Visualization of the Information Flow Through Human Oculomotor Cortical Regions by Transcranial Magnetic Stimulation

YASUO TERAO,[1] HIDEKI FUKUDA,[2] YOSHIKAZU UGAWA,[1] OKIHIDE HIKOSAKA,[3] RITSUKO HANAJIMA,[1] TOSHIAKI FURUBAYASHI,[1] KATSUYUKI SAKAI,[1] SATORU MIYAUCHI,[4] YUKA SASAKI,[4] AND ICHIRO KANAZAWA[1]

[1]*Department of Neurology, Division of Neuroscience, Graduate School of Medicine, University of Tokyo, Tokyo 113-8655;* [2]*Department of Industrial Physiology, National Institute of Industrial Health, Kawasaki 214-0023;* [3]*Department of Physiology, School of Medicine, Juntendo University, Tokyo 113-0033; and* [4]*Communications Research Laboratory, Tokyo 184-0015, Japan*

Terao, Yasuo, Hideki Fukuda, Yoshikazu Ugawa, Okihide Hikosaka, Ritsuko Hanajima, Toshiaki Furubayashi, Katsuyuki Sakai, Satoru Miyauchi, Yuka Sasaki, and Ichiro Kanazawa. Visualization of the information flow through human oculomotor cortical regions by transcranial magnetic stimulation. *J. Neurophysiol.* 80: 936–946, 1998. We investigated the topography of human cortical activation during an antisaccade task by focal transcranial magnetic stimulation (TMS). We used a figure-eight shaped coil, with the stimulus intensity set just above the threshold for activation of the hand motor areas but weak enough not to elicit blinks. TMS was delivered at various time intervals (80, 100, and 120 ms) after target presentation over various sites on the scalp while the subjects performed the antisaccade task. It was possible to elicit a mild but significant delay in saccade onset over *1*) the frontal regions (a region 2–4 cm anterior and 2–4 cm lateral to hand motor area) and *2*) posterior parietal regions (6–8 cm posterior and 0–4 cm lateral to hand motor area) regardless of which hemisphere was stimulated. The frontal regions were assumed to correspond to a cortical region including the frontal eye fields (FEFs), whereas the parietal regions were assumed to represent a wide region that includes the posterior parietal cortices (PPCs). The regions inducing the delay shifted from the posterior parietal regions at an earlier interval (80 ms) to the frontal regions at a later interval (100 ms), which suggested an information flow from posterior to anterior cortical regions during the presaccadic period. At 120 ms, the effect of TMS over the frontal regions still persisted but was greatly diminished. Erroneous prosaccades to the presented target were elicited over a wide cortical region including the frontal and posterior parietal regions, which again showed a forward shift with time. However, the distribution of effective regions exhibited a clear contralateral predominance in terms of saccade direction. Our technique provides a useful method not only for detecting the topography of cortical regions active during saccadic eye movement, but also for constructing a physiological map to visualize the temporal evolution of functional activities in the relevant cortical regions.

INTRODUCTION

Most functional mappings of the human cerebral cortex have utilized positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). PET and fMRI visualize multiple brain regions that are activated during task performance such as saccades, whereas EEG and MEG reveal the time course of such cortical activation (PET: Fox et al. 1985; O'Sullivan et al. 1995; Petit et al. 1995; Sweeney et al. 1996; fMRI: Darby et al. 1996; Müri et al. 1996a; Petit et al. 1997; EEG: Barrett et al. 1986; Deecke et al. 1969; Evdokimidis et al. 1992, 1996; Moster and Goldberg 1990; Shibasaki et al. 1980; Thickbroom and Mastaglia 1985; MEG: Jousmaki et al. 1996; extensive review by Paus (1996).

To be more sure about the actual physiological roles played by each of the activated regions, i.e., which of the activated regions are necessary for performance, we need to remove the function of each region in a manner similar to that for lesioning experiments in animals. As a complementary measure to the techniques above, transcranial magnetic stimulation (TMS) could be used to produce such ''temporary lesions'' in human studies. TMS is known to exert both excitatory and inhibitory effects on the cerebral cortex. Stimulation of the motor cortex is an example of its excitatory effect, which results in the activation of muscles. TMS occasionally facilitates cutaneous perception when applied over the parietal cortex (Seyal et al. 1995). On the other hand, the prolongation of onset latencies by TMS that has been described in various reaction time tasks is an example of the inhibitory effect; TMS is known to delay the onset of hand reaction (Day et al. 1989) and saccadic eye movement (Priori et al. 1993) or suppresses visual (Amassian et al. 1989) or somatosensory (Cohen et al. 1991; Seyal et al. 1992, 1997) perception when applied over the cerebral cortex. These studies were based on the assumption that, if the performance of a task is delayed or facilitated by TMS at a certain time, this should indicate that the focal cortical area just underneath the coil is then active and necessary. By comparing the effect of TMS given at various time periods, we would be able to see how the physiological activities of those cortical regions change with time. This approach would thus be a useful method for physiological mapping, telling us not only which cortical regions are active during task performance but also when they are active and necessary.

The goal of our study was not only to detect the locations of active cortical regions during task performance but also to construct a dynamic physiological map by visualizing the temporal evolution of functional activities in the relevant cortical regions. We adopted saccade tasks as the behavioral paradigm because they are quite stably performed by human

0022-3077/98 $5.00

subjects, and the neuroanatomy and physiology of saccadic cortical regions have already been studied in detail (Goldberg and Colby 1992). Nevertheless, few studies have addressed the time course of the shift of activities in these cortical regions. Our TMS experiments suggested that information necessary for initiation of antisaccades is transmitted from the parietal to the frontal cortical areas within a short time interval between 80 and 100 ms after target onset.

METHODS

Subjects

Eight normal right-handed volunteers (30–45 yr old, 34.0 ± 6.6 yr, mean ± SD) participated in this study. The following studies were approved by the Ethics Committee of the National Institute of Industrial Health, and informed consent was obtained from the subjects before the examinations.

Recording procedures

The computer system for target presentation was originally developed by Kato et al. (detailed descriptions in Kato and Hikosaka 1992; Kato et al. 1995) for behavioral and physiological studies in trained animals, which was modified for human use by Hikosaka et al. (1993) (Nakazawa Seisakusho Company). A microcomputer (NEC 9801DA, NEC, Tokyo, Japan) controls the behavioral paradigms for human and primate subjects in an interactive manner and stores analog (e.g., eye movement) and digital (e.g., the time of pressing and releasing the switch button) data for further analysis.

The subjects were seated in front of a black, concave dome-shaped screen of 90-cm diam with their heads placed on a chin rest to restrain head movement. They faced the center of the screen with a viewing distance of ~66 cm, where the pinhole used for the central fixation point was located. Each subject held a microswitch button connected to the microcomputer, allowing him to initiate and terminate a task trial by pressing and releasing the button. The two possible locations of the target were 20° to the right and to the left of the fixation point, where pinholes containing a light-emitting diode (LED) were located. For the antisaccade task described later, these locations were also marked with doughnut-shaped pieces of tape on the screen beforehand. The appearance time and duration of each LED was under program control of the microcomputer. The time interval between button press and the initiation of the task (i.e., the appearance of the fixation point) could be randomized within a certain range (1.2–2.0 s).

Electrooculographic (EOG) recordings were made by two Ag-AgCl gel electrodes placed at the bilateral outer canthi, and the signals were fed to a DC-amplifier (EOG amplifier, AN-601G, Nihon-Kohden, Tokyo, Japan), low-pass filtered at 20 Hz, and then digitized (500 Hz). Throughout the task performance, the gain of EOG was adjusted so that the current eye position displayed on the monitor was always aligned with the target position simultaneously displayed on the same screen. The room for recording was dimmed so that the unlit pinholes were not seen. After placing the electrodes, we waited for a period of at least 30 min to allow the subjects to become adapted to the dark and ready to start. Vertical EOG was also recorded by electrodes placed just above the upper lid and below the lower lid, which, together with the video camera, monitored the occurrence of blinks.

Behavioral paradigms

In the present study, two kinds of behavioral paradigms were used: visually guided saccades (VGS) and antisaccades (AS). In the VGS task, a central spot of light came on shortly after the subject pressed a button, and the subject was required to fixate on this spot. After a random period of time (1.2–2.0 s), the spot was extinguished, and a target stimulus appeared randomly 20° either to the left or to the right of the fixation point without a gap period, which the subjects were instructed to foveate as quickly as possible. The subject had to release the finger from the button after each saccade was completed. In the AS task, the behavioral paradigm was the same as above, except that the instruction was to fixate on a point just to the opposite of the target. Because the saccade onset of the VGS task was relatively unaffected by focal TMS, we mainly investigated the effects of TMS on AS tasks (see DISCUSSION).

TMS

We used a prototype figure-eight shaped coil thinly covered with insulation tape that enabled close contact with the skin (diameter of each coil 10 cm) to perform powerful cortical stimulation. The coil was connected to a magnetic stimulator, Magstim 200 (Magstim). TMS was delivered over various regions on the scalp while the subjects performed the saccade tasks. For this purpose, nasion, inion, vertex, and preauricular points were located according to the 10–20 international electrode system, and a 2-cm grid reference system covering the skull was constructed for each subject (Meyer et al. 1991). Lines were drawn between nasion and inion and between the vertex and preauricular points on a tightly fitting rubber cap made for each subject. Then a grid was made by drawing additional lines parallel to these lines such that the distance between these parallel lines was 2 cm. The threshold for motor evoked potentials (MEPs) at each grid point was defined as the minimal intensity required for obtaining electromyographic (EMG) responses in the contralateral first dorsal interosseous (FDI) muscle over 50 μV at a display gain of 50 μV per 1 cm division in more than one-half of the trials while the subjects maintained an EMG activity of 10% maximal voluntary contraction. Hand motor areas were then defined as the sites where the lowest stimulus intensity (threshold) of TMS was capable of eliciting MEP; these positions were used as reference points to the areas where saccades were most affected. The center of the coil was placed flat and tangential to the scalp surface at each of the grid points with the induced current flowing in the posterior-to-anterior direction. The total number of the grid points over which TMS delivered ranged from 80 to 120, depending on the scalp size and shape of the subject. In preliminary studies, TMS was applied at various intervals (60–200 ms in 20-ms steps) after the appearance of the visual target and before the expected onset of saccades (~260 ms). Next, three intervals, 80, 100, and 120 ms, were selected for further study because these time intervals were considered to be critical in determining the saccade parameters.

TMS over the scalp can evoke various additional sensory inputs, such as current in the skin, contraction of the muscle in the scalp, and a click sound. If the coil is not sufficiently effective to block any cortical region, saccade reaction time may even be accelerated. Indeed, saccade onset was accelerated by TMS in some studies (FitzGibbon et al. 1993), and this may well have been due to intersensory facilitation. Among the sensory inputs accompanying the magnetic pulse, the click sounds serve as the most potent accessory cues (Terao et al. 1997). To control for the nonspecific effect of click sound accompanying TMS, we interspersed control trials (30–40 trials in total per 1 mapping procedure) in which the magnetic coil was held *off* the scalp with conditioned trials in which TMS (10–20 times per site) was delivered over the grid points at the same interval; we then compared the saccade parameters between these trials. When the subjects performed the saccade tasks in control trials, they heard the click sounds accompanying the magnetic pulse at the three intervals (80, 100, and 120 ms).

Data processing

The data, composed of an event-data file and an analog-data file, were analyzed off-line. For each trial, four parameters were determined for further analyses: saccade onset latency, amplitude, duration, and peak velocity. After these parameters for each task trial were determined, statistical analyses and displaying of the parametric data were performed. The onset of an eye movement was defined as the time when velocity and acceleration exceeded predetermined values (28°/s and 90°/s^2, respectively). Eye movement was accepted as a saccade on the basis of its velocity and duration. After the onset, the velocity had to exceed 88°/s, and this suprathreshold velocity had to be maintained for at least 10 ms. The end of the eye movement was determined where the velocity decreased below 40°/s. The above process was performed automatically by the computer, although the final judgment of appropriate and inappropriate results was based on visual inspection of the individual eye movement records on the computer monitor. Small, slow saccades and saccades contaminated by a significant amount of noise were discarded from analysis. Saccades with onset latency $<$100 ms were classified as anticipatory and were excluded from analysis. The median and mean of the saccadic parameters were calculated for each stimulation condition (stimulation site and interval). Statistical analysis was first performed using the Mann-Whitney *U* test by comparing the mean values of these four parameters at each site with those of the control trials in which TMS was delivered off the scalp at the same time interval. Subsequently, three-dimensional plots for these values were constructed against the stimulation site over the scalp to find the areas where the most prominent effects were observed. To help identify the scalp regions where the saccade parameters were most affected, we constructed a map plotting each parameter (*z*-axis) against the site of TMS (*x-y* axis), which was then transformed into a contour map with gradation by using a commercially available software (ContFlexa ver0.1.1.1., Kissei Comtec, Matsumoto, Japan). For example, saccade onset latency (*z*-axis) was plotted against the scalp site (*x-y* axis) over which TMS was delivered. At each interval of TMS, the four saccade parameters at each scalp site were statistically compared with the control values. By this procedure, we confirmed that the regions affecting these parameters with statistical significance actually coincided with those regions detected by visual inspection of the maps. Because the effect of TMS on the parameters differed slightly for saccades made in the rightward and leftward directions, the parameters for these two directions were analyzed separately. For five of eight subjects, we proceeded to construct maps at different intervals (80, 100, and 120 ms) to visualize how the areas affecting the parameters shifted with the time of TMS.

This led us to define five regions of interest (ROIs) over each hemisphere that were considered where the changes in saccade parameters were most remarkable, and the boundaries of these regions were defined relative to the location of the hand motor areas in each subject. The five regions were as follows: *1*) frontal regions: 2–4 cm anterior to the hand motor areas, 2–4 cm lateral; *2*) motor regions: from 2 cm anterior to 2 cm posterior, and from 2 cm medial to 2 cm lateral to the hand motor areas; *3*) anterior parietal region: 2–4 cm posterior, and from 2 cm medial to 2 cm lateral to the hand motor areas; *4*) posterior parietal region: 6–8 cm posterior and 0–4 cm lateral to the hand motor areas; and *5*) occipital region: 10–12 cm posterior to the hand motor areas, 0–2 cm lateral to the midline.

Statistical analyses

In each subject, we subtracted the control values of each saccade parameter from the saccade parameters with TMS delivered at each grid point, and these subtracted values were averaged over all of the grid points within each ROI. Then the mean values for each ROI were averaged across five subjects. The averaged mean values thus obtained (ordinate) were plotted against the ROIs (abscissa) as bar graphs showing how the saccade parameters changed with various time intervals and ROIs (Figs. 2 and 4). First, the averaged mean of parameters was compared at each ROI with the control value in each subject using a paired Student's *t*-test. This was done to find out the general trend of the effect of TMS in terms of the ROIs that elicited the most significant delays in saccade onset at each time interval of TMS and for each saccade direction. Subsequently, analysis of variance (ANOVA) with two factors was performed to confirm the observations obtained by visual inspection of the maps. For each ANOVA, we chose two factors considered appropriate for analysis out of four possible factors, the interval of TMS (80, 100, and 120 ms), the ROIs (see above), the saccade direction (leftward or rightward), and the side of hemisphere stimulated (left or right). Finally, post hoc analysis by Bonferroni's method was carried out to see what differences contributed to the significant differences detected by ANOVA.

Finally, we investigated the regions over which it was possible to elicit prosaccades by TMS above baseline level. The incidence of prosaccades was calculated by dividing the total number of prosaccades by the number of trials in which the target was presented to the same side in the same session (i.e., in which the saccade had to be made in the opposite direction). This was plotted against the site of TMS as above. Statistical analysis was first performed by comparing the incidence of prosaccades at each grid point with those in control trials by a χ^2 test (significance level set at $P < 0.05$). As in the studies of other parameters, the regions detected by visual inspection coincided with the areas where there was a significant increase in the incidence of prosaccades. In each subject, the incidence of prosaccades above baseline level was averaged over the five ROIs as above, and the averaged mean values across subjects were again plotted against the ROIs to construct bar graphs. To find out where a remarkable laterality was observed in the incidence of prosaccades between TMS over the left and right hemispheres, the incidences of prosaccades elicited by stimulation over both hemispheres were compared at each ROI, separately for rightward and leftward prosaccades, using a paired Student's *t*-test. Then, to confirm the observations obtained by visual inspection of the maps, ANOVA with two factors was performed as described above for other saccadic parameters.

RESULTS

The mean onset latencies of antisaccades, measured from the time of target presentation, in control trials were 263.4 ± 8.5, 270.7 ± 9.5, 260.4 ± 9.1 (SE) ms for rightward saccades and 260.7 ± 5.7, 270.0 ± 7.0, 264.3 ± 7.9 ms for leftward saccades (click sounds accompanying the magnetic pulse at 80, 100, and 120 ms, respectively). Thus the saccade onset invariably occurred at ~260–270 ms, and there was no statistical difference between these values regardless of the time of the click sounds.

When we used a strong intensity of TMS (>60% of the maximal output of the stimulator), eye blinks were readily induced by TMS delivered over the frontal and parietal areas, which conspicuously altered the saccade gain. The initial saccade became markedly hypometric and tended to begin early with a relatively constant latency. Such hypometric saccades are actually accelerated in onset latency followed later by a corrective saccade. Therefore we considered it essential that the stimulus intensity be above the threshold for MEPs in active FDIs over the hand motor areas (i.e., an intensity strong enough to stimulate the cerebral cortex just

underneath the coil) but weak enough to avoid eliciting blinks. Thus the intensity was set 5–10% above the motor threshold over the hand motor areas, which came within 30–45% of the maximal output of the magnetic stimulator.

TMS had a most remarkable effect on the onset latency and the incidence of prosaccades. Because the effects of TMS on other saccadic parameters were mild, these will not be detailed further in this paper.

TMS effect on saccade latency

Figure 1 shows the map for saccade latency in one subject. The regions eliciting onset delay of leftward antisaccades are illustrated in red. At 80 ms, onset latency was most effectively delayed over the posterior parietal regions, 6–8 cm posterior to the hand motor areas (Fig. 1, *left*). At 100 ms (Fig. 1, *right*), the most prominent delay was induced over the frontal regions just anterior and somewhat lateral to the hand motor areas that are marked by white dots in the figure. Thus, during the period from 80 to 100 ms, we see a forward shift of effective areas from the posterior parietal to frontal regions. Although TMS was delivered focally and unilaterally, the effect was observed regardless of which hemisphere was stimulated (we describe this as a ''bilateral'' effect). By a later interval (120 ms), the delay over both the frontal and parietal regions had subsided.

The map constructed for all subjects exhibited the same trend, with the zones eliciting the most prominent delay consistently over the bilateral frontal regions, 2–4 cm anterior and 2–4 cm lateral to the hand motor areas, and the posterior parietal regions, 6–8 cm posterior to the hand motor areas and 0–4 cm lateral. Bar graphs constructed from these data confirmed the impressions obtained by visual inspection of the contour maps (Fig. 2). The vertical axis of the graphs show the changes in saccade latency. The average saccade latency for normal saccades was ~260 ms as described above. Saccade onset latency was significantly delayed over the bilateral posterior parietal regions at an inter-

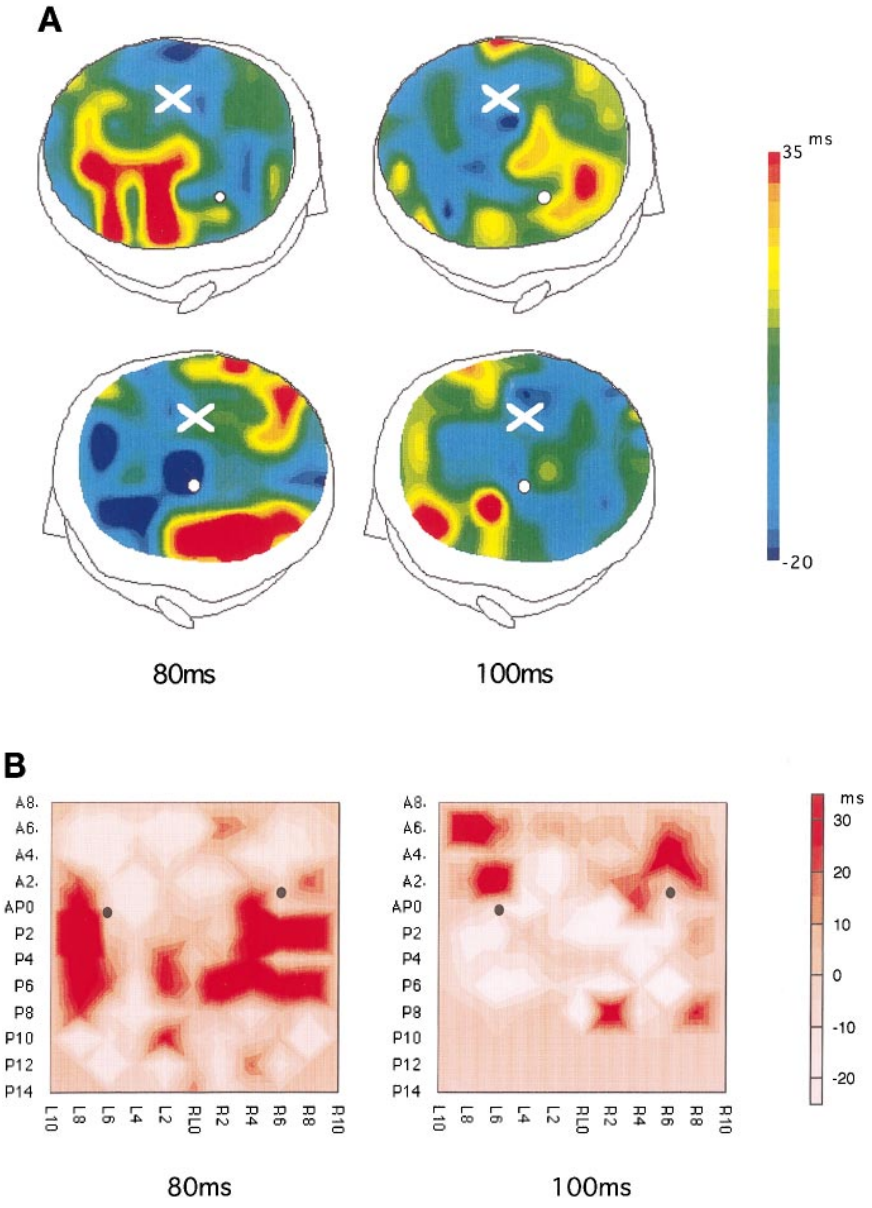

FIG. 1. Spatiotemporal shift of regions affecting the saccade latency in one subject. *A*: latency of antisaccades (*z*-axis) was plotted against the site (*x*-*y* axis), which was then transformed into a contour map. The map was shown as viewed from 2 sides (right lateral view in the *top row* and left lateral view in the *bottom row*). White dots mark the positions of bilateral hand motor areas, and the white cross indicates the position of the vertex. Although plots were constructed separately for rightward and leftward saccades (target eccentricity 20°), we show here only the maps for antisaccades made to left. Gradation was introduced to help identify the effective regions. Bar on the *right* depicts the tints used, corresponding to how much delay was induced by transcranial magnetic stimulation (TMS; −20 to +35 ms). Therefore the red areas indicate the regions where considerable saccade delay was noted, and the green and blue areas indicate the regions where delay was minimal. At 80 ms, delay was maximal over an area 6–8 cm posterior to hand motor areas bilaterally, somewhat lateral (posterior parietal regions). At 100 ms, the regions shifted forward to an area 2–4 cm anterior and 2–4 cm lateral to the hand motor areas bilaterally (frontal regions). Delay persisted at 120 ms (not shown) but was greatly diminished. *B*: diagram showing the same data in a 2-dimensional plot. The map covers a scalp region, ranging from 8 cm anterior to 14 cm posterior to C_z (vertex), and from midline to 8 cm lateral, as indicated by the labels on the *x*- and *y*-axes. *Top* of the figure is to the anterior, and the *left* and *right sides* correspond to the left and right sides of the head. For example, A6 is 6 cm anterior to Cz, and R6 is 6 cm right to midline. Black dots denote the locations of hand motor areas. Dark red areas indicate regions where considerable saccade delay was induced. Bar on the right depicts the tints used, corresponding to how much delay was induced by TMS (−20 to +30 ms). As described in *A*, delay was maximal over the posterior parietal regions at 80 ms and over frontal regions at 100 ms.

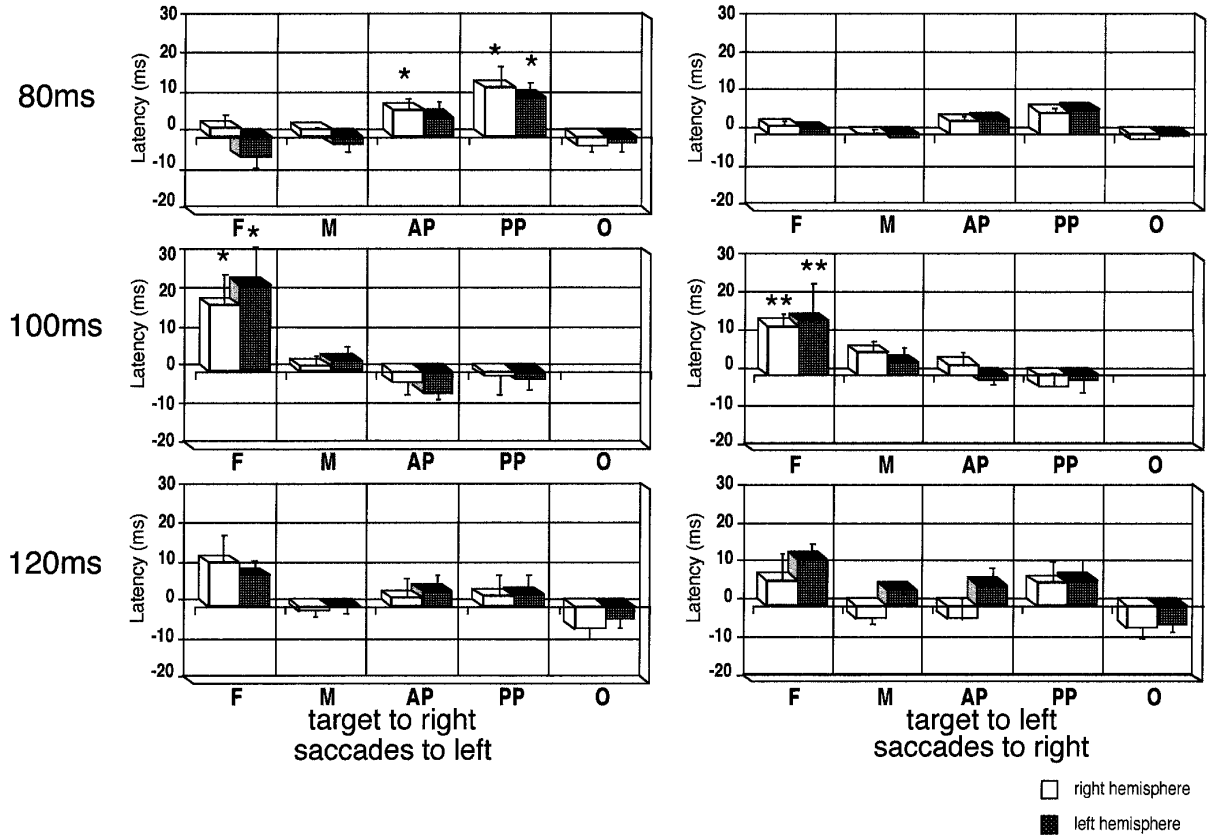

FIG. 2. Changes in saccade latency with TMS applied at various intervals. In all 5 subjects, the saccade latency showed a similar pattern of change with TMS applied at various intervals (80, 100, and 120 ms after target presentation). The vertical axis of the graphs show the changes in saccade latency (positive values are for delays). White bars are for stimulation over the right hemisphere, and stippled bars show stimulation over the left hemisphere. Because the exact location of scalp regions affecting the parameters varied slightly among the subjects, the results were combined by averaging them over 5 predetermined scalp regions on each hemisphere, the positions of which were defined relative to the location of hand motor areas in each subject (further definition in *Data analyses*). F, frontal regions; M, motor regions; AP, anterior parietal regions; PP, posterior parietal regions; O, occipital regions. In these figures, the averaged saccade parameters are plotted against the regions of interest (ROIs). Error bars on each column show standard errors. ROIs where saccadic parameters differed significantly from control values are marked with asterisks (significance level: $**P < 0.01$, $*P < 0.05$). Bars for the occipital regions at 100 ms are not shown because we could not obtain enough data for this site at this interval. At interval 80 ms, saccade latency was delayed over the posterior parietal region. At 100 ms, delay was most evident over the frontal regions, whereas at 120 ms it persisted but greatly subsided. The overall pattern is the same for leftward and rightward antisaccades, and the delay was elicited to a similar extent over both hemispheres for both saccade directions, although leftward saccades were generally more affected than rightward saccades. These plots clearly show a tendency for posterior regions to be more involved at earlier intervals and for anterior regions to be involved at later intervals.

val of 80 ms. At 100 ms, delay over the bilateral frontal regions became prominent. At 120 ms, delay over the frontal regions persisted but was greatly diminished. Therefore the areas inducing delay exhibited a forward shift from the posterior parietal to frontal regions as TMS was applied at later intervals. For both rightward and leftward antisaccades, TMS delivered at the homologous ROIs over the right and left hemispheres elicited approximately the same amount of delay.

Statistical analyses were performed to confirm these observations. ANOVA with two factors, interval of TMS, and ROI showed a significant interaction between these factors, indicating that the effect of interval was different among the ROIs [$F(4,159) = 9.042$, $P < 0.001$]. Post hoc analysis revealed the following difference. Over the frontal region, the delay of latency at 100 ms was significantly greater than that at 80 ms ($P = 0.0024$). Over the posterior parietal region, latency at 80 ms was significantly greater than that at 100 ms ($P = 0.0191$). Therefore it can be concluded that, over the posterior parietal region, the delay was elicited at 80 ms and subsided after 100 ms, whereas, over the frontal region, the delay was not apparent at 80 ms but became apparent after 100 ms. ANOVA with two factors, side of stimulation and direction of antisaccades, indicated no effect of either of these factors nor any interaction between them [effect of side: $F(1,164) = 0.021$, $P = 0.8861$; effect of saccade direction: $F(1,164) = 0.101$, $P = 0.7516$; side X direction: $F(1,164) = 68.88$, $P = 0.3371$]. Thus, for saccades of both directions, the delay was equally induced regardless of the hemisphere stimulated. Leftward antisaccades were generally more affected than rightward antisaccades, but this difference did not reach statistical significance ($P > 0.2$).

TMS effect on the incidence of prosaccades

The subjects made relatively few saccade errors. Most of them were either due to anticipatory saccades that were excluded from analysis, or reflexive saccades inadvertently made in the direction of the presented target (prosaccades). The incidence of prosaccades was quite low: rightward prosaccades when TMS was applied at 80 ms 1.9 ± 0.5%, at 100 ms 1.9 ± 0.9%, at 120 ms 1.5 ± 0.5%; the incidence of leftward prosaccades at 80 ms 1.3 ± 0.4%, at 100 ms 1.6 ± 0.7%, at 120 ms 0.9 ± 0.2%.

Prosaccades were induced significantly more frequently when TMS was applied to the contralateral hemisphere, i.e., rightward prosaccades by TMS over the left hemisphere and leftward prosaccades by TMS over the right hemisphere. Figure 3 shows how the regions affecting the incidence of prosaccades changed with the time of TMS in one of the subjects. At interval 80 ms, prosaccades made to the right target were increased over both the left frontal and posterior parietal regions, each 2–4 cm anterior and 6–8 cm posterior to the hand motor area. At interval 100 ms, however, the effective regions shifted forward and relatively converged into the left frontal region. By a later interval (120 ms), the incidence of prosaccades had returned to baseline level over all of the scalp regions.

A similar trend was observed for the combined data for all five subjects that were plotted in bar graphs (Fig. 4). At interval 80 ms, prosaccades were elicited over a wide scalp region covering the contralateral frontal through occipital regions. At interval 100 ms, the effective regions converged mostly into the frontal regions, although some effect remained over the parietal regions. The effect of TMS was predominantly contralateral in terms of saccadic direction (asterisks in Fig. 4 indicate significant laterality detected by paired Student's *t*-test, $P < 0.05$). By interval 120 ms, the incidence of prosaccades had returned to the baseline level.

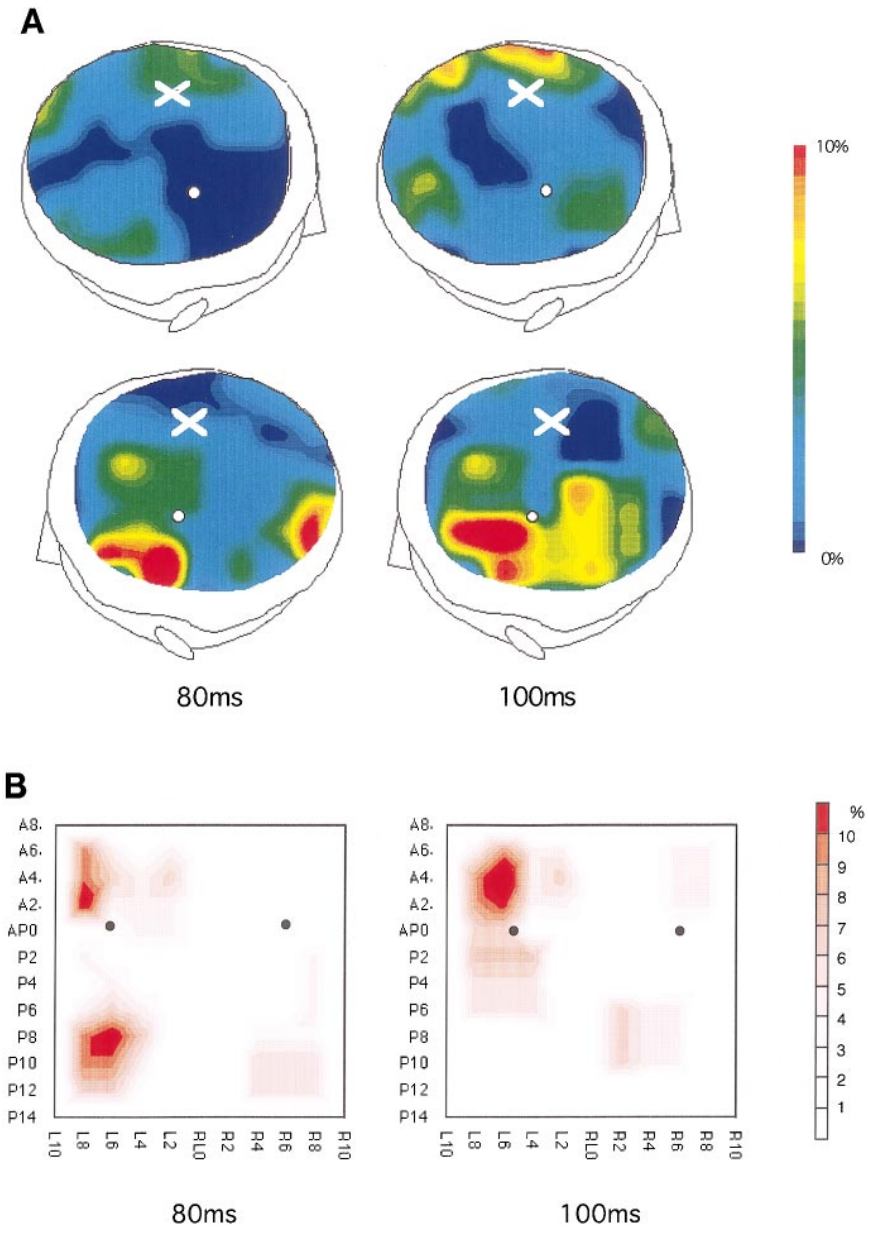

FIG. 3. Spatiotemporal shift of regions eliciting prosaccades. Prosaccades were elicited above baseline level when TMS was applied over certain scalp regions. This figure plots the incidence of prosaccades against the site of TMS for one subject. Conventions used are as in Fig. 1. Incidence of error was expressed as the percentage of saccades made in the wrong direction in the total trial numbers in which the target was presented to the same side (in this case, right). Areas in red indicate the regions eliciting a high incidence of prosaccades, and those in blue or green show regions with a low incidence of prosaccades (for gradation, see bars at the *right*). In this subject, who made baseline errors of 3–5% prosaccades in control trials, the incidence of prosaccades increased with TMS over the left frontal and posterior parietal regions at interval 80 ms. Maximum error rate reached 14%. Relevant areas converged into the frontal region at interval 100 ms. At 120 ms, the incidence returned to baseline level throughout all of the scalp regions. Here again, there was a tendency for posterior parietal regions to be more involved at earlier intervals, whereas the frontal regions became more remarkable at later intervals. Some effect remained over the parietal region. The only difference was that the distribution of regions was predominantly contralateral to the direction of saccades made. *B*: diagram depicting the same data as in *A*. Conventions as in Fig. 1*A*, except that the dark red areas indicate where the incidence of prosaccades increased by TMS. Bar on the right depicts the tints used, corresponding to the incidence of prosaccades at each scalp site (0–10%). As described in Fig. 2*A*, the incidence of prosaccades was maximal over the contralateral frontal and posterior parietal regions at 80 ms and over the contralateral frontal regions at 100 ms.

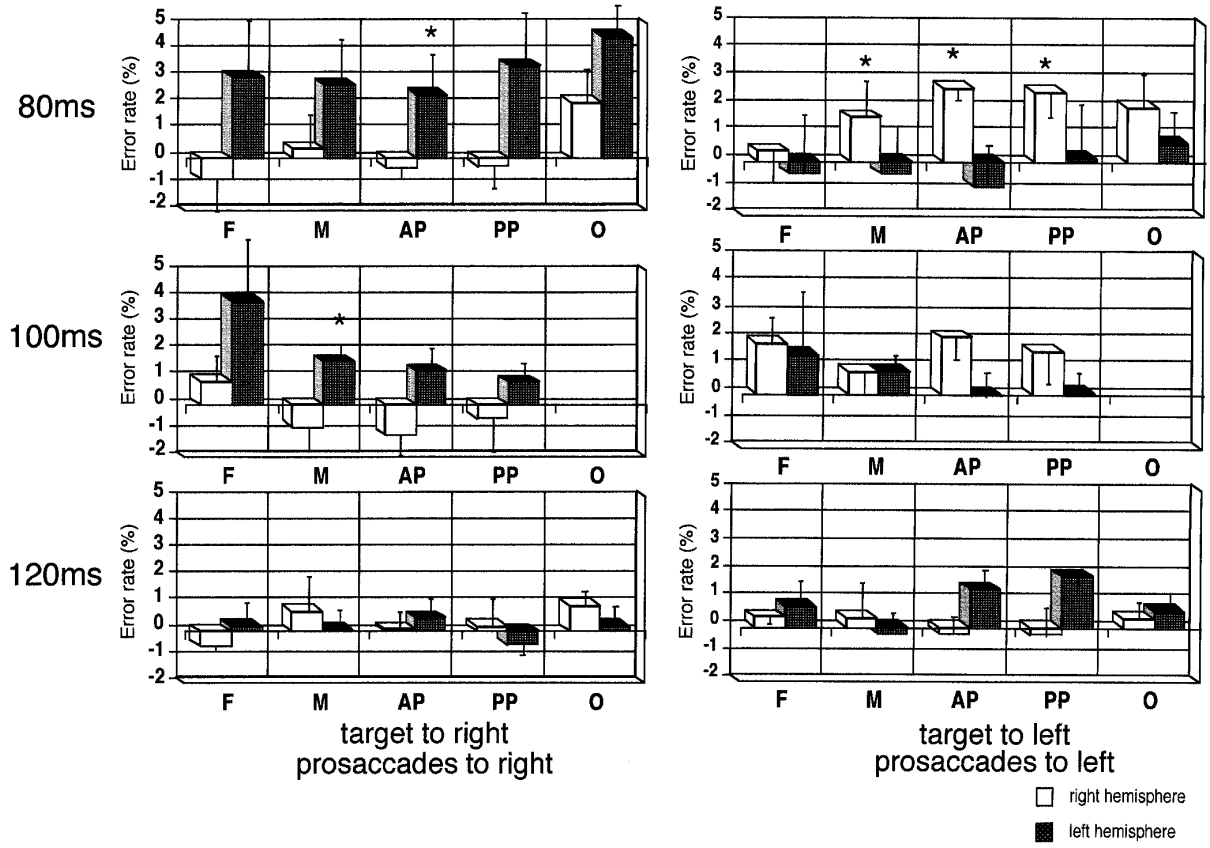

FIG. 4. Changes in the incidence of prosaccades with TMS applied at various intervals. Maps for the incidence of prosaccades were similar among the 5 subjects investigated, and the results were combined. The mean prosaccade rates were averaged within the 5 ROIs of each hemisphere. Thereafter, the incidence of prosaccades made above baseline level (ordinate) was plotted against the ROIs (abscissa). Conventions used are as in Fig. 2. At interval 80 ms, the incidence of prosaccades was increased with TMS over a wide scalp region covering the frontal through occipital regions. Rightward prosaccades were more readily elicited with TMS over the left hemisphere, whereas leftward prosaccades were more frequent with TMS over the right hemisphere (not shown here). Asterisks indicate the ROIs where significant laterality was present. By interval 100 ms, increased errors became remarkable over the frontal regions (paired Student's *t*-test, $P < 0.05$). At 120 ms, the incidence of errors nearly returned to the baseline level.

The latencies of rightward prosaccades elicited by TMS over the contralateral hemisphere were 236.1 ± 5.0 ms at 80 ms and 235.2 ± 18.0 ms at 100 ms, whereas those of leftward prosaccades were 227.8 ± 8.1 ms at 80 ms and 241.9 ± 12.0 ms at 100 ms. These were significantly shorter than the control latencies of antisaccades made in the same direction, which were ~260 ms as stated above (Wilcoxon's signed-rank test, $P < 0.05$).

Statistical analyses were performed to confirm these observations. ANOVA with two factors, the interval of TMS and ROI, indicated a significant effect of the interval of TMS [$F(2,158) = 5.298, P = 0.0059$], but no interaction between these factors [$F(4,158) = 1.606, P = 0.1753$]. Post hoc analysis revealed a significant difference between the incidence of prosaccades at different intervals over the frontal regions. The incidence of prosaccades significantly increased between intervals 80 and 100 ms, whereas it decreased to the baseline level between intervals 100 and 120 ms ($P = 0.0287$ and 0.0029, respectively). ANOVA with two factors, side of stimulation and prosaccade direction, revealed a significant interaction between the side of stimulation and the direction of the prosaccades [side X direction: $F(1,164) = 6.003, P = 0.0153$]. Post hoc analysis revealed that prosaccades to targets presented to the right increased when TMS was delivered over the left hemisphere ($P = 0.0096$). Similarly, the increase of leftward prosaccades tended to increase on stimulation over the right hemisphere, but this did not reach significance ($P = 0.4000$). Rightward prosaccades were generally more readily elicited than leftward prosaccades, i.e., saccades that were inadvertently made to right were more often provoked than those that were inadvertently made to the left, although again this did not reach statistical significance ($P > 0.2$).

Correlation of the TMS map with the underlying cortical anatomy

The areas under the magnetic coil were matched with the cortical regions activated in previous PET studies as follows. First, we first performed fMRI in one subject while he made self-paced saccades at 1 Hz to the left and right, which would activate the presumed locations of frontal eye fields (FEFs). Then the same subject performed finger opposition at 2 Hz, which activated the hand motor areas of bilateral hemispheres. The location of FEF in this subject came ~1.7 cm anterior and 2 cm lateral to the hand motor areas over both

hemispheres. The location corresponded to the ''frontal regions,'' which was 2–4 cm anterior to the hand motor areas and 2–4 cm lateral. It is important to remember that our frontal regions occupied a wide area, and were not restricted to a small region within the precentral sulcus such as those activated in previous fMRI studies (Müri et al. 1996a; Petit et al. 1997).

Second, the head shape of another subject was digitized three dimensionally using the SPI (sensor position indicator) system of Magnes. With the use of methods previously described (Uesaka et al. 1993; Yamamoto et al. 1988), the head shape data as well as the digitized position of three reference points were employed to put the head shape of the subject in register with the contour of the MRI of the same subject (Siemens Magnetom, 1.5 Tesla). This enabled us to locate the digitized position of the center grid points of frontal and posterior parietal regions onto the appropriate slices of MRI and to identify the cortical region just underneath these scalp points. The frontal regions thus corresponded mostly to the FEF and the posterior parietal region to a wide region activated over the parietal lobe as reported by Sweeney et al. (1996) and Doricchi et al. (1997).

DISCUSSION

Topography of oculomotor cortical regions

The effects of TMS on saccadic eye movements have been explored in various ways. Although single-pulse TMS over the FEFs cannot elicit a saccade (Müri et al. 1991; Wessel and Kömpf 1991), it can delay the onsets of visually and auditory-triggered saccades. This was ascribed to the blocking of FEF or posterior parietal cortex (PPC) (Beckers et al. 1992; Lueck et al. 1990; Priori et al. 1993; Zangemeister et al. 1995). However, no detailed account of the topography of oculomotor regions was given in these studies. Using TMS, Thickbroom et al. (1996) undertook a detailed mapping of the human FEF and located it between the face and finger representations of the motor area, which was just on the intra-aural line or slightly behind it. This is somewhat at variance with our results because the frontal regions in our study were 2–4 cm anterior to the hand motor areas. On the other hand, using the memory-guided saccade paradigm, Oyachi and Otsuka (1995) located PPC to a region 5–6 cm posterior to the hand motor area, which roughly corresponds to that of our posterior parietal region.

Our present investigation confirmed and extended some of these previous observations by mapping the entire scalp region and furthermore succeeded in describing the spatiotemporal evolution of activities in the relevant regions. Focal TMS revealed cortical regions implicated in the AS task over the frontal and parietal lobes, whereas the VGS were relatively unaffected. These regions were *1*) the frontal regions, 2–4 cm anterior to the hand motor areas and 2–4 cm lateral and *2*) the posterior parietal regions, 6–8 cm posterior to the hand motor areas and 0–4 cm lateral. This result is consistent with recent PET studies in which AS relative to visual fixation activated widespread bilateral frontal regions extending from the dorsolateral prefrontal cortex (DLPFC) to the FEF and supplementary eye field (SEF), as well as large parietal regions bilaterally bounded by striate cortex, marginal gyrus, and posterior temporal cortex (Doricchi et al. 1997; Sweeney et al. 1996). The frontal regions may thus correspond to a wide frontal area including the FEF, whereas the posterior parietal regions may correspond to a large parietal area including the PPC. Most of the previous PET studies have located FEF to an area 2 cm anterior to the hand motor areas (Fox et al. 1985; Paus 1996), and the location of frontal regions mapped in our study seems to be consistent with these results.

In primates, neurons discharging primarily in response to visual stimuli and neurons related to the preparation of saccades have been described in the FEF (Bruce and Goldberg 1985; Bruce et al. 1985) and PPC (Barash et al. 1991a,b; Colby et al. 1996). Thus it is likely that the activities of such neurons in FEF and PPC were temporarily disrupted by TMS.

Recently, Schlag-Rey et al. (1997) have recorded the activities of visual and movement neurons in the primate SEF during randomly mixed pro- and antisaccade trials. They detected a higher activity of movement cells in SEF during antisaccade performance than during prosaccade trials. In view of the important role that SEF plays in saccade preparation (Schlag and Schlag-Rey 1987), we would have expected a delay in latency or increase in saccade errors when TMS was delivered over the SEF. This was, however, not the case because stimulation over the midline scalp regions did not induce any significant change in these saccade parameters. One possible explanation for this lack of effect over SEF may be that the human SEF is buried deeply within the intracerebral fissure (Anderson et al. 1994; Fox et al. 1985), so that with the moderate intensity of TMS used we could not effectively block the activity of cells in this area.

Time course of information flow through the oculomotor cortical regions

We were able to visualize how the activities of relevant cortical areas changed with time by comparing the maps at different intervals. The regions inducing saccade delays shifted from posterior parietal regions at an earlier interval (80 ms) to frontal regions at a later interval (100 ms), which suggested an information flow from the posterior to anterior cortical regions with time. By 120 ms, the effect of TMS had subsided. Unit recordings in primates have demonstrated long-lasting activities before a saccade in the frontal cortex (Boch and Goldberg 1989; Bruce and Goldberg 1985; Bruce et al. 1985) and the parietal cortex (Mazzoni et al. 1996a,b) but have not indicated the exact time when the activity culminated at each region. In this sense, TMS was useful in monitoring the macroscopic functional state of each cortical area, representing the integral activity of individual neurons.

The first component of visual signals is known to reach the primary visual cortex in ~40 ms (Pratt et al. 1982, 1994). Amassian et al. (1989, 1993) showed that TMS applied over the human calcarine cortex can suppress the perception of letters briefly presented 60–140 ms earlier. Together with these results, we propose a hypothetical scheme for the information flow during AS (Fig. 5*A*). The visual input presented as a target in the right hemifield reaches the left primary visual cortex by 40–60 ms, which is then transmitted to the parietal cortex by 80 ms. In the case of

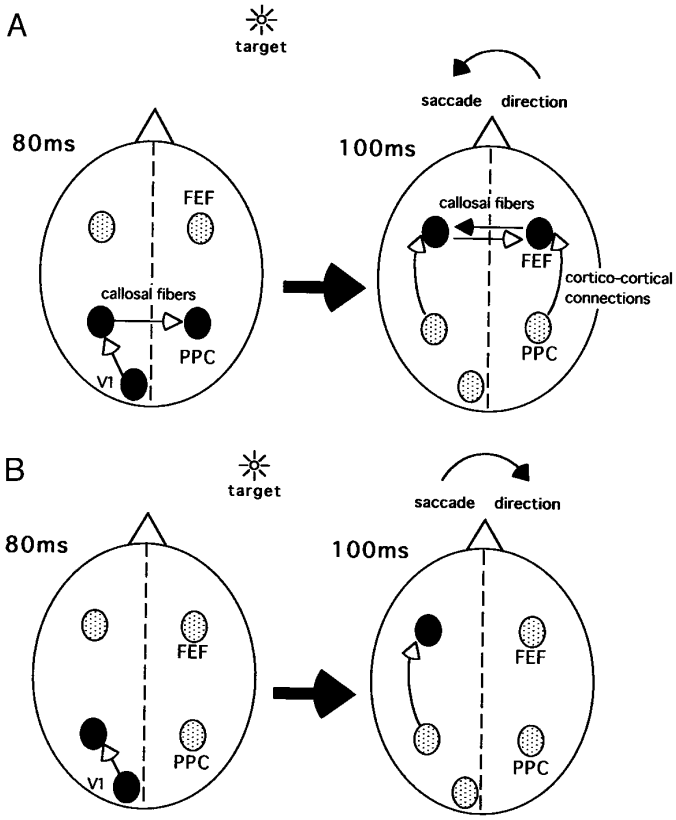

FIG. 5. Cortical processing during antisaccades and elicited prosaccades. Schematic diagram showing the cortical processing presumed to occur during antisaccades and elicited prosaccades. Black ellipses represent the active areas at each time shown in the *top left-hand corner*, and stippled areas indicate the regions whose activities are low or have subsided. *A*: during antisaccades, posterior parietal cortices (PPCs) are active at 80 ms, and frontal eye fields (FEFs) become active at 100 ms. The information flow through these cortical areas may be mediated by the corticocortical fibers connecting the FEF and PPC and the callosal fibers linking the counterpart cortical regions of both hemispheres (shown by white arrows). At 100 ms, the FEF ipsilateral to the target generates the antisaccades, while it has to inhibit the action of contralateral FEF (shown by a black arrow). *B*: during prosaccades, TMS activates the corticofugal fibers sending outputs to the superior colliculus, thereby releasing saccades in the contralateral direction (i.e., in the direction of the target). In this case, only the FEF and PPC contralateral to the target are effective in eliciting the prosaccades. Another explanation for the occurrence of prosaccades may be that TMS interfered with the inhibitory mechanism suppressing prosaccades, which reflexively released the saccade to the target before the required antisaccade was made.

AS, the parietal information is sent to the corresponding region in the opposite (right) hemisphere. At 100 ms, the bilateral information is sent to the frontal cortex including the FEF via corticocortical connections (Andersen 1989; Petrides and Pandya 1984; Stanton et al. 1995) (Fig. 5*A*). The activity in the left FEF is immediately sent to the right FEF. The final saccadic motor output is sent out from the right FEF to produce a saccade to the left, opposite to the visual stimulus. For the bilateral effect of TMS to occur, there must be an interhemispheric transfer of information. This transfer may be mediated by callosal fibers, which are known to connect the FEFs and PPCs of both hemispheres (Andersen 1989; Gould et al. 1986).

We propose a similar cortical information flow for the mechanism of prosaccades (Fig. 5*B*). AS requires the subject to inhibit prosaccade to the presented target, and instead to generate a saccade in the opposite direction (Hallett 1978). TMS interfered with such a dual process, leading to an increase in the incidence of prosaccades toward the target. This time the distribution of effective regions was unilateral, i.e., contralateral to the side of the visual stimulus; there was no interhemispheric transfer of information.

Presaccadic activity of FEF neurons is composed of at least two components, visual and saccadic motor (Bruce and Goldberg 1985; Bruce et al. 1985). These components are often continuous and appear inseparable. Using a go–no go paradigm, Thompson et al. (1996) demonstrated that the motor component emerges at ~120 ms after visual stimulus onset. TMS at 100 ms may disrupt the emergence of the saccadic motor signals in the FEF at 120 ms. Thus the culmination of FEF activity at 100 ms in our study would roughly correspond to this finding.

In our model (Fig. 5), the parietal region is presumed simply to pass information from the visual to frontal cortex. However, TMS can exert its action on PPC through two other different mechanisms. First, during the preparation for AS, the excitability of PPC is enhanced, so that TMS could directly stimulate the corticofugal axons within the region. Previous studies (Keating et al. 1983; Pierrot-Deseilligny et al. 1991; Shibutani et al. 1984) suggest that PPC participates in saccade triggering, probably through its direct projection to the superior colliculus (Pierrot-Deseilligny et al. 1995). The activation of PPC at 80 ms would be short enough for the initiation of express saccades (Fischer and Boch 1983). Therefore the involvement of PPC at 80 ms, well before the onset of antisaccades (260 ms), does not seem to be too early. An alternative mechanism is that TMS interfered mainly with the inhibitory mechanism within the PPC, which reflexively released a saccade toward the target before a required antisaccade was made (Kurylo et al. 1991).

Müri et al. (1996b) also describe a similar information flow from posterior to anterior cortical regions during saccade task performance. Using TMS, they studied memory-guided saccades with a memorization period of 2,000 ms and suggested that PPC was active during the early phase of this period (260 ms after target presentation), which was then followed by DLPFC activation at a later stage (700–1,500 ms after target presentation). However, this mainly concerns the information flow during the memorization period of a memory-guided saccade and not for the preparation of saccades per se. PPC was active again at 80 ms after the extinction of the central fixation point that served as the go-signal. In AS (our study), PPC was active at 80 ms and FEF (and probably also the frontal regions including DLPFC) at 100 ms after the target presentation (i.e., the go-signal). Thus the time of PPC activation after the go-signal would roughly correspond between the two studies (in their study 100 ms after the go-signal and in ours 80 ms).

Problems in interpreting the results

Two interpretational problems should be addressed for this mapping technique. First, one may argue that TMS can delay the task performance in such a way that the area under the coil exerts a suppressive effect over the ''really'' active and necessary areas. However, we think that this is unlikely

because there was a general correspondence between the areas detected by TMS mapping and the regions activated in PET studies using oculomotor tasks.

Second, the onset delay we obtained by focal TMS was fairly modest, although significant. This would be explained as follows. In primate studies, a lesion either in the FEF or PPC produces only a mild delay in the saccade onset of VGS (Deng et al. 1986; Lynch 1992; Lynch and McLaren 1989; Schiller et al. 1980), whereas a marked delay occurs when both lesions are made in combination (Lynch 1992). It is likely that the cortical control of purposeful saccadic eye movements is distributed among various cortical and subcortical structures, not only among the FEF and PPC, which serve as the major nodes, but also among the DLPFC, SEF, superior temporal polysensory area, and the superior colliculus (Colby and Miller 1986; Funahashi et al. 1991; Ó Scalaidhe et al. 1995; Schiller et al. 1980; Schlag and Schlag-Rey 1987; Tian and Lynch 1996). This kind of redundancy may support the stable performance of saccades because at least two or more of these systems should be destroyed before a measurable change occurs.

We thank Dr. Shujiro Sugita for helpful technical assistance.

This study was supported by grants from the JSPS (the Japan Society for the Promotion of Science) fellowships for young scientists, the Brain Science Foundation, the Life Science Foundation of Japan, and by research project Grant-in-Aid for Scientific Research 9670640 from the Ministry of Education, Science, Sports and Culture of Japan.

Address for reprint requests: Y. Terao, Dept. of Neurology, Division of Neuroscience, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.

Received 3 November 1997; accepted in final form 9 April 1998.

REFERENCES

AMASSIAN, V. E., CRACCO, R. Q., MACCABEE, P. J., CRACCO, J. B., RUDELL, A. P., AND EBERLE, L. Suppression of visual perception by magnetic coil of human occipital cortex. *Electroencephalogr. Clin. Neurophysiol.* 74: 458–462, 1989.

AMASSIAN, V. E., MACCABEE, P. J., CRACCO, R. Q., CRACCO, J. B., RUDELL, A. P., AND EBERLE, L. Measurement of information processing delays in human visual cortex with repetitive magnetic coil stimulation. *Brain Res.* 605: 317–321, 1993.

ANDERSEN, R. A. Visual and eye movement functions of the posterior parietal cortex. In: *Annual Review of Neuroscience*, edited by W. M. Cowan, E. M. Shooter, C. F. Stevens, and R. F. Thompson. California: Annual Reviews, 1989, p. 377–403.

ANDERSON, T. J., JENKINS, I. H., BROOKS, D. J., HAWKEN, M. B., FRACKOWIAK, R.S.J., AND KENNARD, C. Cortical control of saccades and fixation in man. *Brain* 117: 1073–1084, 1994.

BARASH, S., BRACEWELL, R. M., FOGASSI, L., GNADT, J. W., AND ANDERSEN, R. A. Saccade-related activity in the lateral intraparietal area. I. Temporal properties; comparison with area 7a. *J. Neurophysiol.* 66: 1095–1108, 1991a.

BARASH, S., BRACEWELL, R. M., FOGASSI, L., GNADT, J. W., AND ANDERSEN, R. A. Saccade-related activity in the lateral intraparietal area. II. Spatial properties. *J. Neurophysiol.* 66: 1109–1124, 1991b.

BARRETT, G., SHIBASAKI, H., AND NESHIGE, R. Cortical potentials preceding voluntary movement: evidence for three periods of preparation in man. *Electroencephalogr. Clin. Neurophysiol.* 63: 327–339, 1986.

BECKERS, G., CANAVAN, A.G.M., ZANGEMEISTER, W. H., AND HÖMBERG, V. Transcranial magnetic stimulation of human frontal and parietal cortex impairs programming of periodic saccades. *Neuro-ophthalmol.* 12: 289–295, 1992.

BOCH, R. A. AND GOLDBERG, M. E. Participation of prefrontal neurons in the preparation of visual guided eye movements in the rhesus monkey. *J. Neurophysiol.* 61: 1064–1084, 1989.

BRUCE, C. J. AND GOLDBERG, M. E. Primate frontal eye fields. I. Neurons discharging before saccades. *J. Neurophysiol.* 53: 603–635, 1985.

BRUCE, C. J., GOLDBERG, M. E., BUSHNELL, M. C., AND STANTON, G. B. Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *J. Neurophysiol.* 54: 714–734, 1985.

COHEN, L. G., STEFANIA, B., SATO, S., KUFTA, C., AND HALLETT, M. Attenuation in detection of somatosensory stimuli by transcranial magnetic stimulation. *Electroencephalogr. Clin. Neurophysiol.* 81: 366–376, 1991.

COLBY, C. L., DUHAMEL, J.-R., AND GOLDBERG, M. E. Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *J. Neurophysiol.* 76: 2841–2852, 1996.

COLBY, C. L. AND MILLER, E. K. Eye movement related responses of neurons in superior temporal polysensory area of macaque. *Soc. Neurosci. Abstr.* 12: 1184, 1986.

DARBY, D. G., NOBRE, A. C., THANGARAJ, V., EDELMAN, R., MESULAM, M.-M., AND WARACH, S. Cortical activation in the human brain during lateral saccades using EPISTAR functional magnetic resonance imaging. *Neuroimage* 3: 53–62, 1996.

DAY, B. L., ROTHWELL, J. C., THOMPSON, P. D., MAERTENS DE NOORTHOUT, A., NAKASHIMA, K., SHANNON, K., AND MARSDEN, C. D. Delay in the execution of voluntary movement by electrical or magnetic brain stimulation in intact man. *Brain* 112: 649–663, 1989.

DEECKE, L., SCHEID, P., AND KORNHUBER, H. H. Distribution of readiness potential, premotion positivity and motor potential of the human motor cerebral cortex preceding voluntary finger movements. *Exp. Brain Res.* 7: 158–168, 1969.

DENG, S. Y., GOLDBERG, M. E., SEGRAVES, M. A., UNGERLEIDER, L. G., AND MISHKIN, M. The effect of unilateral ablation of the frontal eye fields on saccadic performance in the monkey. In: *Adaptive Processes in Visual and Oculomotor Systems*, edited by E. L. Keller and D. S. Zee. Oxford, UK: Pergamon, 1986, p. 201–208.

DORICCHI, F., PERANI, D., INCOCCIA, C., GRASSI, F., CAPP, S. F., BETTINARDI, V., GELATI, G., PIZZAMIGLIO, L., AND FAZIO, F. Neural control of fast-regular saccades and antisaccades: an investigation using positron emission tomography. *Exp. Brain Res.* 116: 50–62, 1997.

EVDOKIMIDIS, I., LIAKOPOULOS, D., CONSTATINIDIS, T. S., AND PAPAGEORGIOU, C. Cortical potentials with antisaccades. *Electroencephalogr. Clin. Neurophysiol.* 98: 377–384, 1996.

EVDOKIMIDIS, I., MERGNER, T., AND LÜCKUNG, C. H. Dependence of presaccadic cortical potentials on the type of saccadic eye movements. *Exp. Brain Res.* 83: 179–191, 1992.

FISCHER, B. AND BOCH, R. Saccadic eye movements after extremely short reaction times in monkeys. *Brain Res.* 260: 21–26, 1983.

FITZGIBBON, E. J., COLBY, C. L., WASSERMANN, E. M., PASCUAL-LEONE, A., AND HALLETT, M. Effects on saccades of the frontal eye fields. *Soc. Neurosci. Abstr.* 19: 785, 1993.

FOX, P. T., FOX, J. M., RAICHLE, M. E., AND BURDE, R. M. The role of cerebral cortex in the generation of voluntary saccades: a positron emission tomography study. *J. Neurophysiol.* 54: 348–369, 1985.

FUNAHASHI, S., BRUCE, C. J., AND GOLDMAN-RAKIC, P. S. Neuronal activity related to saccadic eye movements in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* 65: 1464–1483, 1991.

GOLDBERG, M. E. AND COLBY, C. L. Oculomotor control and spatial processing. *Curr. Opin. Neurobiol.* 2: 198–202, 1992.

GOULD, H. J., CUSICK, C. G., PONS, T. P., AND KAAS, J. H. The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. *J. Comp. Neurol.* 247: 297–325, 1986.

HALLETT, P. E. Primary and secondary saccades to goals defined by instructions. *Vision Res.* 18: 1279–1296, 1978.

HIKOSAKA, O., FUKUDA, H., KATO, M., UETAKE, K., NOMURA, Y., AND SEGAWA, M. Deficits in saccadic eye movements in hereditary progressive dystonia with marked diurnal fluctuation. In: *Hereditary Progressive Dystonia With Marked Diurnal Fluctuation*, edited by M. Segawa. New York: The Parthenon Publishing Group, 1993, p. 159–177.

JOUSMAKI, V., HAMALAINEN, M., AND HARI, R. Magnetic source imaging during a visually guided task. *Neuroreport* 7: 2961–2964, 1996.

KATO, M. AND HIKOSAKA, O. Saccade related responses of external pallidal neurons in monkey (Abstract). *Neurosci. Res. Suppl.* 17: S218, 1992.

KATO, M., MIYASHITA, N., HIKOSAKA, O., MATSUMURA, M., USUI, S., AND KORI, A. Eye movements in monkeys with local dopamine depletion in the caudate nucleus. I. Deficits in spontaneous saccades. *J. Neurosci.* 15: 912–927, 1995.

KEATING, E. G., GOOLEY, S. G., PRATT, S. E., AND KESLEY, J. E. Removing

the superior colliculus silences eye movements normally evoked from stimulation of the parietal and occipital eye fields. *Exp. Brain Res.* 296: 145–148, 1983.

KURYLO, D. D. Interaction of visually guided saccades with saccades induced by electrical stimulation of the posterior parietal cortex in the monkey. *Vision Res.* 31: 2065–2073, 1991.

LUECK, C. J., INGRAM, D. A., CRAWFORD, T. J., AND KENNARD, C. The effect of transcranial magnetic stimulation on saccades in man (Abstract). *J. Physiol. (Lond.)* 434: 15P, 1990.

LYNCH, J. C. Saccade initiation and latency deficits after combined lesions of the frontal and posterior eye fields in monkeys. *J. Neurophysiol.* 68: 1913–1916, 1992.

LYNCH, J. C. AND MCLAREN, J. W. Deficits of visual attention and saccadic eye movements after lesions of parietooccipital cortex in monkeys. *J. Neurophysiol.* 61: 74–90, 1989.

MAZZONI, P., BRACEWELL, R. M., BARASH, S., AND ANDERSEN, R. A. Spatially tuned auditory responses in area LIP of Macaques performing delayed memory saccades to acoustic targets. *J. Neurophysiol.* 75: 1233–1241, 1996a.

MAZZONI, P., BRACEWELL, R. M., BARASH, S., AND ANDERSEN, R. A. Motor intention activity in the macaque's lateral intraparietal area. I. Dissociation of motor from sensory memory. *J. Neurophysiol.* 76: 1439–1456, 1996b.

MEYER, B.-U., BRITTON, T. C., KLOTEN, H., STEINMETZ, H., AND BENECKE, R. Coil placement in magnetic brain stimulation related to skull and brain anatomy. *Electroencephalogr. Clin. Neurophysiol.* 81: 38–46, 1991.

MOSTER, M. AND GOLDBERG, G. Topography of scalp potentials preceding self-initiated saccades. *Neurology* 40: 644–648, 1990.

MÜRI, R. M., HESS, C. W., AND MEIENBERG, O. Transcranial stimulation of the human frontal eye field by magnetic pulses. *Exp. Brain Res.* 86: 219–223, 1991.

MÜRI, R. M., IBA-ZIZEN, M. T., DEROSIER, C., CABANIS, E. A., AND PIERROT-DESEILLIGNY, C. Location of the human posterior eye field with functional magnetic resonance imaging. *J. Neurol. Neurosurg. Psychiatry* 60: 445–448, 1996a.

MÜRI, R. M., VERMERSCH, A.-I., RIVAUD, S., GAYMARD, B., AND PIERROT-DESEILLIGNY, C. Effects of single-pulse transcranial magnetic stimulation over the prefrontal and posterior parietal cortices during memory-guided saccades in humans. *J. Neurophysiol.* 76: 2102–2106, 1996b.

Ó SCALAIDHE, S. P., ALBRIGHT, T. D., RODMAN, H. R., AND GROSS, C. G. Effects of superior temporal polysensory area lesions on eye movements in the Macaque monkey. *J. Neurophysiol.* 73: 1–19, 1995.

O'SULLIVAN, E. P., JENKINS, I. H., HENDERSON, L., KENNARD, C., AND BROOKS, D. J. The functional anatomy of remembered saccades: a PET study. *Neuroreport* 6: 2141–2144, 1995.

OYACHI, H. AND OTSUKA, K. Transcranial magnetic stimulation of the posterior parietal cortex degrades accuracy of memory guided saccades in humans. *Invest. Ophthalmol. Vis. Sci.* 36: 1–9, 1995.

PAUS, T. Location and function of the human frontal eye-field: a selective review. *Neuropsychologia* 34: 475–483, 1996.

PETIT, L., CLARK, V. P., INGEHOLM, J., AND HAXBY, J. V. Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fMRI. *J. Neurophysiol.* 77: 3386–3390, 1997.

PETIT, L., TZOURIO, N., ORSSAUD, C., PIETRZYK, U., BERTHOZ, A., AND MAZOYER, B. Functional neuroanatomy of the human visual fixation system. *Eur. J. Neurosci.* 7: 169–174, 1995.

PETRIDES, M. AND PANDYA, D. N. Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *J. Comp. Neurol.* 228: 105–116, 1984.

PIERROT-DESEILLIGNY, C., RIVAUD, S., GAYMARD, B., AND AGID, Y. Cortical control of memory guided saccades in man. *Exp. Brain Res.* 83: 607–617, 1991.

PIERROT-DESEILLIGNY, C., RIVAUD, S., GAYMARD, B., MÜRI, R. M., AND VERMERSCH, A.-I. Cortical control of saccades. *Ann. Neurol.* 37: 557–567, 1995.

PRATT, H., BLEICH, N., AND BERLINER, E. Short latency visual evoked fields in man. *Electroencephalogr. Clin. Neurophysiol.* 54: 55–62, 1982.

PRATT, H., MARTIN, W. H., BLEICH, N., ZAAROOR, M., AND SCHACHAM, S. E. A high-intensity, goggle-mounted flash stimulator for short-latency visual evoked potentials. *Electroencephalogr. Clin. Neurophysiol.* 92: 469–472, 1994.

PRIORI, A., BERTOLASI, L., ROTHWELL, J. C., DAY, B. L., AND MARSDEN, C. D. Some saccadic eye movements can be delayed by transcranial magnetic stimulation. *Brain* 116: 355–367, 1993.

SCHILLER, P. H., TRUE, S. D., AND CONWAY, J. L. Deficits in eye movements following frontal eye-field and superior colliculus ablations. *J. Neurophysiol.* 44: 1175–1189, 1980.

SCHLAG, J. AND SCHLAG-REY, M. Evidence for supplementary eye field. *J. Neurophysiol.* 57: 179–200, 1987.

SCHLAG-REY, M., AMADOR, N., SANCHEZ, H., AND SCHLAG, J. Antisaccade performance predicted by neuronal activity in the supplementary eye field. *Nature* 390: 398–401, 1997.

SEYAL, M., MASUOKA, L. K., AND BROWNE, J. K. Suppression of cutaneous perception by magnetic pulse stimulation of the human brain. *Electroencephalogr. Clin. Neurophysiol.* 85: 397–401, 1992.

SEYAL, M., RO, T., AND RAFAL, R. Increased sensitivity to ipsilateral cutaneous stimuli following transcranial magnetic stimulation of the parietal lobe. *Ann. Neurol.* 38: 264–267, 1995.

SEYAL, M., SIDDIQUI, I., AND HUNDAL, N. S. Suppression of spatial localization of a cutaneous stimulus following transcranial magnetic pulse stimulation of the sensorimotor cortex. *Electroencephalogr. Clin. Neurophysiol.* 105: 24–28, 1997.

SHIBASAKI, H., BARRETT, G., HALLIDAY, E., AND HALLIDAY, A. M. Components of the movement related cortical potential and their scalp topography. *Electroencephalogr. Clin. Neurophysiol.* 49: 213–226, 1980.

SHIBUTANI, H., SAKATA, H., AND HYVARINEN, J. Saccade and blinking evoked by microstimulation of the posterior parietal association cortex of the monkey. *Exp. Brain Res.* 55: 1–8, 1984.

STANTON, G. B., BRUCE, C. J., AND GOLDBERG, M. E. Topography of projections to posterior cortical areas from the Macaque frontal eye fields. *J. Comp. Neurol.* 353: 291–305, 1995.

SWEENEY, J. A., MINTUN, M. A., KWEE, S., WISEMAN, M. B., BROWN, D. L., ROSENBERG, D. R., AND CARL, J. R. Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *J. Neurophysiol.* 75: 454–468, 1996.

TERAO, Y., UGAWA, Y., SUZUKI, M., SAKAI, K., GEMBA-SHIMIZU, K., AND KANAZAWA, I. Shortening of the simple reaction time by peripheral electrical and sub-motor-threshold magnetic cortical stimulation. *Exp. Brain Res.* 115: 541–545, 1997.

THICKBROOM, G. W. AND MASTAGLIA, F. L. Cerebral events preceding self-paced and visually triggered saccades. A study on presaccadic potentials. *Electroencephalogr. Clin. Neurophysiol.* 62: 277–289, 1985.

THICKBROOM, G. W., STELL, R., AND MASTAGLIA, F. L. Transcranial stimulation of the human frontal eye field. *J. Neurol. Sci.* 144: 114–118, 1996.

THOMPSON, K. G., HANES, D. P., BICHOT, N. P., AND SCHALL, J. D. Perceptual and motor processing stages identified in the activity of macaque frontal eye field neurons during visual search. *J. Neurophysiol.* 76: 4040–4055, 1996.

TIAN, J.-R. AND LYNCH, J. C. Corticocortical input to the smooth and saccadic eye movement subregions of the frontal eye field in *Cebus* monkeys. *J. Neurophysiol.* 75: 2754–2771, 1996.

UESAKA, Y., UGAWA, Y., YUMOTO, M., SAKUTA, M., AND KANAZAWA, I. Giant somatosensory evoked magnetic field in patients with myoclonic epilepsy. *Electroencephalogr. Clin. Neurophysiol.* 87: 300–305, 1993.

WESSEL, K. AND KÖMPF, D. Transcranial magnetic brain stimulation: lack of oculomotor response. *Exp. Brain Res.* 86: 216–218, 1991.

YAMAMOTO, T., WILLIAMSON, S. J., KAUFMAN, L., NICHOLSON, C., AND LLINÁS, R. Magnetic localization of neuronal activity in the human brain. *Proc. Natl. Acad. Sci. USA* 85: 8732–8736, 1988.

ZANGEMEISTER, W. H., CANAVAN, A.G.M., AND HOEMBERG, V. Frontal and parietal transcranial magnetic stimulation (TMS) disturbs programming of saccadic eye movements. *J. Neurol. Sci.* 133: 42–52, 1995.