidelines established by the *Guide for the Care and Use of Laboratory Animals* and approved by the Vanderbilt Animal Care and Use Committee. Monkeys were seated within a magnetic field to monitor eye movements by using the scleral search coil technique. Data collection was under the control of a computer running TEMPO software (Reflective Computing, St. Louis) that controlled stimulus presentation (vertical refresh 90 Hz), recorded eye movements (250 Hz), controlled electrical microstimulation, and delivered fruit juice reward. Saccades were defined by an algorithm that first detected a significant elevation in eye velocity (>30°/s) then located the beginning and end of the monotonic change in eye position lasting at least 12 ms before and after the high velocity gaze shift.

Monkeys were trained to perform a color singleton visual search task with reward contingent on producing a prosaccade or an antisaccade cued by the orientation of the singleton. After fixation of a central spot for 400–700 ms, a circular search array of four isoeccentric stimuli was presented. One of the four stimuli was a color singleton target that was discriminated among isoluminant distractors [14.2 cd/m^2 on a black background; i.e., red [Commission Internationale de l'Eclairage (CIE) $x = 638$, $y = 335$] target among green (CIE $x = 272$, $y = 617$) distractors or green target among red distractors, which alternated randomly across trials]. The singleton was a vertical or horizontal rectangle (1.3 aspect ratio) and the distractors were squares of equal area (1°). The vertical singleton required a prosaccade to its location, whereas the horizontal singleton required an antisaccade to the distractor opposite the singleton. Monkeys were required to shift gaze to the correct location within 1,000 ms of array presentation and maintain fixation of that saccade target for at least 500 ms to obtain juice reward.

FEF microstimulation with tungsten microelectrodes (FHC, 2–4 MΩ; 60-ms trains of 0.2-ms biphasic pulses at 500 Hz) was delivered on 50% of randomly interleaved prosaccade and antisaccade trials. Results were the same with lower fractions of

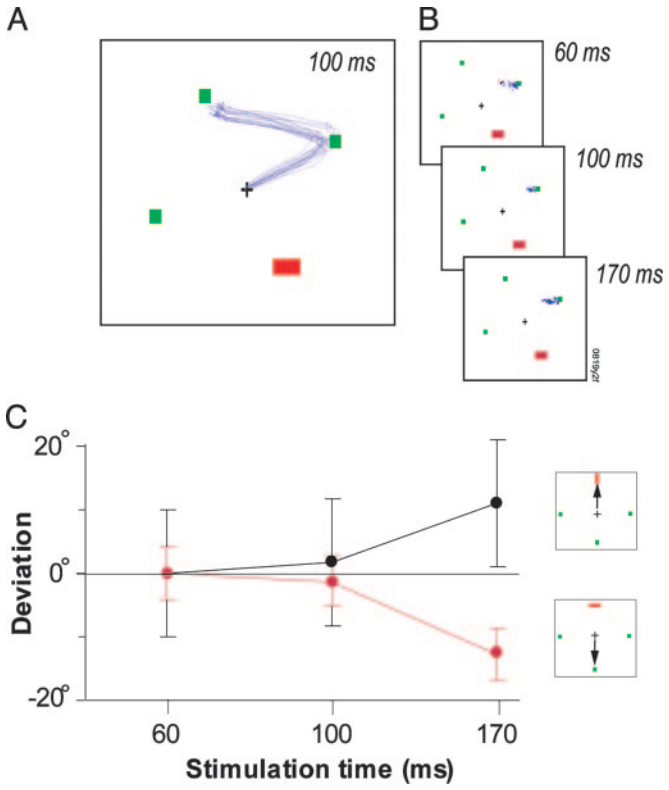

Fig. 2. Saccades evoked by FEF microstimulation during one session (monkey L). (*A*) Plot of saccade trajectories in 20 trials requiring an upward antisaccade in which electrical stimulation occurred 100 ms after array presentation. The search array was adjusted so that the endpoint of the evoked saccade was orthogonal to the axis of the singleton and task saccades. Monkeys made corrective saccades to fixate the correct location on most stimulated trials. (*B*) Endpoints of saccades evoked in antisaccade trials with stimulation delivered 60 ms ($n = 24$), 100 ms ($n = 21$), and 170 ms ($n = 28$) after appearance of the search array. Evoked saccade endpoints deviated progressively closer to the antisaccade endpoint at later stimulation times. (*C*) Angular deviation of evoked saccades plotted as a function of microstimulation time for prosaccade (black) and antisaccade (red) responses. Error bars represent ±1 SEM.

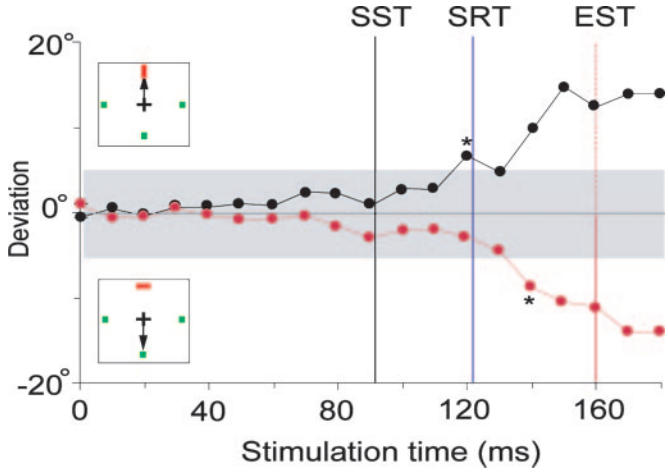

Fig. 3. Saccade deviation as a function of microstimulation time. Data from two monkeys across all sessions (monkey L, 16,507 trials; monkey P, 6,613 trials). Error bars are smaller than the symbols; SEMs ranged from 0.01° to 0.06°. The time at which neural activity in FEF first selected the singleton (SST), encoded the stimulus–response mapping rule based on the shape of the singleton (SRT), and selected the endpoint of the antisaccade (EST) are indicated (20). The 95% confidence interval (±5°) around deviations of 0° is indicated in gray. Asterisks indicate the first stimulation time at which the deviation was significantly different from 0°. The deviations became significant when the shape of the singleton was encoded but before the endpoint of the antisaccade was selected.

stimulation trials. Onset of stimulation was controlled in 10-ms increments from 0 to 180 ms after the appearance of the search array. Monkeys were given an additional 500 ms to view the array after stimulation to fixate the appropriate target; reward was contingent on the corrective saccades on these trials.

After a cortical site was located where fixed-vector saccades were elicited reliably with <50 μA (37), ≈30 saccades were evoked in darkness to map the movement field. The visual search array was then adjusted so that one distractor was located at the endpoint of the saccade evoked in the dark with the singleton located 90° away. This orthogonal arrangement permitted optimal measurement of the influence of processing of the singleton on the direction of the saccade evoked by microstimulation. Saccade vectors evoked in darkness ranged in eccentricity from 6° to 13°.

Results

Results are based on stimulation at 65 sites in two monkeys. In trials with no electrical stimulation, antisaccade latencies were equal to or longer than prosaccade latencies [monkey L prosaccade 231 ± 44 ms; antisaccade 231 ± 41 ms ($t_{6249} = -1.28$); monkey P prosaccade 206 ± 41 ms; antisaccade 215 ± 40 ms ($t_{4261} = 12.37, P < 0.001$)]. The absent or weaker antisaccade cost occurred because the singleton appeared only at the two locations orthogonal to the evoked saccade to optimize data collection for this study. When tested with the singleton appearing at each of the four locations with interleaved microstimulation trials, antisaccade latencies were significantly longer than prosaccade latencies [monkey L prosaccade 198 ± 40 ms; antisaccade 215 ± 38 ms ($t_{6170} = 26.33, P < 0.001$)].

By design, FEF microstimulation evoked a saccade that was an error in the context of the task, but monkeys produced a corrective saccade to fixate the correct target (Fig. 2). Microstimulation at progressively later times in prosaccade and antisaccade trials evoked saccades with endpoints that deviated progressively away from the 0° baseline. For the data shown in Fig. 2, the distribution of the angles of the saccades evoked in prosaccade and antisaccade trials deviated significantly from 0° when stimulation was delivered at 100 and 170 ms (one-sample t tests, both $P < 0.05$) but not at 60 ms. In prosaccade trials, the endpoints always deviated toward the singleton. In antisaccade trials, the evoked saccade endpoints never deviated toward the singleton but only toward the endpoint of the ultimate saccade.

To ensure that a transient deviation was not overlooked, the set of three stimulation times was adjusted to sample a range of times across sessions. Significant deviations in prosaccade and antisaccade trials were observed at 97% of the stimulation sites, and no qualitative differences distinguished the two monkeys. Fig. 3 shows the deviations of the evoked saccades for both monkeys for all stimulation times, 0–180 ms after presentation of the array. In prosaccade trials, the endpoints of the evoked saccades deviated significantly from 0° in none of the 65 experimental sessions for early stimulation times (0–60 ms), in 22% of sessions for intermediate stimulation times (70–120 ms), and in 60% of sessions for late stimulation times (130–180 ms) (one-sample t tests, $P < 0.05$ with Bonferroni correction), and the deviations were always toward the singleton. In antisaccade trials, the endpoints of the evoked saccades deviated significantly from 0° in <1% of the sessions for early stimulation times, in 15% for intermediate stimulation times, and in 72% for late stimulation times; the deviations were never toward the singleton but always toward the endpoint of the antisaccade. To examine when the deviations in prosaccade and antisaccade trials became

significantly different from 0°, an ANOVA was performed to define the 95% confidence interval. For prosaccade trials, stimulation at least 120 ms after array presentation evoked saccades with significant deviations. For antisaccade trials, deviations were significant after 140 ms. These values were almost identical for the monkeys' data examined individually [monkey L, 120 ms (pro) and 140 ms (anti); monkey P, 120 ms (pro) and 130 ms (anti)]. The deviations became significant only after the orientation of the singleton was encoded but before the endpoint of the saccade was selected, as assessed by the time of modulation of FEF neurons (7, 20).

It is possible that on individual antisaccade trials, the deviations may have been biased initially toward the singleton, followed by a reversal to the saccade endpoint (i.e., the mean deviations may conceal more subtle deviations that may have occurred on some fraction of trials). To quantify this, the variability in the endpoints of saccades evoked in antisaccade trials was compared to the baseline dispersion of the endpoints of the saccades evoked in prosaccade trials at the earliest stimulation time before any systematic deviation occurred. Deviations in antisaccade trials exceeding the 95th percentile of the distribution of baseline deviations toward the singleton were vanishingly rare (monkey L, 0.032%; monkey P, 0.020%).

Discussion

In the present task, attention is allocated initially to the location of the singleton because it is conspicuous and its shape must be resolved to produce the appropriate response (26, 27). Our results are consistent with the evidence that target selection is not sufficient for saccade preparation. The absence of deviations toward the singleton when it was being selected by neurons in FEF during attention allocation demonstrates that saccade preparation is not an obligatory or immediate outcome of visual selection and so challenges the premotor theory of attention. Evidence using transcranial magnetic stimulation of the FEF in humans (31) and electrically stimulating the intermediate layers of the macaque superior colliculus (38) reinforces this conclusion. Also, the independence of preparing an eye movement and allocating attention has been demonstrated in dual-task paradigms when shifting attention is volitional (15), as well as when attention gets captured reflexively by a stimulus with an abrupt onset (39). Consequently, the deviations of the endpoints of evoked saccades reveal only the state of saccade preparation and do not necessarily measure the moment-by-moment locus of attention within the visual field (14) or the current state of sensory evidence from which saccade production is derived (34). Covert attention and overt gaze may be linked under many conditions, but the present results demonstrate that the link is not obligatory or immediate (40). Such a dissociation can come about if different pools of neurons within the network of sensorimotor structures convey distinct signals. Identifying such distinctions is necessary to elucidate the proper mapping between cognitive processes and neural processes.

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