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Locating the Human Frontal Eye Fields With Transcranial Magnetic Stimulation

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ABSTRACT

The variability in the location and function of the human frontal eye fields (FEFs) was assessed using transcranial magnetic stimulation (TMS). Ten subjects performed a saccadic eye movement task previously shown to be influenced by TMS of the FEFs. A sequence of points over the prefrontal cortex was stimulated until an effective site of the TMS was found that induced contralateral saccade delays. In 7 out of the 10 subjects, we were able to localize a region in the prefrontal cortex that when stimulated produced delays in the execution of contralateral saccadic eye movements. The location of this functionally defined FEF region across these subjects was approximately 1.5 cm anterior to the motor hand area, although there was considerable variability in this measure. In the remaining 3 subjects, no site within our circumscribed probing was found that when disrupted with TMS produced delays in contralateral saccadic eye movements. The inter-individual differences in the location and function of the FEFs highlights the importance of using functional as well as anatomical landmarks when attempting to localize brain structures.

Typically when we open our eyes, our visual systems are bombarded with an enormous mass of information that seems so effortlessly processed. One mechanism through which we effectively cope with all this information is through selective sampling and integration of pertinent visual information with attention and eye movements. In our everyday lives, our attention system is usually tightly coupled with the eye movement system such that our eyes shift via saccades to locations of the world that are of interest to us. How the brain generates these shifts of attention and saccadic eye movements to select relevant information has been a topic of considerable interest. Here we explore regions of the prefrontal cortex with transcranial magnetic stimulation (TMS) to more precisely determine the variability in the location and function of the frontal eye fields (FEFs) in the generation of saccadic eye movements.

It has been previously shown that patients with lesions to the prefrontal cortex have difficulties in suppressing reflexive saccades (Guitton, Buchtel, & Douglas, 1985; Ladavas, Zeloni, Zaccara, & Gangemi, 1997; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991). The neurophysiological mechanisms underlying these disinhibited reflexive saccades after prefrontal damage has been suggested to involve cortico-collicular inhibition. For example, in a series of studies reported by Rafal and colleagues, patients with chronic unilateral lesions involving the FEFs were administered different types of saccadic eye movement tasks. In one study (Henik, Rafal, & Rhodes, 1994), two different types of eye movements were required of the patients: a reflexive, visually-guided task with saccades made towards a lateralized light onset and a voluntary, endogenous task with saccades required in the lateral direction indicated by a central arrow. Henik et al.

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(1994) found that their FEF lesioned patients had increased latencies for voluntarily generated saccades towards the contralesional field. In addition, in that same study it was shown that latencies for reflexive visually guided saccades towards the ipsilesional field were abnormally inflated. From these results, Henik et al. proposed that the FEFs are normally involved with generating contralateral voluntary eye movements as well as facilitating ipsilateral reflexive eye movements via a fronto-collicular interaction. Specifically, it was proposed that the FEF lesions disinhibited the colliculus on the ipsilesional side, which consequently resulted in an increased inhibition of the opposite colliculus. The delayed ipsilateral reflexive saccades have been attributed to this increased inhibition of the contralesional colliculus.

More recently, the role of fronto-collicular interactions was further explored in a group of similar patients on an antisaccade task where patients were asked to make saccades away from a visual onset presented in the contralesional or ipsilesional visual field (Rafal, Machado, Ro, & Ingle, 2000). In this antisaccade study, it was shown that patients with lesions involving the FEFs made more erroneous reflexive glances towards visual onsets in the contralesional hemifield. This suggests that the disinhibition of the ipsilesional colliculus from the FEF lesions not only results in a contralesional inhibition of the colliculus as shown in the Henik et al. (1994) study, but also a hypersensitivity of the ipsilesional colliculus in generating contralesional reflexive saccades. The picture emerging from these patient studies is a complex interaction of fronto-collicular contributions to the coordination of generating different types of saccadic eye movements.

Recently we, as well as others (e.g., Priori, Bertolasi, Rothwell, Day, & Marsden, 1993; Terao et al., 1998; Thickbroom, Stell, & Mastaglia, 1996; Zangemeister, Canavan, & Hoemberg, 1995), have sought converging evidence for the role of the human FEFs in different forms of saccadic eye movements using transcranial magnetic stimulation (for recent reviews of TMS, see Hallett, 2000; Jahanshahi & Rothwell, 2000; Walsh & Cowey, 2000). TMS is a technique that allows one to safely induce transient and reversible ''brain lesions.'' Unlike most of the other techniques available to cognitive neuroscientists, TMS has both high spatial and temporal resolution and can determine whether a given region of the brain is necessary for, not just correlated with, a particular psychological function. The spatial resolution of the technique is dependent on the configuration of the stimulating coil. Our coil with the highest spatial resolution has a maximum focus at the intersection of two small circular components, producing a relatively small area of stimulation, small enough to induce twitches of an individual finger of the contralateral hand following motor cortex stimulation in the appropriate corresponding location. Furthermore, the coil can be placed anywhere on the surface of the head, allowing for borders of cortical regions to be precisely mapped by systematically moving the coil in very small increments. The temporal specificity of the technique is dependent on the size and orientation of the cells in the area that is being stimulated, with longer lasting effects of stimulation over the motor cortex than the visual cortex. Thus the disruption of cortical activity with TMS is in the order of tens to hundreds of milliseconds depending on the susceptibility of the region being stimulated.

TMS has been used to investigate issues in neuropsychology by experimentally inducing transient lesions, thereby producing transient behavioral deficits similar to those observed by neuropsychological patients who experienced natural forms of brain damage. For example, some studies with the technique have shown that stimulation of the visual cortex can produce scotomas and phosphenes (Amassian et al., 1989), impairment of motion perception (Beckers & Zeki, 1995; Hotson, Braun, Herzberg, & Boman, 1994; Walsh, Ellison, Battelli, & Cowey, 1998), and that stimulation of the parietal cortex can produce attentional biases, providing clues to the underlying mechanisms observed in patients with hemispatial neglect (Ashbridge, Walsh, & Cowey, 1997; Fierro et al., 2000; Seyal, Ro, & Rafal, 1995). Recently, we have also adopted TMS to investigate the role of the FEFs in generating saccadic eye movements and to localize this region within the frontal lobes of humans.

Some further evidence for differential roles of the FEFs and superior colliculus in generating different forms of saccadic eye movements was demonstrated in a study using single-pulse TMS (Ro, Henik, Machado, & Rafal, 1997). In that study, it was shown that TMS of the prefrontal cortex, including the FEFs, delayed contralateral endogenous saccades. However, there was no influence of the TMS on reflexive, visually guided saccades suggesting that the disruption of neuronal activity with TMS was restricted to the cortex. They further suggested that the cortico-collicular modulations observed in the studies with chronic patients might only take place after a considerable period of time and reorganization following the brain lesion.

In a follow-up study, it was demonstrated by mapping with TMS and MRI that stimulation of the prefrontal cortex in an area approximately 2 cm anterior to the motor hand area in the frontal eye fields delayed contralateral endogenous saccades (Ro, Cheifet, Ingle, Shoup, & Rafal, 1999). This localization was consistent with reports of localization of the human FEFs with functional neuroimaging (Paus, 1996). Only 2 subjects were extensively mapped in that follow-up TMS study, however, and this 2 cm anterior to the motor hand area landmark for the FEFs was determined by the area of common overlap between the two subjects. In fact, both subjects in that study had more extensive regions in prefrontal cortex that when disrupted with TMS, induced delays in contralateral saccadic eye movements. Thus, the generalizability of this localization to other subjects is currently unclear. The main goal of the current experiment was to functionally determine with TMS whether there is a consistent spatial separation between the motor cortex and the frontal eye fields in a larger number of subjects.

METHOD

Subjects

After informed consent, 10 subjects (7 females) participated in this experiment. All subjects reported having normal or corrected vision and no history of any neurological or psychiatric disorders at the time of testing. They had participated in other TMS studies in our laboratory, but had not been subjects in any of our previous eye movement studies with TMS. The mean age of the subjects was 23.9. The mean head circumference of each subject was 56.8 cm (see Table 1). All were recruited from the Rice University campus and were paid for their participation.

Table 1. Measurements of Each Subject's TMS Threshold Intensity and Head Size and Position of the Initial Localization of the Motor Cortex.

Subject	Intensity (%)		Measurements of scalps (in cm)						
	Motor	Test	HC	NI	LR	MN	MI	LM	RM
1	58.0	64.0	55.0	32.0	30.0	16.2	15.7	18.2	13.2
2	50.0	55.0	56.5	36.5	30.5	16.2	21.2	18.8	11.8
3	56.0	62.0	57.5	36.0	30.5	18.2	16.2	19.8	11.8
4	55.0	60.0	57.0	36.0	30.5	17.2	18.7	18.8	12.2
5	64.0	70.0	55.5	37.0	29.5	17.7	19.2	19.2	10.6
6	48.0	53.0	60.0	34.0	30.0	17.7	18.7	22.2	8.2
7	48.0	53.0	56.0	34.0	29.0	16.0	17.7	19.2	10.2
8	62.0	68.0	56.0	33.0	29.5	15.2	18.7	20.2	9.6
9	68.0	75.0	54.0	32.0	30.0	15.7	16.7	19.8	11.2
10	65.0	71.5	60.0	39.5	32.5	19.2	20.2	21.2	12.8
Mean	57.4	63.2	56.8	35	30.2	17.0	18.3	19.8	11.2

Note. All distances were measured along the scalp. HC: head circumference; NI: distance from the nasion to the inion; LR: distance from the top of left ear to the top of the right ear. MN: distance from the right motor hand area to the nasion; MI: distance from the inion to the right motor hand area; LM: distance from the left ear to the right motor hand area; RM: distance from the right ear to the right motor hand area.

Apparatus, Stimulus, and Procedure

The apparatus, stimuli, and procedures are very similar to our previous study localizing the human FEFs with TMS and MRI (Ro et al., 1999). The position of the left eye was monitored using an Applied Science Laboratories (Bedford, Massachusetts) Eye-Trac 210 that was connected to the parallel port of the computer. The 8-bit digital output from the eye movement monitor was sampled at a rate of 1000 Hz and was stored by the computer after each trial. Following the experimental session, the digitized data representing eye position were filtered with a 200 Hz low-pass filter. Saccadic eye movement latencies were then identified and defined in this experiment as the point at which the velocity of the eye movement exceeded 50 degrees per second.

Transcranial magnetic stimulation was conducted using a Cadwell Laboratories MES-10 stimulator (Kennewick, Washington). The MES-10 stimulator at maximum intensity creates a 2.2 Tesla field (Cadwell, 1990). A focal, figure-eight shaped coil was used for this experiment. Each component of the figure-eight coil measured 4.5 cm in diameter with a maximum focus at the intersection of the two components. Based on the topography of activation of finger movements with this coil, which frequently produced twitches of individual digits on the contralateral hand, it is estimated that this coil consistently disrupted less than 1 cm^3 of cortex. However, the exact spatial, as well as temporal, extent of the TMS disruption is likely to be variable across brain areas and subjects due to differences in neuronal architecture.

An IBM compatible personal computer was used to trigger the MES-10, to record the eye position, and for stimulus presentation. Millisecond (ms) timing, used to trigger the MES-10 and to sample the eye position, was achieved by setting the 8253 chip of the computer to millisecond ticks. The computer was connected to a Sony Trinitron Multiscan 220 GS video graphics array (VGA) stimulus monitor via a Diamond Monster Fusion video graphics adapter. The timing of the visual displays was controlled by the vertical synchronization of the computer monitor at 16.7 ms intervals (60 Hz).

Prior to the start of the experiment, we localized the hand area of the right motor cortex with TMS. After localizing the area of motor cortex that produced the most reliable, visible contraction of the contralateral hand at a suprathreshold TMS output intensity, a scalp marking was made with a grease pencil on each subject over this location. There was more than one optimal location in 2 subjects (see Table 2). This marking served as the physiological landmark and origin for our further explorations in the prefrontal cortex. The output intensity of the TMS device was then decreased and the coil positioned until a visible contraction of the hand was barely visible. This location and intensity setting was defined as the hand area motor threshold point. The mean TMS threshold intensity across the sessions and subjects was 57.4% of maximum output and the mean intensity used for the experiment was 63.2% of maximum output (see Table 1).

The subjects were then seated 57 cm from the computer monitor in a dimly and diffusely lit, sound-attenuated room. Their chins were placed into a chin-rest to minimize movement of the head. A small filled circle that measured 0.1° in diameter served as the initial fixation point and was presented in the center of

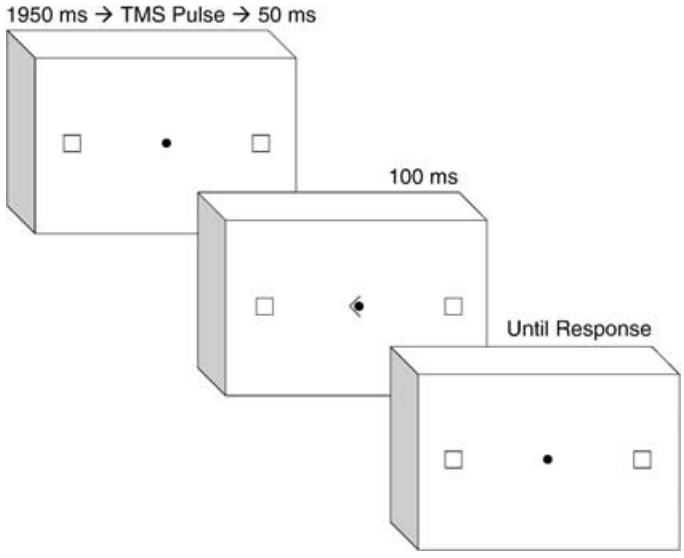

Fig. 1. Depicts an example of the sequence of stimulus events.

the monitor until the start of each trial. Two unfilled squares that measured 1° on each side were used as marker boxes and were present throughout the experiment. These boxes were placed 10° to the left and right of the fixation point. Following an intertrial interval of 2000 ms, a go signal, which was an arrowhead, was presented in the center of the display. The arrowhead measured 1° in height and 0.5° in width. The direction of the go signal was randomly determined on each trial and was presented for 100 ms (see Fig. 1). All stimuli were light gray on a black background.

The subjects were then instructed to keep their eyes on fixation until the arrowhead go signal appeared. The subjects were instructed to make a saccade, as quickly and as accurately as possible, to the box that the arrowhead was pointing towards. Following the saccade, the subjects were asked to return their eyes back to the fixation point and to maintain fixation until the next go signal appeared. Subjects were asked to suppress blinks during a trial and to ignore the TMS pulse as best as possible. The subjects completed 50 trials within a block, 25 trials for each eye movement direction.

TMS was administered over the right hemisphere in all subjects while they performed blocks of the eye movement task. TMS of different sites in the rostral direction from hand area of the motor cortex was conducted at small separations in variable locations (see Table 2). Blocks of eye movement trials were run

Table 2. Mean Saccadic Latencies (RT), Standard Deviations (*SD*), Number of Trials in Session (*n*), and *p* Values for the Different TMS Sites in All Subjects. Subjects 4 and 8 Each Had One Session Without TMS.

Subject #	Motor CX		TMS site		Contralateral			Ipsilateral			*p* value
	x	*y*	*x*	*y*	RT	*SD*	*n*	RT	*SD*	*n*	
1	0	0	2	0	216	31.8	22	202	16.0	22	.039
1	0	0	2.5	0	205	25.9	24	200	31.7	21	*ns*
1	0	0	2	−0.5	218	20.7	23	207	31.4	23	.088
1	0	0	2	0	220	21.7	23	200	15.4	24	.001
2	0	0	2	0	184	32.4	19	186	27.5	21	*ns*
2	0	0	1.8	0	187	29.3	22	187	23.2	19	*ns*
2	0	0	1.3	0	174	22.0	22	159	16.6	19	.010
3	0	0	2	0	232	29.4	24	235	32.3	24	*ns*
3	0	0	1.5	0	237	17.0	24	247	24.1	24	*ns*
3	0	0	1.5	0	222	28.6	22	220	21.0	23	*ns*
3	0	0	2	0	227	21.6	24	239	26.7	23	*ns*
4	0	0	2	0	213	26.9	24	224	23.5	19	*ns*
4	0	0	1.5	0	217	18.1	17	219	18.8	19	*ns*
4	0	0	2	0	232	20.1	21	227	21.2	22	*ns*
4	0	0	2	−0.5	227	19.1	20	225	19.0	19	*ns*
4	0.5	−0.5	2	0	205	21.2	20	215	18.3	23	*ns*
4	0.5	−0.5	1.5	−0.5	202	18.5	22	217	29.4	22	*ns*
4	1.5	0	1.5	−0.5	202	14.7	23	202	18.8	23	*ns*
4	1.5	0	no TMS		242	14.2	23	236	22.1	24	*ns*
4	2	−1.5	2	0	205	17.4	24	205	25.1	24	*ns*
4	1.5	−2.5	2	0	200	21.6	25	201	18.0	21	*ns*
4	1.5	−2.5	2	−0.7	208	25.0	25	200	25.2	22	*ns*
4	1.5	−2.5	1.5	0	211	15.5	22	205	20.9	22	*ns*
5	0	0	2	0	197	28.8	24	189	30.5	22	*ns*
5	0	0	1.5	0	224	27.6	22	214	30.6	22	*ns*
5	0	0	1.5	−0.5	217	21.1	22	200	25.0	19	.009
6	0	0	2	0	258	24.6	23	255	24.3	19	*ns*
6	0	0	1.5	0	273	25.1	23	256	27.2	22	.018
7	0	0	2	0	269	26.0	19	265	36.1	20	*ns*
7	0	0	1.5	0	260	28.8	21	259	30.7	22	*ns*
7	1.3	0	2	0	289	37.2	20	270	29.8	20	.041
7	1.3	0	1.5	0	321	29.4	17	299	39.1	20	.033
7	1.3	0	1.5	0.5	329	51.2	22	299	59.2	19	.043

Table 2. (*continued*).

Subject #	Motor CX		TMS site		Contralateral			Ipsilateral			*p* value
	x	*y*	*x*	*y*	RT	*SD*	*n*	RT	*SD*	*n*	
8	0	0	2	0	206	26.5	22	233	24.7	22	*ns*
8	0	0	1.5	0	194	38.8	25	225	27.8	21	*ns*
8	0	0	no TMS		229	29.7	24	242	17.8	25	*ns*
8	0	0	1.5	0.5	210	45.6	24	226	25.6	24	*ns*
8	0	0	2	0.5	194	22.0	25	205	32.7	23	*ns*
9	0	0	2	0	214	32.6	23	230	35.6	22	.063
9	0	0	1.5	0	230	30.8	21	207	24.8	19	.006
10	0	0	1.5	0	225	22.5	23	221	20.2	22	*ns*
10	0	0	1.8	−0.8	207	28.1	21	212	20.1	20	*ns*
10	0	0	1.25	−0.5	221	11.4	21	213	22.8	23	.079
10	0	0	1.25	0	211	29.6	23	204	32.4	19	*ns*
10	0	0	1.25	1	211	22.1	23	197	22.7	22	.018

Note. The *x*-values indicate positions (in cm) varying along the sagittal plane, with positive values rostral and negative values caudal, and the *y*-values indicate positions (in cm) varying along the coronal plane, with positive values dorsal and negative values ventral. For the "Motor CX" column, $(x, y) = (0, 0)$ indicates the first localized motor hand area. If $(x, y) \neq (0, 0)$, the value indicates the location of another area that elicited hand movements at the same threshold intensity. In the "TMS site" column, all (x, y) pairs are defined relative to the hand area in the same row. For example, the fifth TMS site of Subject 4 has $(0.5, -0.5)$ in the hand area column and $(2, 0)$ in the TMS site column. Therefore, the location of the TMS site is $(2+0.5, 0-0.5) = (2.5, -0.5)$ relative to the first localized hand area. CX = Cortex

at each TMS position until a site that delayed the contralateral eye movements was found. The non-effective TMS sites served as the within-subject control conditions in this study since everything apart from the TMS coil position was identical. Our initial placement of the TMS coil was 2 cm anterior to the motor hand area since this region was the area of common overlap in our previous mapping study with TMS and MRI (Ro et al., 1999). We then moved the coil in small steps until a TMS site was found that induced delays in contralateral eye movements. In all blocks, a TMS pulse was administered on each trial 50 ms before the onset of the go signal. This SOA setting was determined to be optimal in our previous studies. The axis of the TMS coil was angled at approximately 90° from the mid-sagittal axis while the subjects were seated upright and performed the eye movement task.

RESULTS

The location of the motor hand area with respect to different head landmarks, as well as other properties of each subject, is shown in Table 1. In two subjects, different regions of the motor hand area were localized and used as references in different testing sessions. The spatial relationship between the different TMS sites and the respective motor hand area is listed in Table 2 for each run in each subject. Trials with saccades made in the wrong direction or with saccade latencies faster or slower than two standard deviations (*SDs*) from the mean were excluded from analysis. The remaining latencies for contralateral and ipsilateral saccades in each session were subjected to a one-tailed *t* test. The results from the different TMS sites are graphically depicted in the top two rows of Figure 2 for each subject.[1] The bottom row of Figure 2 superimposes all of the data from the top two rows. The numerical data are presented in chronological order of testing in Table 2.

Across the 10 subjects, 10 out of 43 (23%) TMS sites induced significant delays in saccadic onset latencies in the contralateral direction (see Fig. 2 and Table 2). These active sites were found in 7 out of 10 subjects. The remaining

[1]The two-dimensional plots in this figure were generated using MATLAB (Mathworks, Inc., Natick, MA).

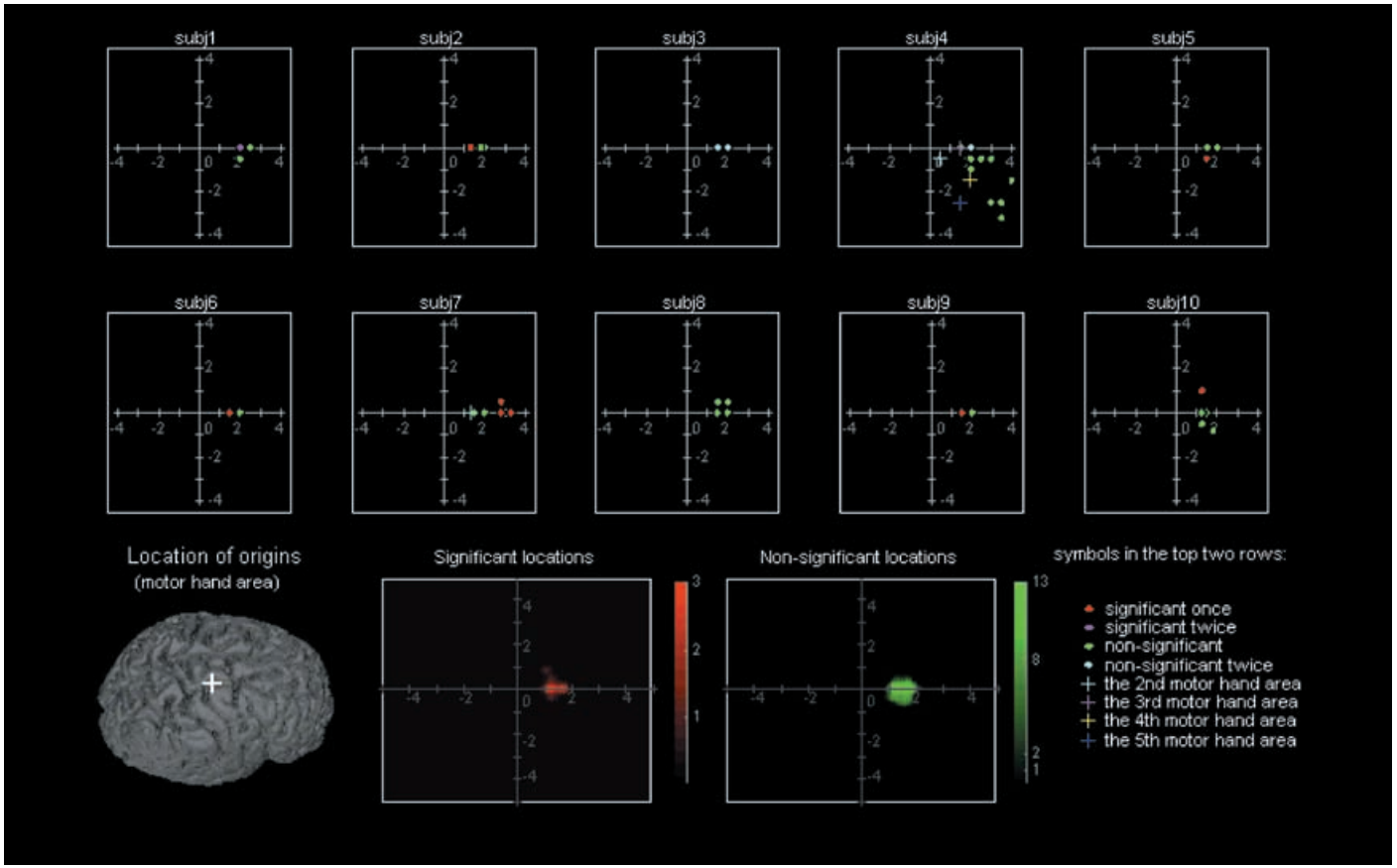

Fig. 2. Each of the ten grids in the top two rows shows the TMS locations in each subject referenced to the initial motor hand area (see Table 2). The origin of the plots represents the scalp marker placed over the motor hand area in each subject, which is schematically shown as a crosshair on the 3D volume rendered MRI scan in the leftmost portion of the bottom row. The horizontal *x*-axis represents deviations within the sagittal plane and the vertical *y*-axis for deviations within the coronal plane. The numbers within each grid represent the deviation in centimeters from the origin, which is the location of the motor cortex. The color codes for the locations stimulated are shown in the legend in the bottom right. Green dots indicate nonsignificant sites, whereas red dots indicate significant sites. A purple dot represents locations that were tested twice and significant both times. If a location was tested twice, and was not significant both times, a cyan dot was used. The two grids in the bottom row show the significant (left grid) and the nonsignificant TMS sites (right grid) across all subjects. The number of overlapping TMS sites at the same location is represented by differences in color intensity.

sites (77%) did not turn out to be significant with our one-tailed *t* tests. Five of these nonsignificant sites would have been significant if tested with a two-tailed *t* test (sites 3-2, 3-4, 4-6, 8-1, 8-2; note that some of these conditions are in the same location with respect to the motor hand area across subjects) and five other sites would have been marginally significant in the same manner (sites 4-1, 4-5, 8-4, 8-5, 8-6; again some of these conditions are in the same location across subjects). These ''inactive'' sites were found in only 3 out of 10 subjects. The significant TMS sites spread within the region 1.25–2 cm anterior and −0.5–1 cm lateral to the right motor hand area. The locations between 1 and 2 cm anterior to the motor hand area most readily induced delays in the generation of contralateral saccades. The mean location of the FEF within the sagittal (anterior–posterior) plane as defined by our task was 1.6 cm ($SD = 0.29$) anterior to the motor hand area.[2] The mean location of the FEF within the coronal plane (medial–lateral) was −0.1 cm ($SD = 0.39$) lateral to the motor hand area. The median location was 1.5 cm directly anterior to the motor hand area. The mode location of the FEF was also 1.5 cm directly anterior to the motor hand area.

There were 3 subjects (Subjects 3, 4, and 8) in whom we were not able to locate any TMS site producing significant slower contralateral saccades. Each of these 3 subjects were the same subjects who would have showed significant ipsilateral delays if a one-tailed *t* test was used in this direction. Due to the difficulty in locating the FEFs in these 3 subjects, and the opposite response time pattern than expected, 2 of them (Subjects 4 and 8) were tested in one session without TMS. While Subject 4 did not show a bias toward either direction without TMS, Subject 8 showed significantly slower rightward saccades without TMS. Therefore, in 1 of these subjects there may be a natural tendency to execute faster leftward saccades making delays of contralateral leftward saccades with TMS more difficult to measure.

[2]To compute the mean location of the FEF across subjects, the Cartesian coordinates used to represent the stimulation sites were converted into polar coordinates, allowing any given position to be represented by a single number. The average vector of our 10 significant positions in polar coordinates was then computed and transferred back into Cartesian space.

DISCUSSION

In a larger group of subjects than our previous FEF localization study with MRI, we have shown that TMS of the region approximately 1.5 cm anterior to the motor hand is involved with the generation of voluntary endogenous saccades. When this FEF region was stimulated, the generation of saccades towards the contralateral hemifield was delayed in most of our subjects. Our previous study with TMS and MRI used a very similar protocol as the current study and demonstrated that stimulation of the cortex approximately 2 cm anterior to the motor hand area induced delays in the generation of contralateral endogenous saccades (Ro et al., 1999). This 0.5 cm posterior shift in the localization of the FEF between the previous and current study may have been due to spatial undersampling in the previous study. In that study, locations on the cortex were stimulated at 1 cm separations whereas in the current study locations were stimulated at much smaller separations, as small as 0.2 cm (see Table 2), until a site was localized that delayed contralateral saccades.

The coil in this study was maneuvered until a spot was located that induced these contralateral saccadic delays because we were interested in finding the FEFs as quickly as possible in order to probe other functions of the FEFs in visual attentional processing within the same session. Thus, there were differences in the number of sites that were probed with TMS across the subjects since the location that produced these delays were found more easily in some subjects in comparison to others. Furthermore, there may have been other locations within the prefrontal cortex that would have produced similar contralateral saccadic delays. Even though in some subjects, like in the previous study, stimulation of the cortex 2 cm anterior to the motor hand area produced delays in contralateral saccades, this

was certainly not the case for all subjects. This variability also highlights the importance of using functional criteria to localize brain regions in each subject rather than a standardized coordinate space (see Fig. 2, lower panels).

Although the cortex 1.5 cm anterior to the motor hand area was never directly stimulated in our previous FEF mapping study, it is likely that TMS of this region of cortex may have also resulted in contralateral saccadic delays in those subjects. In 1 of those 2 subjects, the hand area of the motor cortex, the cortex 1 cm anterior to it, and the cortex 2 cm anterior to the hand area all produced contralateral saccadic delays. It is therefore likely that the region 1.5 cm anterior to the motor hand area would have produced similar reaction time increases for contralateral saccades. In the other subject in that mapping study with TMS and MRI, the area of cortex 1 cm anterior to the motor hand area did not induce contralateral increases in saccadic latencies when stimulated, but the cortex 2 cm and 3 cm anterior to the motor hand area did, in addition to other regions medial and lateral to these positions. Thus, it may be that the caudal extent of the FEF in this subject may have extended posteriorly to include the cortical region located 1.5 cm anterior to the motor hand area, as in the current study.

We concluded from our previous study that the region of cortex 2 cm anterior to the motor hand area was the location of the FEF also because of its consistency with the then recent review of the neuroimaging literature on the FEFs (Paus, 1996). However, a more recent fMRI study on the FEFs using an antisaccade task found that the FEFs may be more posterior than previously thought, extending no further anterior than the lip of the precentral sulcus (Luna et al., 1998; also see Petit, Clark, Ingeholm, & Haxby, 1997). The results from the current study are also demonstrating a more posterior localization of the FEFs and are consistent with Luna et al.'s interpretation that the precentral sulcus may be the human analogue of the arcuate sulcus, where at its intersection with the principal sulcus is where the frontal eye fields are located in monkeys (Bruce & Goldberg, 1985). The cortex approximately 1.5 cm anterior to the motor hand area is likely to be very close to the precentral sulcus in most subjects.

It is important to note, however, that our precision in determining the location of the FEFs is dependent on our precision in localizing the human motor hand area, which was used as an anatomical and physiological landmark. As demonstrated in our results (see Subjects 4 and 7 in Tables 1 and 2), the motor hand area is sometimes not very focal and infrequently difficult to precisely localize. Since we used the motor hand area as a physiological landmark and because we did not fully map the borders of it or the FEFs, any variability in localizing the motor hand area will be carried over into our localization of the FEFs. However, since in most subjects there was only one clear optimal position where TMS elicited robust, visible contractions of the contralateral hand with the coil that we used, this source of error in localization of the FEFs in our study is likely to be minimal. Nonetheless, when possible, further studies that are being conducted in our laboratory are also relying on physiological, that is, behavioral, landmarks for localizing different brain regions with TMS in addition to ones based on morphology and/or spatial and anatomical relations between brain areas.

We were unable to functionally locate the FEFs in 3 subjects with TMS and our endogenous saccadic eye movement task. However, in all 3 of these subjects, there were locations in the prefrontal cortex that when stimulated induced enhancements rather than delays, that is, faster eye movements, in generating contralateral saccades. Since we used a one-tailed t test, these conditions did not achieve significance but would have had we used a two-tailed t test or a one-tailed t test in the opposite direction. It is unclear why this opposite pattern of eye movement latencies resulted in these subjects. One possibility is that the SOA between the TMS pulse and the go signal, which was selected from our previous studies, was not optimal to observe the expected effects in these subjects. If such were the case, we may have been stimulating these subjects too early or too late with respect to the eye movement go-signal, causing the effects on eye movements to be facilitatory rather than inhibitory. Such differential effects are often observed with TMS, as is most apparent with TMS over the motor cortex, which typically induces an initial activa-

tion and contraction of the corresponding limb followed by a silent period of inhibition below baseline activity (Wassermann, Pascual-Leone, & Hallett, 1994). More precise spatial as well as temporal mappings are necessary to determine the source of the differences observed in our subjects. Despite the differential effect found in 3 out of 10 subjects, the results of the present study were consistent in showing that the portion of cortex located about 1.5 cm anterior to the hand motor area is most likely to correspond to the FEF area in humans.

This study demonstrates that by using TMS as a tool for investigating brain function, we can precisely find areas within the prefrontal cortex that are involved with the generation of endogenous saccades. These results provide converging evidence with studies conducted in patients with frontal lobe lesions that demonstrate saccadic abnormalities following brain injury. By using these complementary approaches to studying brain function, we can appreciate and gain a much fuller understanding of the brain mechanisms for visually guided behaviors. Our ongoing research is now using this marker of contralateral saccadic delays following TMS of the FEFs to probe the roles of the human frontal eye fields in visual attention and other forms of cognitive processing.

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