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Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography

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ABSTRACT **Increasing interest in the role of the frontal lobe in relation to psychiatric and neurologic disorders has popularized tests of frontal function. One of these is the antisaccade task, in which both frontal lobe patients and schizophrenics are impaired despite normal performance on (pro)saccadic tasks. We used positron emission tomography to examine the cerebral blood flow changes associated with the performance of antisaccades in normal individuals. We found that the areas of the brain that were more active during antisaccades than saccades were highly consistent with the oculomotor circuit, including frontal eye fields (FEFs), supplementary motor area, thalamus, and putamen. Superior parietal lobe and primary visual cortex were also significantly more active. In contrast, prefrontal areas 46 and 9 were not more active during antisaccades than during saccades. Performance of some frontal patients on the antisaccade task has been likened to a bradykinesia, or the inability to initiate a willed movement. It is the necessity to will the movement and inhibit competing responses that intuitively linked this task to the dorsolateral prefrontal cortex in frontal patients. Our data suggest that it is the FEFs in prefrontal cortex that differentiate between conditions in which the required oculomotor response changes while the stimulus remains the same, rather than areas 46 and 9, which, in human studies, have been linked to the performance of complex cognitive tasks. Such a conclusion is consistent with single-unit studies of nonhuman primates that have found that the FEFs, the executive portion of the oculomotor circuit, can trigger, inhibit, and set the target of saccades.**

Recent interest in the role of frontal lobe dysfunction in the symptoms of a variety of psychiatric and neurologic disorders has led to the increased study of many putative frontal neuropsychological tasks (1–5). One of these, the antisaccade task (6), apparently fits the profile of a dorsolateral prefrontal task in that correct responses are not reflexive but require deliberation and planning (7).

The antisaccade task requires the subject to inhibit a saccade toward a briefly appearing peripheral target and to immediately generate a saccade to an equivalent point in the opposite hemifield without the use of a target. The increased latency of antisaccades relative to saccades has been attributed to the time necessary to cancel a reflexive saccade toward the target (8, 9). Conceiving of the task as one that requires active inhibition of a prepotent response, the reflexive saccade, lends theoretical coherence to findings of performance impairment in conditions in which frontal pathology is known (8) or suspected (10–13).

Guitton *et al.* (8) reported that patients with frontal lesions frequently either failed to inhibit the reflexive glance to the flash of a peripheral target before generating the antisaccade or successfully inhibited the reflexive glance but did not initiate the antisaccade. Because of the large size of the lesions in these patients, it was not possible to distinguish between the role of the frontal eye fields (FEFs) and more anterior frontal cortex in the behavioral deficit. However, the task demands led investigators to interpret the increased directional errors and increased latency to response in impaired populations as "executive" prefrontal dysfunction (10, 11).

However, Hallett and Adams (9) showed that antisaccade performance in normal individuals is lawfully related to saccadic performance, in that the latency of an antisaccade can be predicted from the latency of a saccade. These researchers concluded that any nonmotor component of antisaccade performance is minor.

Studies of nonhuman primates have reported results from a task similar to the antisaccade task, in which a monkey must move its hand either to a target or to a position 90 degrees counterclockwise from the target. Much of the increased latency for the hand movement appears to be associated with a "shift in the population vector"—that is, a pattern whereby premotor neurons whose directional preference is in the target direction have their maximal response first, followed by those intermediate between the target direction and the response direction, and finally by those whose preferred direction is in the location of the required motor movement (14–16). When maximal firing is from neurons whose directional preference matches that of the required motor response, the hand movement follows within 40 msec.

We used positron emission tomography (PET) to study the neural correlates of successful antisaccade performance in normal controls. If antisaccade performance taxes cognitive executive resources more than saccade performance does, we would expect to see increased activation of areas 46 and 9 and their main target in the basal ganglia, the caudate nucleus, during antisaccades. Caudate has been implicated specifically in intentional saccades (17). If antisaccade executive demands were more motor than cognitive, one would not expect areas 46 and 9 to show greater activation than they already do in saccades; instead one would expect activation of the putamen, the primary target of the FEFs and the supplementary motor area (SMA) in basal ganglia. The FEFs, on the border of the precentral gyrus and the middle frontal gyrus, are thought to inhibit the superior colliculus "visual grasp reflex" (8), and the SMA (medial area 6) has been implicated in learned motor behavior (18) and in fixation maintenance (19). We were also interested in the superior parietal lobe, implicated in the shift of attention from one hemifield to another (20), and thalamus, implicated in attentional shifts and voluntary saccades (21, 22).

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Abbreviations: PET, positron emission tomography; FEF, frontal eye field; SMA, supplementary motor area; fwhm, full width at half-maximum.

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MATERIALS AND METHODS

Subjects. Informed consent was obtained from the subjects in accordance with guidelines approved for this study by the Human Studies Committee of Massachusetts General Hospital. Twelve subjects were scanned, and 10 subjects, 6 women and 4 men, yielded usable data and were included in the analyses. Their mean age was 26.2 years (range, 22–39 years) and they had a mean of 15.7 years of education. No subject had a history of major affective disorder or psychosis as determined by the Structured Clinical Interview for DSM-III-R (23). One subject had a history of cannabis dependence in full remission for 5 years, and one subject had a history of cannabis abuse in college with no symptoms in the last 4 years. Based on a family-history interview, no subject had a relative with a psychotic disorder. Subjects had normal smooth pursuit eye movements and were screened during a 15-trial session on the antisaccade task to ensure that they could perform the task. Subjects were right-handed by self-report, with the exception of one subject who was left-handed. This subject was right-eye dominant.

PET Techniques. The PET camera was a General Electric PC4096 15-slice whole-body scanner used in the stationary mode. Detailed descriptions of the reconstruction software have been published (24). The slices are contiguous with a 6.5-mm center-to-center distance (axial field equal to 97.5 mm) and intrinsic axial resolution of 6.0 mm full width at half-maximum (fwhm). Image reconstruction was performed with a measured attenuation correction from transmission scans and a Hanning-weighted reconstruction filter to an in-plane resolution of 8.0 mm fwhm. The reconstruction process includes routine corrections for random coincidences, counting losses due to dead time in the camera electronics and scattered radiation.

The $C^{15}O_2$ inhalation technique was used. The subject's head was aligned in a head-holder and held in place with a thermoplastic mask. A nasal cannula was placed at the subject's nose and attached to the gas source. A mask attached to the vacuum tube was placed over the subject's nose and mouth. The subject was instructed to breathe through the nose. The concentration of the gas, ^{15}O-labeled CO_2, was 80 mCi/liter (1 mM = 37 MBq) with a flow rate of 2 liters/min. During a scan the counts rise rapidly in the brain, with maximum counts being 100,000–200,000 events per second. For the emission scans, the subject began inhaling the gas 15 sec after beginning the task. Data were collected for 1 min. By a rapid inhalation exchange reaction in the lungs, the $C^{15}O_2$ is converted to water in the lungs and is distributed throughout the body, including the brain, in proportion to blood flow.

The $C^{15}O_2$ buildup technique has been studied by Lammertsma *et al.* (25). Unpublished work in the Massachusetts General Hospital PET laboratory has confirmed that the integrated counts over inhalation periods up to 90 sec is a linear function of the flow over the expected range; that is, the amount of radiation that gets into tissue is proportional to blood flow. Therefore data in units of flow relative to whole brain can be produced without radial artery cannulation.

Activation Paradigms. A Macintosh computer was mounted on a table above the subject so that the computer screen was fully visible to the subject. The distance from the eye to the stimulus was 52 cm. All subjects were scanned twice in the two conditions, once while performing the saccade task and once while performing the antisaccade task. During each scan, the subject completed 45 trials. A trial began with the appearance of a filled circle of ≈0.5-degree diameter (the fixation point) at the center of the screen for 800, 1000, or 1200 msec. Coincident with the fixation point's offset, a peripheral target, a 1 degree-by-1 degree filled square, appeared for nominally 100 msec 15 degrees to the left or right of the central point. Direction was randomized with the restrictions that the peripheral target appear the same number of times to the left and right in each 15-sec interval and that it appear no more than four times consecutively on the same side. After the peripheral target appearance, the screen remained blank for 1 sec to allow the subject to make a saccade either toward the target location (saccade condition) or to the mirror location on the opposite side (antisaccade). The same stimulus files were used in both tasks; only the instructions differed. The subjects were instructed not to wait at the periphery after making a saccade, but to return their eyes immediately to center to await the reappearance of the fixation point. Order of presentation of the two conditions was counterbalanced, and four different stimulus files were used to prevent subjects from learning any one sequence.

To monitor the subject's horizontal eye movements, silver chloride skin electrodes were placed near the outer canthi and a ground electrode was placed at mid-forehead. Eye movements were recorded on an electrooculograph and a direct current recording was made with a high-frequency cutoff of 100 Hz. Electrooculographic position tracings were displayed by using a pen recorder to document task compliance. Eye position was calibrated with three target positions on the screen.

Data Analysis. The acquired image of each subject's brain in the scanner was transformed into the coordinate system of Talairach and Tournoux (26) by deformation of the standard atlas to match the individual brain (27). After transformation it was possible to identify the same stereotactic coordinates in all subjects, within the limits imposed by anatomic variability.

The mean concentration in each run was calculated as an area-weighted sum of the concentration of each slice. After normalization, the data were rescaled and smoothed with a two-dimensional Gaussian filter (20 mm fwhm) (28) to help desensitize the analysis to slight variations in gyral anatomy and to improve the local signal-to-noise ratio.

Statistical parametric maps were created as described by Friston *et al.* (28) to illustrate the region of most reliable difference between the antisaccade and saccade conditions. These images were generated by performing pairwise subtractions within subjects between conditions and then converting the t of differences for each pixel to its standard normal deviate (Z). The threshold for statistical significance includes adjustments for image smoothness and number of pixels in the region of interest. Image smoothness as measured by the method of Friston *et al.* (28) was 14.2 mm. Since the highest pixel in the *a priori* region is reported, the P value was adjusted for multiple comparisons according to the number of pixels in the region. If the region was identified *post hoc*, the correction was applied according to the number of pixels in the whole slice. All test statistics, *a priori* and *post hoc*, are two-tailed. The especially stringent criterion of significance for *post hoc* findings means that the Z score of an unanticipated finding generally had to be above 3.7, that is, above 3.7 standard deviations from a mean of zero (indicating no mean difference between conditions) to reach statistical significance.

RESULTS

Table 1 shows the stereotactic coordinates, the Z score, and the P value based on the size of the region, of the local maxima in areas that were significantly more active during the antisaccade than during the saccade task. Fig. 1 illustrates the location in the brain, from the medial and lateral viewpoints, of these maxima.

Performance of the antisaccade task significantly activated FEFs, SMA, thalamus, putamen, and superior parietal lobe. Primary visual cortex was also significantly more active during antisaccade. Activation of areas 46 and 9 did not differ in the two conditions. The finding that primary visual cortex was activated during the antisaccade task was not predicted, but the effect was large enough to be statistically significant after we controlled for the number of pixels in the slice.

Table 1. Areas more active during antisaccade than during saccade

Brain region	Coordinates*			Z score	P value†
	x	y	z		
Thalamus (left)	−13.4	−13.1	8.0	3.2	0.02
SMA	−1.9	9.8	44.0	3.3	0.01
FEF (left)	−31.2	−2.9	48.0	3.0	0.05
FEF (right)	24.9	−1.7	56.0	3.5	0.00
SPL (right)	14.7	−61.6	52.0	3.3	0.01
Putamen (right)	19.8	−1.7	8.0	2.7	0.02
DLPFC (areas 9, 46)	40.2	60.3	8.0	1.9	NS‡
Area 17	−4.5	−85.8	8.0	3.9	0.02§

SPL, superior parietal lobe; DLPFC, dorsolateral prefrontal cortex.
*Positive *x* coordinates are right of the center line, positive *y* coordinates are anterior to the origin (the anterior commissure), and positive *z* coordinates are above the anterior commissure–posterior commissure line.
†Two-tailed.
‡Not significant.
§*Post hoc* finding met Bonferroni correction for multiple comparisons.

The electrooculographic tracings documented that the subjects were performing the tasks correctly; during the antisaccade task all subjects made <5% errors. Neither the amplitude of saccades and antisaccades nor the amplitude of eye movements to the left and right differed significantly. In half of the subjects, latencies to antisaccades and saccades were measured by infrared oculography. In all subjects, latencies to antisaccades were longer than latencies to saccades [mean saccade latency, 224.99 ± 59.39 msec.; mean antisaccade latency, 242.32 ± 47.11 msec.; t = 2.52, df = 1,4, P = 0.035 (one-tailed)].

DISCUSSION

Our data show that the FEFs and the SMA, as well as the thalamus, the putamen, and the superior parietal lobe, are more active during antisaccades than during saccades. However, contrary to expectation, areas 46 and 9 were not significantly more active during antisaccades than during saccades. That these areas were not implicated in the difference between antisaccades and saccades is not unprecedented: Guitton *et al.* (8) believed that the site of the crucial lesion that impaired antisaccade performance but not saccade performance in his patients was in the FEFs; Paus *et al.* (19) found in a saccadic inhibition task that dorsomedial lesions, not dorsolateral prefrontal lesions, were associated with a deficit in inhibiting forbidden glances to peripheral distracters. Although monkey data have implicated the principal sulcus (the probable homologue of areas 46 and 9 in humans) in both saccades and antisaccades (29), activation of these areas during saccades relative to baseline has eluded PET investigators (22, 30). The principal sulcus is known to be critical to working memory, and it is possible that the crucial difference between studies activating this area and studies not doing so is the necessity, in the former, to store the location of the target in working memory during an imposed delay.

The finding that the caudate was not more activated during antisaccade may be accounted for by the same difference in study paradigms. Hikosaka and Wurtz (31) found caudate to be involved in learned saccades, and their paradigms interposed a delay between the stimulus and the eye movement. The caudate, which receives significant projections from areas 46 and 9, has been hypothesized to be more involved in "complex behavior", whereas the putamen, which receives significant cortical projections from motor areas, is thought to be more involved in motor functions (31). Petit *et al.* (22) found activation of the putamen but not the caudate during a self-paced voluntary saccade paradigm when compared with baseline. We found putamen activation during the antisaccade task.

Behavioral data acquired during the scans made it possible to address the question of whether there were motor differences in the execution of these two tasks that could account for

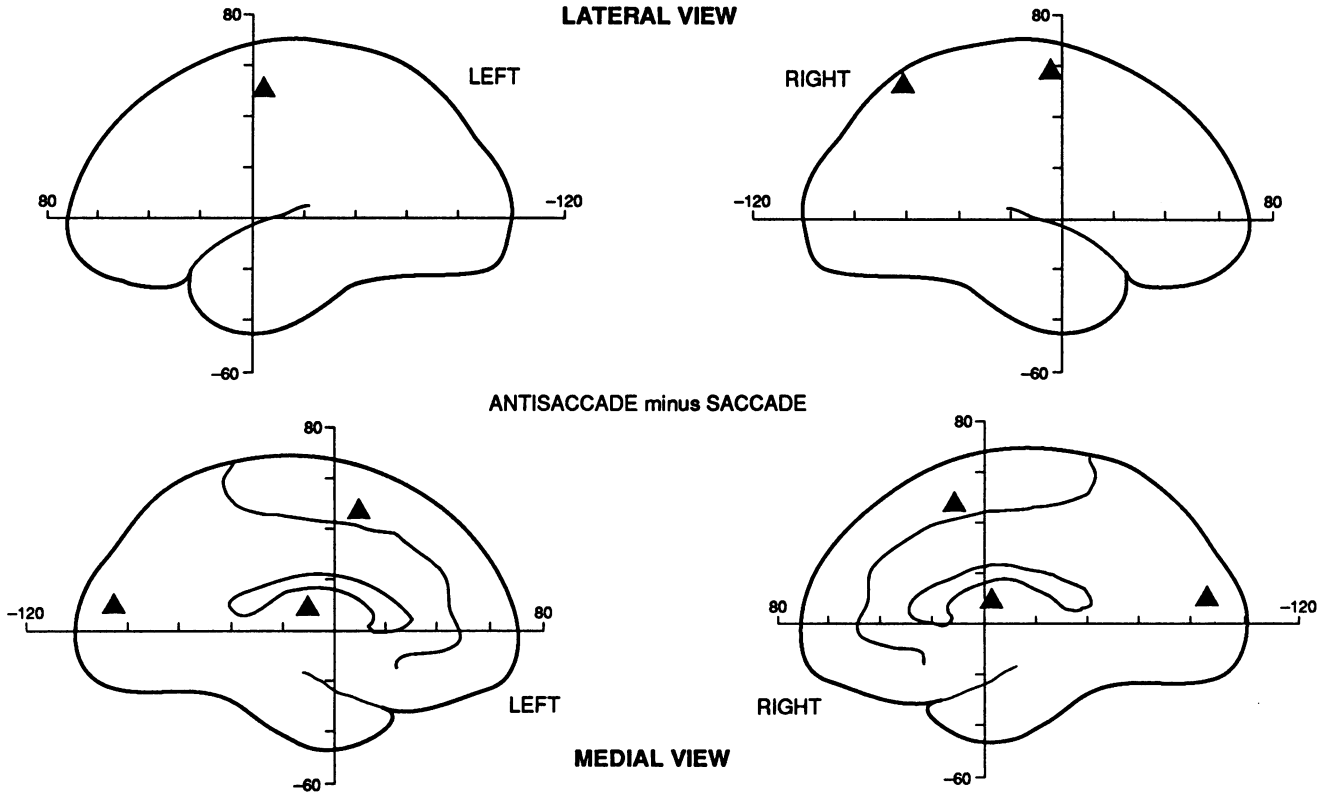

FIG. 1. Sites of significant localized activation during the antisaccade task compared with the saccade task. Coordinates are in millimeters from the origin, halfway between the anterior and posterior commissures.

increased activation of the FEFs and SMA and of the putamen. Matched-pair analysis of saccade and antisaccade amplitude found no difference between the two conditions ($P > 0.1$).

In primates, projections from precentral motor fields to the basal ganglia are mainly excitatory glutaminergic projections to the putamen. Cortically induced increases in firing by the putamen inhibit, through γ-aminobutyrate and substance P efferents, the output nuclei of basal ganglia (including the globus pallidus), that normally exert tonic inhibition on the thalamus. There is evidence that the decrease in firing by the output nuclei and resulting disinhibition of the thalamus "gat[e] or facilitat[e] cortically initiated movements... and that phasic increases in GPi [internal globus pallidus] and SNr [substantia nigra pars reticulata] firing may have the opposite effect (32)." Both putamen and caudate receive significant afferents from the intralaminar nuclei of the thalamus and have γ-aminobutyratergic projections to the substantia nigra pars reticulata (responsible for inhibiting superior colliculi and preventing saccades) (32). Both our findings and those of Petit *et al.* (22) are consistent with the description by Alexander *et al.* (33) of the oculomotor circuits as paralleling other motor circuits, including precentral motor fields and basal ganglia, globus pallidus, thalamus, and projections back to the SMA. However, both our study and that of Petit *et al.* suggest that the putamen may be a major target of cortical projections in the oculomotor circuit as it is in the skeletal motor circuit.

That areas 46 and 9 were equally active during antisaccades and saccades whereas FEFs and other areas of the oculomotor circuit were in fact more active during antisaccades suggests that, at least for normals, the antisaccade task may involve a significant motor inhibition and programming component and not necessarily a significant cognitive inhibition component. Thus, intentional saccade paradigms may not be a unitary group but may possibly be divided into those with and without a spatial memory component, with the former involving areas 46 and 9 and caudate, and the latter involving primarily the oculomotor circuit and taxing particularly the FEFs.

Fox *et al.* (30) investigated whether the FEFs were more important for voluntary than for reflexive saccades, by comparing activation patterns during visually elicited saccades with those generated in synchrony with a tone in the dark. Based on their finding of no difference in FEF activity between the two conditions, they concluded that the FEFs are a nonspecific motor center that does not distinguish between reflexive and volitional saccades. However, in our study, FEFs were significantly more active during the antisaccade task than during saccade, as were most other motor centers involved in saccades.¶

This discrepancy between our results and those of Fox *et al.* (30) can probably be explained by the differences in the task demands. Our finding may reflect the fact that the antisaccade task involves the association of an arbitrary eye movement with the appearance of a stimulus, whereas Fox's paradigm, requiring voluntary saccades in the dark, did not. One study of learned motor behavior (34) has found that increases in firing in the premotor cortex, the executive portion of the skeletal motor circuit, are associated with the routine performance of well-learned, arbitrary motor responses to visual stimuli. (It is probable that cells involved in the actual learning of the association are most active early in the learning period, so that premotor neurons are involved not in acquiring the association, but in retrieving it in the appropriate context.) If the FEFs, as the executive portion of the oculomotor circuit, have a similar role to that of the premotor area in the skeletal circuit, increases in firing may be associated with the accessing of learned, arbitrary motor programs. Our finding that prefrontal activation was limited to the FEFs seems consistent with this interpretation and with reports from single-unit studies in nonhuman primate research that the FEFs can trigger and set the target of saccades (35, 36).

It seems possible at this point to propose that in normal individuals the primary difference between antisaccade and reflexive saccade performance is not increased activation of dorsolateral prefrontal cortex (areas 9 and 46) in the former. However, it is worth considering the possibility that a study of the differences in the blood flow patterns associated with antisaccade and saccades in normal subjects may not reveal the site of dysfunction in impaired populations. For example, the possibility remains that an area of the brain involved in learning the behavior shows maximal differences in activation only while the behavior is being acquired. Such an area would show no difference in activation in a PET study where images are averaged over performance that quickly reaches a ceiling, but could nonetheless underlie the chronic performance deficits in clinical populations.

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1. Goldberg, T. E., Berman, K. F., Mohr, E. & Weinberger, D. R. (1990) *Arch. Neurol.* **47,** 418–422.
2. Jonides, J., Smith, E. F., Koeppe, R. A., Awn, E., Minoshima, S. & Mintun, M. A. (1993) *Nature (London)* **363,** 623–625.
3. Pardo, J. V., Pardo, P. J., Janer, K. W. & Raichle, M. E. (1990) *Proc. Natl. Acad. Sci. USA* **87,** 256–259.
4. Rezai, K., Andreasen, N. C., Alliger, R., Cohen, G., Swayze, V. & O'Leary, D. (1993) *Arch. Neurol.* **50,** 636–642.
5. Weinberger, D. R., Berman, K. F. & Zec, R. F. (1986) *Arch. Gen. Psychiatry* **43,** 114–124.
6. Hallett, P. E. (1978) *Vision Res.* **18,** 1279–1296.
7. Fuster, J. M. (1980) *The Prefrontal Cortex* (Raven, New York).
8. Guitton, D., Buchtel, H. A. & Douglas, R. M. (1985) *Exp. Brain Res.* **58,** 455–472.
9. Hallett, P. E. & Adams, B. D. (1980) *Vision Res.* **20,** 329–339.
10. Fukushima, J., Fukushima, K., Morita, N. & Yamashita, I. (1990) *Biol. Psychiatry* **28,** 943–958.
11. Fukushima, J., Morita, N., Fukushima, K., Chiba, T., Tanaka, S. & Yamashita, I. (1990) *J. Psychiatr. Res.* **24,** 9–24.
12. Pierrot-Deseignilly, C., Rivaud, S., Pillon, B., Fournier, E. & Agid, Y. (1989) *Brain* **112,** 471–481.
13. Tien, A. Y., Pearlson, G. D., Machlin, S. R., Bylsma, F. W. & Hoehn-Saric, R. (1992) *Am. J. Psychiatry* **149,** 641–664.
14. Georgopoulous, A. P., Lurito, J. T., Petrides, M., Schwartz, A. B. & Massey, J. T. (1989) *Science* **243,** 234–236.
15. Georgopoulos, A. P. & Massey, J. T. (1987) *Exp. Brain Res.* **65** (2), 361–370.
16. Lurito, J. T., Georgakopoulos, T. & Georgopoulos, A. P. (1991) *Exp. Brain Res.* **87,** 562–580.
17. Hikosaka, O., Sakamoto, M. & Usui, S. (1989) *J. Neurophysiol.* **61,** 780–797.
18. Dieber, M., Passingham, R., Colebatch, J., Friston, K. J., Niya, P. D. & Frackowiak, R. S. J. (1991) *Exp. Brain Res.* **84,** 393–402.
19. Paus, T., Kline, M., Patockova, L., Angerov, Y., Cerny, R., Mecir, P., Baner, J. & Krabec, P. (1991) *Brain* **114,** 2051–2067.
20. Posner, M. I., Walker, J. A., Freidrich, F. J. & Rafal, R. D. (1984) *J. Neurosci.* **4,** 1863–1874.
21. LaBerge, D. & Buchsbaum, M. S. (1990) *J. Neurosci.* **10,** 613–619.
22. Petit, L., Orssaud, C., Tzourio, N., Salamon, G., Mazoyer, B. & Berthoz, A. (1993) *J. Neurophysiol.* **69,** 1009–1017.

¶Both Petit *et al.* (22) and Fox *et al.* (30) reported coordinates for the FEFs lower than those found in this study. In unpublished results comparing saccades to hand movement we found coordinates more in line with those reported by Fox *et al.* It may be that this represents not the FEFs *per se* but additional areas of precentral cortex that are responding to the motor association demands of the antisaccade task.

23. American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders* (Am. Psychiatric Assoc. Press, Washington, DC).
24. Kops, E. R., Herzog, H., Schmid, A. & Feinendegen, L. E. (1990) *J. Comp. Assist. Tomogr.* **14,** 437–445.
25. Lammertsma, A. A., Frackowiak, R. S. J., Hoffman, J. M., Huang, S.-C., Weinberg, I. N., Dahlbom, M., MacDonald, N. S., Hoffman, E. J., Mazziotta, J. C., Heather, J. D., Forse, G. R., Phelps, M. E. & Jones, T. (1989) *J. Cereb. Blood Flow Metab.* **9,** 461–470.
26. Talairach, J. & Tournoux, P. (1988) *Coplanar Stereotaxic Atlas of the Human Brain: 3 Dimensional Proportional System: An Approach to Cerebral Imaging* (Thieme, Stuttgart).
27. Alpert, N. M., Berdichevsky, D., Weise, S., Tang, J., & Rauch, S. L. (1993) *Quantification of Brain Function: Proceedings of PET 1993*, Akida, Japan, May 31, 1993 (Elsevier, Amsterdam), in press.
28. Friston, K., Frith, C. D., Liddle, P. & Frackowiak, R. (1991) *J. Cereb. Blood Flow Metab.* **11,** 690–699.
29. Funuhashi, S., Chafee, M. & Goldman-Rakic, P. S. (1993) *Nature (London)* **365,** 753–756.
30. Fox, P. T., Fox, J. M., Raichle, M. E. & Burde, R. M. (1985) *J. Neurophysiol.* **54,** 348–369.
31. Hikosaka, O. & Wurtz, R. M. (1985) *J. Neurophysiol.* **53,** 292–308.
32. Alexander, G. E. & Crutcher, M. (1990) *Trends Neurosci.* **13,** 266–271.
33. Alexander, G. E., DeLong, M. & Strick, P. (1986) *Annu. Rev. Neurosci.* **9,** 357–381.
34. Mitz, A. R., Godschalk, M. & Wise, S. P. (1991) *J. Neurosci.* **11,** 1855–1872.
35. Schlag-Rey, M., Schlag, J. & Dassonville, P. (1992) *J. Neurophysiol.* **67,** 1003–1005.
36. Dassonville, P., Schlag, J. & Schlag-Rey, M. (1992) *Exp. Brain Res.* **89,** 300–310.