Success and Failure Suppressing Reflexive Behavior

Clayton E. Curtis and Mark D'Esposito

Abstract

■ The dynamic interplay between reflexive and controlled determinants of behavior is one of the most general organizing principles of brain function. A powerful analogue of this interplay is seen in the antisaccade task, which pits reflexive and willed saccadic mechanisms against one another. Event-related functional magnetic resonance imaging of the human brain showed greater prestimulus preparatory activity in the pre-supplementary motor area before voluntary antisaccades (saccades away from a target) compared with reflexive prosaccades (saccades to a target). Moreover, this preparatory activity was critically associated with reflex suppression; it predicted whether the reflex was later successfully inhibited in the trial. These data illustrate a mechanism for top-down control over reflexive behavior. ■

INTRODUCTION

We often perform behaviors reflexively in response to our environment. For instance, the sudden appearance of a visual stimulus captures our attention automatically (Yantis & Jonides, 1984) causing our gaze to reflexively shift to the location of the stimulus. However, our gaze is not solely visually guided and in general we are capable of using internal motives to bias behavior against strong externally triggered reflexes (Miller & Cohen, 2001). Willful control processes can override a reflex if a cancellation signal can be issued in time (Hanes, Patterson, & Schall, 1998). The source and nature of these control processes are key to understanding behavior but remain largely unknown.The antisaccade task (Hallett, 1978) is an experimental analogue of the dynamic interplay between reflexive and controlled determinants of behavior; it requires willful inhibition of a powerful drive to reflexively saccade to an abrupt visual stimulus. The sudden appearance of the stimulus, which heightens its saliency (Yantis & Jonides, 1984), leads to the prepotency of the reflexive saccade. Conflict between reflexive and controlled saccadic processes arises from the need to use the location of stimulus to guide the direction of the saccade, but to do so without looking at it.

The superior colliculus (SC) in the midbrain primarily mediates reflexive orienting of gaze to an abruptly presented visual stimulus (Dorris, Pare, & Munoz, 1997; Schiller, Sandell, & Maunsell, 1987). In the monkey, prestimulus activity (i.e., activity before the onset of the peripheral saccade stimulus) in the SC determines successful suppression of saccades during antisaccade trials (Everling, Dorris, & Munoz, 1998; Everling, Dorris, Klein, & Munoz, 1999). It is thought that top-down controlling projections from cortical regions to the SC can suppress reflexive saccade generation. Neurophysiological studies of monkeys performing antisaccades identify several cortical regions as likely sources of top-down oculomotor control. Neurons in the lateral intraparietal (LIP) region are thought to mainly convey task relevant visual information, but to a much lesser extent saccade metrics, to the saccadic system through its projection to the SC (Gottlieb & Goldberg, 1999). Importantly, two premotor regions of the frontal cortex—the supplementary eye fields (SEF) (Schlag & Schlag-Rey, 1987), which reside within the rostralmost extent of the supplementary motor area (SMA), and the frontal eye fields (FEF) (Paus, 1996; Bruce, Goldberg, Bushnell, & Stanton, 1985), which reside in the dorsal precentral sulcus near its junction with the superior frontal sulcus—show single-unit activity predictive of successful suppression of unwanted saccades that precedes the appearance of the saccade stimulus (Schlag-Rey, Amador, Sanchez, & Schlag, 1997).

These frontal premotor regions, medial and lateral, have been implicated in general antisaccade performance in humans as well (Kimmig et al., 2001; Connolly, Goodale, Desouza, Menon, & Vilis, 2000; Sweeney et al., 1996; O'Driscoll et al., 1995). The medial wall in area 6 is the substrate for two motor regions whose separation is supported by anatomical connectivity, cytoarchitectonic, and functional differences (Picard & Strick, 2001; Rizzolatti & Luppino, 2001) and whose division is roughly marked by the vertical plane of the anterior commissure (VAC). The SMA proper, including the SEF, lies caudal to the VAC, while pre-SMA sits rostral to the

University of California

Figure 1. Saccade stimuli and eye-position acquisition. (a) Schematic depiction of a trial. Each trial began with a fixation dot that briefly changed colors instructing the participant to make a prosaccade (green) or antisaccade (yellow). The instruction was followed by a 6-sec delay and a 200-msec gap, after which the peripheral saccade stimulus appeared in one of eight radial positions (6° from center). (b) Examples of eight visually guided prosaccades made to targets recorded in the scanner. (c) Examples of four reflexive saccade errors made during antisaccade trials. Each shade and line thickness represents a different trial. Notice the prototypical pattern of a quick reflexive saccade made towards the target followed by a corrective antisaccade away from the target. Participants made reflexive errors on 13.1 ± 6.9% of antisaccade trials.
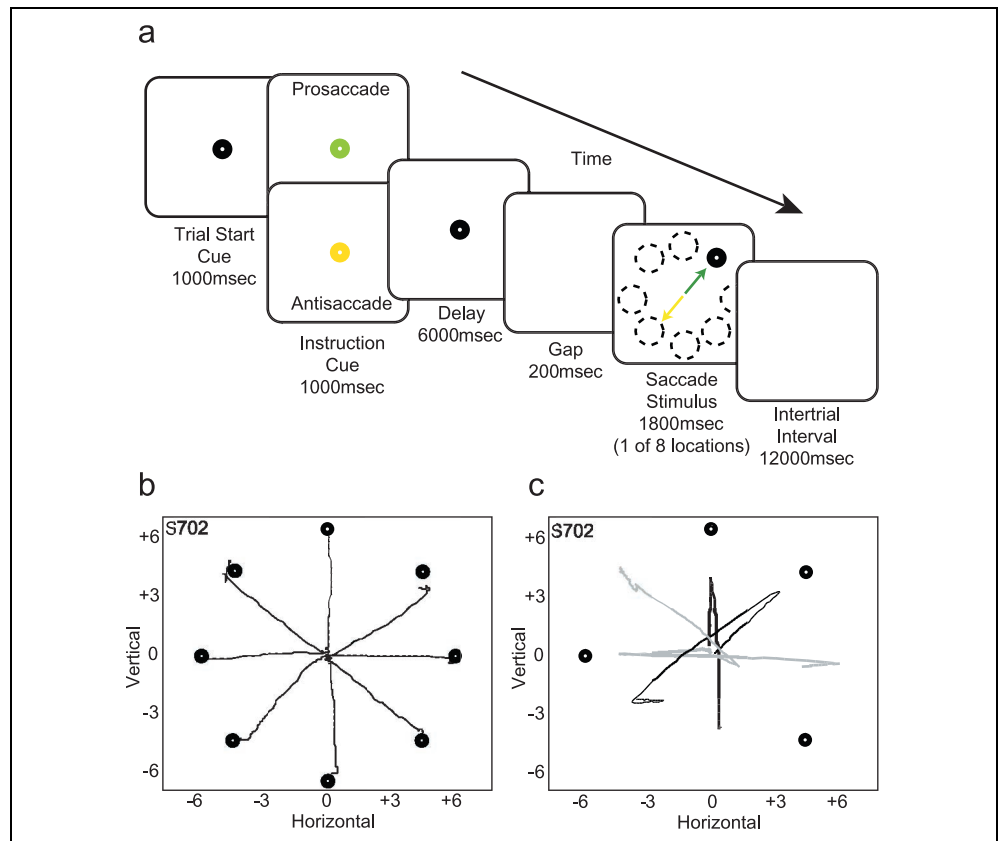
VAC. Importantly, investigations have observed greater activity in the SMA proper during the execution of relatively simple motor acts while greater activity has been found in the pre-SMA during motor responses guided by more demanding sensory–motor transformations (Rushworth, Hadland, Paus, & Sipila, 2002; Grosbras et al., 2001; Kurata, Tsuji, Naraki, Seino, & Abe, 2000; Deiber, Honda, Ibanez, Sadato, & Hallett, 1999; Sakai et al., 1999; Kawashima et al., 1998; Petit, Courtney, Ungerleider, & Haxby, 1998; Hikosaka et al., 1996). Oculomotor control was studied by Merriam et al. (2001), who found greater SEF activity during blocks of endogenously cued (i.e., with the central presentation of the words *LEFT* or *RIGHT*) saccades and greater pre-SMA during endogenously cued antisaccades. These data suggest that greater oculomotor control is associated with increased utilization of the pre-SMA. However, other recent human functional magnetic resonance imaging (fMRI) studies of antisaccade performance have not supported this functional separation of pre-SMA and SEF (Kimmig et al., 2001; Connolly et al., 2000).

Using event-related fMRI of antisaccade performance at high field (4 T), we test whether the pattern of brain activity in the human pre-SMA, SEF, FEF, and intraparietal sulcus (IPS) relates to the heightened need for behavioral control over reflexive orienting of gaze. The previous neuroimaging studies to date (Kimmig et al., 2001; Merriam et al., 2001; Connolly et al., 2000;

Sweeney et al., 1996; O'Driscoll et al., 1995) subtracted activity summed over long blocks of antisaccades, whether correct or not, from activity over blocks of prosaccades, underutilizing the valuable temporal information available in fMRI. We used, instead, an event-related design to capitalize on the temporal resolution of MR signals, allowing us to examine activity specifically from the trial period before the onset of the peripheral stimulus (Figure 1a). Critically, activity in this interval reflects preparatory processes that are separated in time and are thus uncontaminated by saccade production processes. In addition, we recorded eye position in the scanner during functional imaging. This allowed us to later sort and compare the fMRI data by performance (Figure 1b,c). Together, these methodological advances finally permit testing of two predictions that arise from the proposed brain–behavior relationship: (a) Prestimulus activity is greater prior to antisaccades than prosaccades, reflecting the need for greater control; (b) This early prestimulus difference is indeed critical to the success or failure of saccade suppression later in the trial. By requiring both greater activity when inhibitory control is needed and disinhibition or failed suppression when activity is less, these two hypotheses form a strict test of the proposed brain–behavior relationship. In this report, we focus on the SEF, pre-SMA, FEF, and IPS (Gottlieb & Goldberg, 1999) as the potential sources of top-down control over

reflexive saccades. We presented these data in abstract form previously (Curtis & D'Esposito, 2001).

RESULTS

All regions of interest (SEF, pre-SMA, FEF, and IPS) showed significant Trial Type (prosaccade, antisaccade correct, and antisaccade error) × Trial Period (instructional cue, delay, response) interactions (all $ps < .05$). Thus, differences between conditions at each trial period are presented below. Again, the crucial test for each region-of-interest is the difference between antisaccade and prosaccade trials and the difference between antisaccade trials where the initial reflexive prosaccade was successfully and unsuccessfully inhibited.

Instructional Cue Period

Follow-up t tests failed to find any significant differences in any region between any trial types during the instructional cue period. Thus, although each region was responsive to the instructional cue (relative to the intertrial interval), there were no significant differences among the trial types.

Figure 2. Group activations along the medial wall of the frontal cortex in the pre-SMA and the SEF. Preparatory delay period activations are depicted in (a) and (c), while stimulus-response period activations are represented in (b) and (d). Greater correct antisaccade compared with prosaccade activations are depicted in (a) and (b), while greater activations during correct antisaccades compared with reflexive prosaccade errors on antisaccade trials are depicted in (c) and (d). The pre-SMA shows greater preparatory delay period activity when subjects are anticipating the need to inhibit the reflexive prosaccade and make an antisaccade (a) and when subjects fail to suppress the reflex, activity is diminished (c). The SEF does not show greater antisaccade than prosaccade activity during the preparatory delay (a), however, it does show greater delay period activity when comparing correct antisaccades to reflexive prosaccade errors during the delay (c) and the SEF shows strong differential effects at the response period of the trial (b and d). Average time series data from the (e) pre-SMA and (f) SEF regions showing activity during prosaccade trials and antisaccade trials when the reflexive saccade was successfully and unsuccessfully suppressed. The gradated color bar at the bottom approximately references from which epoch of the trial the signal is emanating given the 4- to 6-sec lag in the hemodynamic response.
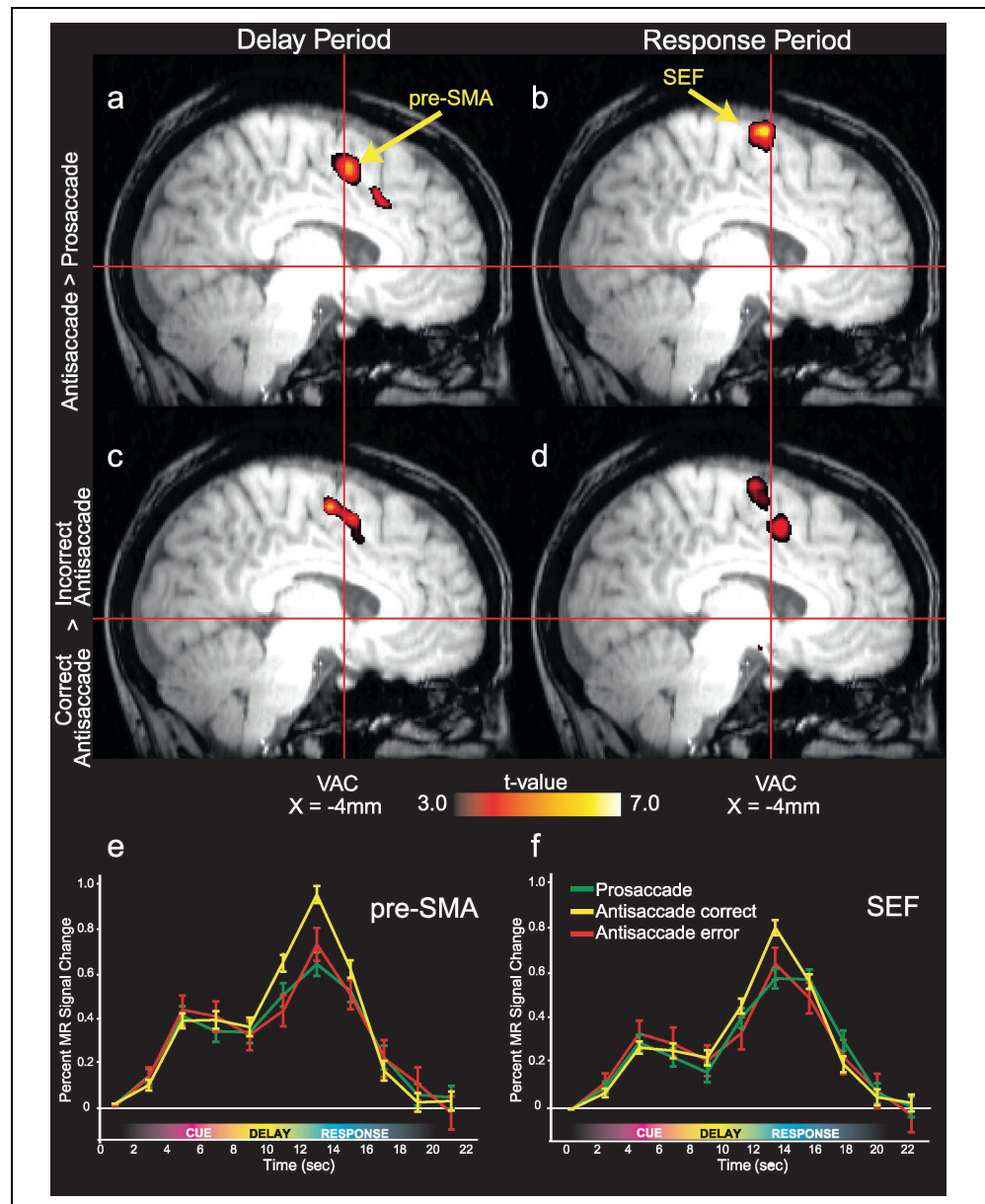
Preparatory Delay Period

Beginning shortly after participants were given the anti-saccade instruction, activity in the pre-SMA began to increase and significantly diverge from the activity seen during prosaccade trials, $t(11) = 6.01$, $p < .00007$. Note that this difference in the pre-SMA, when subjects anticipated an increased need for oculomotor control, occurred during the preparatory delay interval (i.e., 2–4 sec prior to the presentation of the peripheral saccade stimulus that cued where they were to shift their gaze) (Figure 2a). Moreover, on trials when participants failed to successfully suppress the reflexive saccade, activity in the pre-SMA was significantly lower during the preparatory delay interval compared with trials when they were successful, $t(11) = 6.31$, $p < .00006$ (Figure 2c). Inspection of the averaged time-courses from the 12 participants highlights the important role that the pre-SMA plays in oculomotor control (Figure 2e).

Neither the SEF, $t(11) = 2.86$, $p > .01$, right FEF, $t(11) = 2.76$, $p > .01$, left FEF, $t(11) = 2.69$, $p > .01$, right IPS, $t(11) = 2.05$, $p > .06$, nor the left IPS, $t(11) = 1.92$, $p > .08$, showed significantly greater activity during the preparatory delay period for correct antisaccade trials compared with prosaccade trials. However, all of these regions, with the exception of the left IPS, $t(11) = 2.83$, $p > .01$, showed greater activation in the delay interval prior to correct antisaccades compared with reflexive errors made on antisaccade trials (all ps < .008). Thus, the pre-SMA was the only region that showed significantly greater activation during the preparatory delay interval for both comparisons: correct antisaccade versus prosaccade and correct antisaccades versus antisaccade errors.

To confirm the spatial representativeness of the group-level activation in the pre-SMA shown in Figure 2a, the location of each of the 12 subject's delay period activity is plotted separately in Figure 3. As can be seen, all 12 subjects showed robust delay period activity along the medial frontal wall that was greater before antisaccades compared with prosaccades. Importantly, 9 of the 12 subjects showed activations that peaked rostral to the VAC plane in the pre-SMA. Only two subjects had activations that were limited to an area that is consistent with the SEF, caudal to the VAC in or near the paracentral sulcus.

Stimulus-Response Period

All regions of interest showed significantly greater activation at the response period when the execution of correct antisaccades was compared with the execution of prosaccades and compared with instances when reflexive errors were made on antisaccade trials (all ts > 4.11 and all ps < .002). Particularly strong signal differences were found in the FEF [antisaccade > prosaccade, $t(11) = 6.44$, $p > .00005$; antisaccade correct > antisaccade error, $t(11) = 6.35$, $p > .00006$] and the IPS [antisaccade > prosaccade, $t(11) = 10.79$, $p > .0000004$;

Figure 3. Individual subject activations along the medial wall of the frontal cortex illustrating greater preparatory delay interval for antisaccade compared with prosaccade trials. The vertical red lines indicate the vertical anterior commissure (VAC) line. Note that in 9/12 subjects (S1–S9), there is greater preparatory delay activity just rostral to the VAC. Numbers in the upper right-hand corner indicate the y-coordinate of the peak activation in millimeters relative to the VAC. In two subjects (S10 and S11), the activity is limited to a region just behind the VAC about 1–2 mm. In S12, the only activity seen is in the cingulate gyrus, not the SEF or pre-SMA.
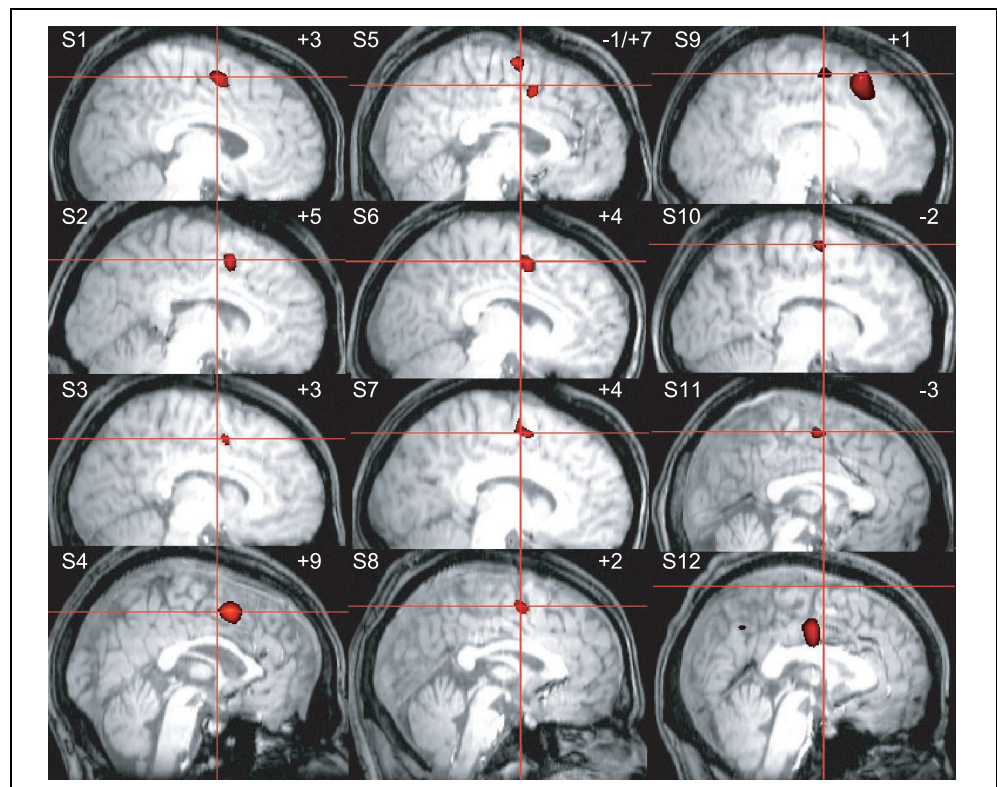
Figure 4. The FEF and IPS, bilaterally, demonstrate increased activation that is limited to the stimulus-response period of the trial during the execution of correct antisaccades compared with (a) the execution of prosaccades and (b) when subjects failed to suppress the reflexive prosaccade. Group statistical parametric maps are overlaid on a single subject's anatomy. Average time series data from the (c) FEF and (d) IPS showing activity during prosaccade trials and antisaccade trials when the reflexive saccade was successfully and unsuccessfully suppressed. Time series are aligned to the onset of the peripheral stimulus prompting an antisaccade or prosaccade.
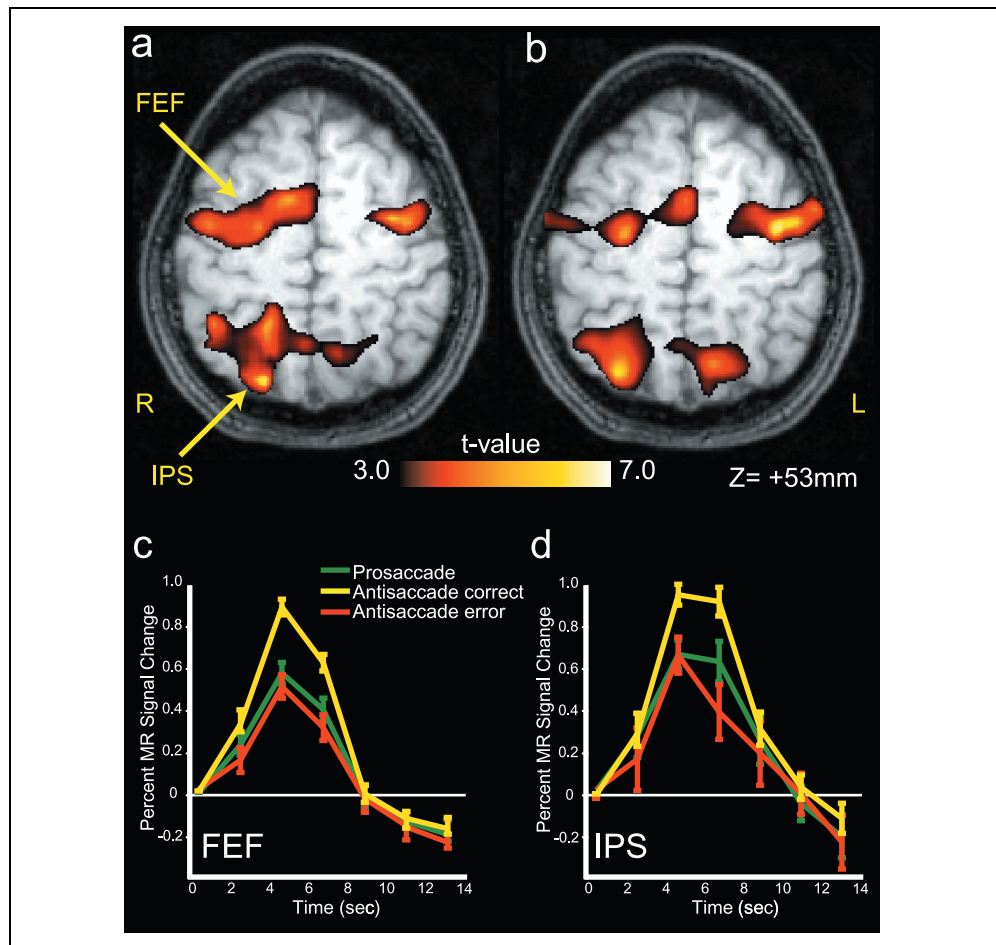
antisaccade correct > antisaccade error, $t(11) = 8.91$, $p > .000002$] regions for each contrast (Figures 2 and 4).

Response Profile Analysis

In order to compare the differential activations of regions across the three periods, effect sizes (Cohen's d) for the main contrasts were computed. As can be seen in Figure 5, the response profiles of the pre-SMA and SEF look qualitatively different than that of the FEF and IPS. The pre-SMA and SEF show the largest effect during the delay period when subjects successfully prepare to inhibit a saccade, while the FEF and IPS show the largest effect at the response period. These different response profiles suggest different roles in oculomotor control.

DISCUSSION

These human data show increased prestimulus, preparatory delay period activity in pre-SMA before antisaccades compared with prosaccades. Beginning shortly after participants were given the antisaccade instruction, activity in the pre-SMA began to increase and diverge from the activity seen during prosaccade trials. This increase in pre-SMA activity 2–4 sec prior to the

presentation of the stimulus that cues the direction of the saccade likely reflects processes relating to supervisory control that facilitate appropriate motor behavior when needed, in this case when participants were anticipating the need to inhibit the visual grasp reflex. On trials when participants subsequently failed to successfully inhibit the reflexive saccade, and presumably failed to sufficiently activate at least one node of the circuit responsible for inhibitory saccadic control, the activity in the pre-SMA was reduced. Thus, pre-SMA activity meets both of the requirements we listed above linking its activity to behavior. Namely, activity during the preparatory delay interval increases when inhibitory control is anticipated, and the level of this activity is critically associated with the successful withholding of unwanted saccades. No other region met these two strict requirements.

Our findings support the view that the pre-SMA is functionally distinct from other frontal premotor regions, including the SMA proper (Picard & Strick, 2001; Rizzolatti & Luppino, 2001). Among the premotor regions, the pre-SMA is situated to play a higher level role in the perception–action hierarchy and may operate more like a heteromodal cortical association area (i.e., like prefrontal cortex) than a unimodal cortical
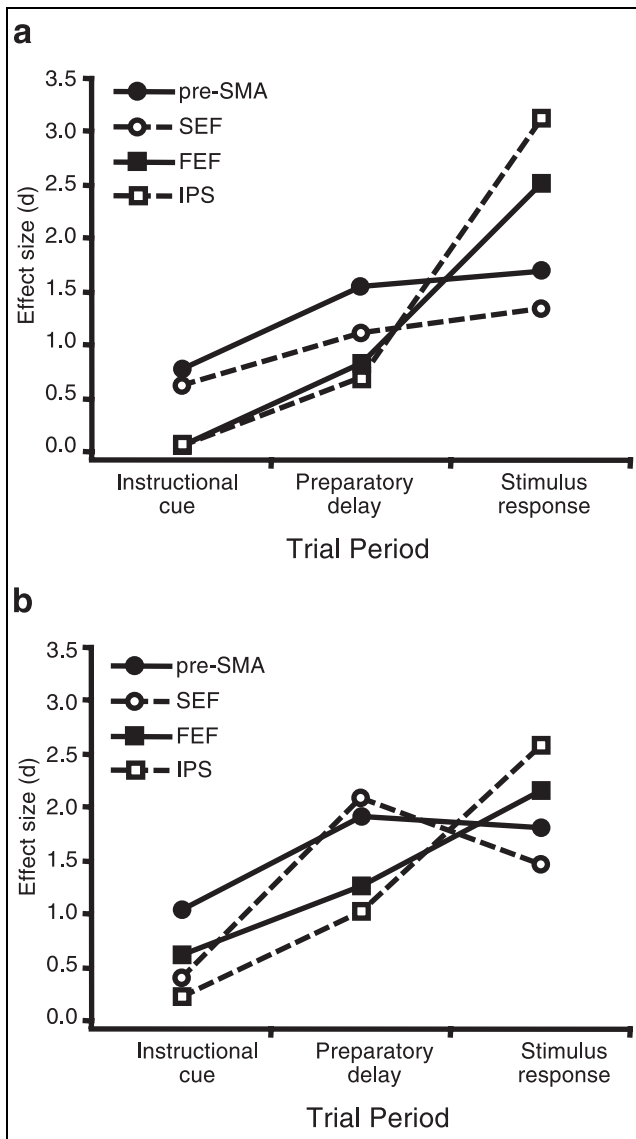
Figure 5. Profile plots summarizing the trial period by region effects. Each element represents the effect size for the region-of-interest during a given trial period, where the effect size (*d*) is equal to the mean parameter estimate for a given contrast divided by the group standard deviation. Effect sizes for (a) antisaccades greater than prosaccades and (b) correct antisaccades greater than errors on antisaccade trials. See text for details.

area (i.e., like premotor cortex). Anatomical and functional evidence in human and nonhuman primates supports this claim. First, the monkey pre-SMA is much more interconnected with the prefrontal cortex than the SMA proper (Lu, Preston, & Strick, 1994; Bates & Goldman-Rakic, 1993; Luppino, Matelli, Camarda, & Rizzolatti, 1993). Second, pre-SMA activity has been implicated in higher level cognitive control rather than motor behavior. The pre-SMA has shown consistent sensitivity to response inhibition during go/no-go and flanker tasks (Menon, Adleman, White, Glover, & Reiss, 2001; Rubia et al., 2001; Ullsperger & von Cramon, 2001; Hazeltine, Poldrack, & Gabrieli, 2000; Kiehl, Liddle, &

Hopfinger, 2000; Garavan, Ross, & Stein, 1999; Humberstone et al., 1997) and the updating or switching of essential visual–motor associations (Rushworth et al., 2002; Grosbras et al., 2001; Heide et al., 2001; Sakai et al., 1999; Kawashima et al., 1998; Shima, Mushiake, Saito, & Tanji, 1996). Consistent with these data, the observed pre-SMA activity during the preparatory delay interval in the current study may reflect the anticipated need for inhibition of the eminent programming of a reflexive, visually guided saccade. However, the pre-SMA may not necessarily be responsible for actually inhibiting the reflexive response. Instead, we propose that the pre-SMA readies or prepares other oculomotor regions, like the SEF, in some fashion such that reflexive responding is less likely.

Of course, temporary maintenance of the instructional cue was required for successful saccade performance; the instruction appeared only briefly at the beginning of the trial, 6 sec before the correct saccadic response could be selected. Thus, it could be argued that the greater activity in the pre-SMA was due to the maintenance of the instructional cue across the delay period (i.e., retrospective memory code) (Petit et al., 1998). However, it does not seem likely that remembering an instruction to later perform a prosaccade (''move eyes towards the stimulus'') versus remembering an instruction to later perform an antisaccade (''move eyes away from the stimulus'') should place a different load upon working memory systems. If this were the case, then one might predict a greater number of responses consistent with forgetting on antisaccade compared with prosaccade trials. In other words, one might expect more prosaccades not followed by corrective antisaccades (i.e., not a reflexive error) during instructed antisaccade trials than antisaccade errors made during instructed prosaccade trials. This was not the case. Rarely (i.e., less than 0.6% of all trials for all subjects) did subjects make the wrong and uncorrected eye movement that would be expected if they had forgotten the instructional cue; these rare instances did not occur disproportionately on antisaccade trials. Although this observation does not exclude the possibility, it is inconsistent with the interpretation that the difference in delay period activity represents a retrospective memory code.

More likely, the differential processing demands during the delay interval on different trial types represent a prospective memory code or a preparatory motor set that would be greater for an upcoming antisaccade compared with a prosaccade given the additional operations required to generate an antisaccade. These additional operations include the inhibition of the visually evoked saccade, the 180° transformation of the saccadic vector, and finally the execution of the antisaccade itself. In this light, the preparatory activity in the pre-SMA might be the source of the *Bereitschaftspotential*, or electrical readiness potential that can be recorded from the scalp, that precedes preinstructed motor acts and

has been shown to be more prominent prior to correct antisaccades than before prosaccades and reflexive prosaccade errors on antisaccade trials (Everling, Spantekow, Krappmann, & Flohr, 1998; Everling, Krappmann, & Flohr, 1997).

The only significant difference in FEF and IPS brain activity was limited to the stimulus-response phase of the task, where correct antisaccades showed greater activity than prosaccades and reflexive errors on antisaccade trials. These data are more difficult to interpret in the context of the current design because the primary effect was found at the stimulus-response interval of the task, when many perceptual and motor operations are presumably co-occurring rapidly. Nonetheless, the increased activity in the FEF and IPS noted here could be related to processes including covert orienting to the visual stimulus (Nobre, Gitelman, Dias, & Mesulam, 2000; Corbetta et al., 1998), cancellation of the reflexive saccade (Hanes et al., 1998), and/or selection of the antisaccade location (Schall & Hanes, 1993).

Saccades are produced when activity in FEF movement-related neurons that drive the eyes to a stimulus increases and activity in fixation-related neurons that lock gaze in place decreases (Everling & Munoz, 2000; Hanes & Schall, 1996). At the time when the peripheral visual stimulus appears, competition between gaze-holding and gaze-shifting mechanisms in the FEF determines, through its efferent projections to the SC, whether the reflexive saccade is triggered or not. If activity in movement-related neurons can be kept below a critical threshold just long enough for the voluntary antisaccade to be programmed and initiated, then the decision to make a correct antisaccade is likely to be achieved. It is known that saccade-related neurons in the SC and FEF decrease their rate of firing before antisaccades compared with prosaccades (Everling & Munoz, 2000; Everling et al., 1999; Everling, Dorris, et al., 1998), but neurons in the SEF increase their rate of firing (Schlag-Rey et al., 1997). These differences start to emerge, however, only about 300 msec before the appearance of the saccade stimulus and would likely contribute statistically to the response period, not to the delay period, covariate. Other studies that are specifically designed to better address differential contributions of the SEF and FEF near the response are currently underway. In this study though, the greater SEF activity during antisaccades compared with prosaccades may reflect neural events just before the saccade stimulus in addition to active fixation, saccade selection, and saccade production processes. The key difference between the pre-SMA and SEF was that the pre-SMA differentiated antisaccades and prosaccades earlier than did the SEF, as early as 4–6 sec before the saccade stimulus even appeared. This signifies a primary role for the pre-SMA in preparing the oculomotor system for the impending need to inhibit the reflexive saccade, even when the direction of the visual stimulus and saccade is unknown. Again, the SEF may be the primary oculomotor region that actually inhibits the reflexive prosaccade to the stimulus, especially given its increased neuronal firing rate just prior to antisaccades (Schlag-Rey et al., 1997) and its projections to omnipause neurons in the brain stem (Huerta & Kaas, 1990; Shook, Schlagrey, & Schlag, 1988) that might mediate halting the planned prosaccade until the antisaccade can be generated.

Because we were able to separate preparatory activity during the delay from the motor activity at response, we are able to propose that the pre-SMA establishes a preparatory oculomotor set that influences how one will respond to the abrupt presentation of a visual stimulus. More specifically, the pre-SMA activity reflects a highly flexible, abstract, and directionally undetermined eye-movement goal that biases the activity in other oculomotor centers, such as the FEF and/or SEF, and reduces the likelihood that a reflex-like saccade to the exogenous cue will be generated. This could be achieved through the excitation of fixation-related neurons in the FEF but is more likely accomplished through the inhibition of movement-related neurons (Everling & Munoz, 2000). Although in the monkey, at least, there is no evidence for monosynaptic projections from the pre-SMA to the FEF, the pre-SMA shares diffuse reciprocal connections with the SEF and the dorsolateral prefrontal cortex (areas 9 and 46), both of which are highly interconnected with the FEF (Bates & Goldman-Rakic, 1993; Luppino et al., 1993; Schall, Morel, & Kaas, 1993; Huerta & Kaas, 1990). Thus, activity in the pre-SMA could readily exert modulatory control over drive related oculomotor neurons elsewhere, either in cortex or subcortex, preventing unwanted glances. Our findings illustrate, in general, a mechanism by which top-down controlling signals can bias bottom-up neural processes to allow for willful adaptive behavior (Miller & Cohen, 2001). This interplay, between voluntary top-down and reflexive bottom-up processes, is one of the most general organizing principles of brain function.

METHODS

Participants and Experimental Methods

Twelve healthy participants (five women; ages 21–33), who gave informed consent according to procedures approved by the University of California, performed 80 antisaccade, 40 fixation, and 32 prosaccade trials in a randomly interleaved order as depicted in Figure 1.

Neuroimaging Methods

Functional images were acquired during eight runs lasting 418 sec each, resulting in 1672 volumes total covering the dorsal cortex. T2*-weighted echo-planar images (EPI) sensitive to blood oxygenation level-dependent (BOLD) contrasts were acquired at 4 T with a Varian INOVA MR scanner (http://www.varianinc.com)

and a TEM send-and-receive RF head coil (http://www.highfieldcoils.com) using a two-shot gradient-echo–EPI sequence (22.4 cm² field of view with a 64 × 64 matrix size resulting in an in-plane resolution of 3.5 × 3.5 mm for each of eighteen 5-mm axial slices with 0.5-mm interslice gap; repetition time = 1 sec per half of k-space (2 s total), echo time = 28 msec, flip angle = 20°. High-resolution MP-Flash 3D T1-weighted scans were acquired for anatomical localization.

Oculomotor Recording Methods

Eye position was monitored in the scanner at 60 Hz with an infrared videographic camera equipped with a telephoto lens (Model 504LRO, Applied Sciences Laboratories, http://www.a-s-l.com) that focused on the right eye viewed from a small dielectric flat surface mirror mounted inside the RF coil. Nine-point calibrations were performed at the beginning of the session and between runs when necessary. Eye-movement data were scored offline with display routines written in MATLAB (http://www.mathworks.com).

Regions of Interest

Given the close proximity of brain regions of interest and the loss of spatial resolution inherent in spatial normalization (Brett, Johnsrude, & Owen, 2002), we performed our analyses within specific regions of interest. The locations of the SEF, pre-SMA, FEF, and IPS were derived from a two-step process. First, sulcal anatomical landmarks in the subject's native space were used to define SEF (in and around the paracentral sulcus of the dorsomedial wall that did not extend rostral past VAC plane or ventral into cingulate sulcus), pre-SMA (dorsomedial cortical wall just rostral to the VAC plane above the cingulate sulcus), FEF (extending laterally along the precentral sulcus of the dorsolateral frontal cortex beginning at the junction with the superior frontal sulcus), and the IPS (lateral sulcus dividing the superior and inferior lobules in parietal cortices) in accord with other studies (Grosbras, Lobel, Van de Moortele, LeBihan, & Berthoz, 1999; Luna et al., 1998). Second, these regions were then functionally tested with a visually guided saccade task (see below), which in all cases the FEF, SEF, and IPS confirmed the presence of significant (p < .05, corrected for multiple comparsons) saccade-related activity within the anatomically defined regions; significant activity in the pre-SMA was less consistent and/or lower in magnitude across subjects.

Data Analysis

For all participants, a hemodynamic response function (HRF) was empirically derived (Aguirre, Zarahn, & D'Esposito, 1998) in response to 20 saccades made to flickering checkerboards (20 Hz) briefly presented (200 msec) to the left or right hemifield. The HRF used was derived from FEF and did not differ in shape from HRFs derived from SEF. Our methods for analyzing temporal patterns of brain activity (i.e., BOLD) within a trial are described in detail elsewhere (Postle, Zarahn, & D'Esposito, 2000). Briefly, we modeled fMRI signal changes evoked by each epoch of the trial with a covariate shaped like the HRF by convolving it with each independent variable (instructional cue, preparatory delay, and saccade response) (Zarahn, Aguirre, & D'Esposito, 1997) and entering the result into the modified general linear model (Worsley & Friston, 1995) for analysis using VoxBo (http://www.voxbo.org). On average, 24±12 SEF, 33±17 pre-SMA, 91±15 bilateral FEF, and 76±22 bilateral IPS voxels were identified for each participant that showed significant task-related activity independent of trial type (p < .05, corrected for multiple comparisons). From these voxels, parameter estimates reflecting the percent MR signal changes relative to baseline were estimated for each covariate by trial type. Group random effects analyses on these parameter estimates were performed, where significant Trial Type (prosaccade, antisaccade correct, antisaccade error) × Trial Period (cue, delay, response) interactions were followed-up with t tests (p < .008, when α = .05 is corrected for multiple comparisons). In addition to region-of-interest analyses, group-level random effects analyses were performed on the entire volumes collected. This was done to aid in the visualization of the data and to aid in relating our data to other studies. Statistical parametric maps (t statistics) of key contrasts were generated for the group after the individual subject data were spatially normalized into standard atlas space (Montreal Neurological Institute reference brain) using routines from SPM99 (http://www.fil.ion.ucl.ac.uk/spm), resampled to 2 mm isotropic voxels, and spatially smoothed with a two-voxel Gaussian kernel.

REFERENCES

Aguirre, G. K., Zarahn, E., & D'Esposito, M. (1998). The variability of human, BOLD hemodynamic responses. *Neuroimage, 8,* 360–369.

Bates, J. F., & Goldman-Rakic, P. S. (1993). Prefrontal connections of medial motor areas in the rhesus monkey. *Journal of Comparative Neurology, 336,* 211–228.

Brett, M., Johnsrude, I. S., & Owen, A. M. (2002). The problem of functional localization in the human brain. *Nature Reviews Neuroscience, 3,* 243–249.

Bruce, C. J., Goldberg, M. E., Bushnell, M. C., & Stanton, G. B. (1985). Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *Journal of Neurophysiology, 54,* 714–734.

Connolly, J. D., Goodale, M. A., Desouza, J. F., Menon, R. S., & Vilis, T. (2000). A comparison of frontoparietal fMRI activation during anti-saccades and anti-pointing. *Journal of Neurophysiology, 84,* 1645–1655.

Corbetta, M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., Linenweber, M. R., Petersen, S. E., Raichle, M. E., Van Essen, D. C., & Shulman, G. L. (1998). A common network of functional areas for attention and eye movements. *Neuron, 21,* 761–773.

Curtis, C. E., & D'Esposito, M. (2001). Dorsal frontal cortical contributions to inhibitory control: fMRI evidence from an antisaccade task. *Society for Neuroscience Abstracts, 27,* 782.6.

Deiber, M. P., Honda, M., Ibanez, V., Sadato, N., & Hallett, M. (1999). Mesial motor areas in self-initiated versus externally triggered movements examined with fMRI: Effect of movement type and rate. *Journal of Neurophysiology, 81,* 3065–3077.

Dorris, M. C., Pare, M., & Munoz, D. P. (1997). Neuronal activity in monkey superior colliculus related to the initiation of saccadic eye movements. *Journal of Neuroscience, 17,* 8566–8579.

Everling, S., Dorris, M. C., Klein, R. M., & Munoz, D. P. (1999). Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. *Journal of Neuroscience, 19,* 2740–2754.

Everling, S., Dorris, M. C., & Munoz, D. P. (1998). Reflex suppression in the anti-saccade task is dependent on prestimulus neural processes. *Journal of Neurophysiology, 80,* 1584–1589.

Everling, S., Krappmann, P., & Flohr, H. (1997). Cortical potentials preceding pro- and antisaccades in man. *Electroencephalography and Clinical Neurology, 102,* 356–362.

Everling, S., & Munoz, D. P. (2000). Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. *Journal of Neuroscience, 20,* 387–400.

Everling, S., Spantekow, A., Krappmann, P., & Flohr, H. (1998). Event-related potentials associated with correct and incorrect responses in a cued antisaccade task. *Experimental Brain Research, 118,* 27–34.

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. *Proceedings of the National Academy of Sciences, U.S.A., 96,* 8301–8306.

Gottlieb, J., & Goldberg, M. E. (1999). Activity of neurons in the lateral intraparietal area of the monkey during an antisaccade task. *Nature Neuroscience, 2,* 906–912.

Grosbras, M. H., Leonards, U., Lobel, E., Poline, J. B., LeBihan, D., & Berthoz, A. (2001). Human cortical networks for new and familiar sequences of saccades. *Cerebral Cortex, 11,* 936–945.

Grosbras, M. H., Lobel, E., Van de Moortele, P. F., LeBihan, D., & Berthoz, A. (1999). An anatomical landmark for the supplementary eye fields in human revealed with functional magnetic resonance imaging. *Cerebral Cortex, 9,* 705–711.

Hallett, P. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Research, 18,* 1279–1296.

Hanes, D. P., Patterson, W. F., II, & Schall, J. D. (1998). Role of frontal eye fields in countermanding saccades: Visual, movement, and fixation activity. *Journal of Neurophysiology, 79,* 817–834.

Hanes, D. P., & Schall, J. D. (1996). Neural control of voluntary movement initiation. *Science, 274,* 427–430.

Hazeltine, E., Poldrack, R., & Gabrieli, J. D. (2000). Neural activation during response competition. *Journal of Cognitive Neuroscience, 12,* 118–129.

Heide, W., Binkofski, F., Seitz, R. J., Posse, S., Nitschke, M. F., Freund, H. J., & Kompf, D. (2001). Activation of fronto-parietal cortices during memorized triple-step sequences of saccadic eye movements: An fMRI study. *European Journal of Neuroscience, 13,* 1177–1189.

Hikosaka, O., Sakai, K., Miyauchi, S., Takino, R., Sasaki, Y., & Putz, B. (1996). Activation of human presupplementary motor area in learning of sequential procedures: A functional MRI study. *Journal of Neurophysiology, 76,* 617–621.

Huerta, M. F., & Kaas, J. H. (1990). Supplementary eye field as defined by intracortical microstimulation—connections in macaques. *Journal of Comparative Neurology, 293,* 299–330.

Humberstone, M., Sawle, G. V., Clare, S., Hykin, J., Coxon, R., Bowtell, R., Macdonald, I. A., & Morris, P. G. (1997). Functional magnetic resonance imaging of single motor events reveals human presupplementary motor area. *Annals of Neurology, 42,* 632–637.

Kawashima, R., Tanji, J., Okada, K., Sugiura, M., Sato, K., Kinomura, S., Inoue, K., Ogawa, A., & Fukuda, H. (1998). Oculomotor sequence learning: A positron emission tomography study. *Experimental Brain Research, 122,* 1–8.

Kiehl, K. A., Liddle, P. F., & Hopfinger, J. B. (2000). Error processing and the rostral anterior cingulate: An event-related fMRI study. *Psychophysiology, 37,* 216–223.

Kimmig, H., Greenlee, M. W., Gondan, M., Schira, M., Kassubek, J., & Mergner, T. (2001). Relationship between saccadic eye movements and cortical activity as measured by fMRI: Quantitative and qualitative aspects. *Experimental Brain Research, 141,* 184–194.

Kurata, K., Tsuji, T., Naraki, S., Seino, M., & Abe, Y. (2000). Activation of the dorsal premotor cortex and pre-supplementary motor area of humans during an auditory conditional motor task. *Journal of Neurophysiology, 84,* 1667–1672.

Lu, M. T., Preston, J. B., & Strick, P. L. (1994). Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *Journal of Comparative Neurology, 341,* 375–392.

Luna, B., Thulborn, K. R., Strojwas, M. H., McCurtain, B. J., Berman, R. A., Genovese, C. R., & Sweeney, J. A. (1998). Dorsal cortical regions subserving visually guided saccades in humans: An fMRI study. *Cerebral Cortex, 8,* 40–47.

Luppino, G., Matelli, M., Camarda, R., & Rizzolatti, G. (1993). Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *Journal of Comparative Neurology, 338,* 114–140.

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, A. L. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping, 12,* 131–143.

Merriam, E. P., Colby, C. L., Thulborn, K. R., Luna, B., Olson, C. R., & Sweeney, J. A. (2001). Stimulus-response incompatibility activates cortex proximate to three eye fields. *Neuroimage, 13,* 794–800.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24,* 167–202.

Nobre, A. C., Gitelman, D. R., Dias, E. C., & Mesulam, M. M.

(2000). Covert visual spatial orienting and saccades: Overlapping neural systems. *Neuroimage, 11,* 210–216.

O'Driscoll, G. A., Alpert, N. M., Matthysse, S. W., Levy, D. L., Rauch, S. L., & Holzman, P. S. (1995). Functional neuroanatomy of antisaccade eye movements investigated with positron emission tomography. *Proceedings of the National Academy of Sciences, U.S.A., 92,* 925–929.

Paus, T. (1996). Location and function of the human frontal eye-field: A selective review. *Neuropsychologia, 34,* 475–483.

Petit, L., Courtney, S. M., Ungerleider, L. G., & Haxby, J. V. (1998). Sustained activity in the medial wall during working memory delays. *Journal of Neuroscience, 18,* 9429–9437.

Picard, N., & Strick, P. L. (2001). Imaging the premotor areas. *Current Opinions in Neurobiology, 11,* 663–672.

Postle, B. R., Zarahn, E., & D'Esposito, M. (2000). Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. *Brain Research. Brain Research Protocols, 5,* 57–66.

Rizzolatti, G., & Luppino, G. (2001). The cortical motor system. *Neuron, 31,* 889–901.

Rubia, K., Russell, T., Overmeyer, S., Brammer, M. J., Bullmore, E. T., Sharma, T., Simmons, A., Williams, S. C., Giampietro, V., Andrew, C. M., & Taylor, E. (2001). Mapping motor inhibition: Conjunctive brain activations across different versions of go/no-go and stop tasks. *Neuroimage, 13,* 250–261.

Rushworth, M. F., Hadland, K. A., Paus, T., & Sipila, P. K. (2002). Role of the human medial frontal cortex in task switching: A combined fMRI and TMS study. *Journal of Neurophysiology, 87,* 2577–2592.

Sakai, K., Hikosaka, O., Miyauchi, S., Sasaki, Y., Fujimaki, N., & Putz, B. (1999). Presupplementary motor area activation during sequence learning reflects visuo-motor association. *Journal of Neuroscience, 19,* 1–6.

Schall, J. D., & Hanes, D. P. (1993). Neural basis of saccade target selection in frontal eye field during visual search. *Nature, 366,* 467–469.

Schall, J. D., Morel, A., & Kaas, J. H. (1993). Topography of supplementary eye field afferents to frontal eye field in macaque: Implications for mapping between saccade coordinate systems. *Visual Neuroscience, 10,* 385–393.

Schiller, P. H., Sandell, J. H., & Maunsell, J. H. (1987). The effect of frontal eye field and superior colliculus lesions on saccadic latencies in the rhesus monkey. *Journal of Neurophysiology, 57,* 1033–1049.

Schlag, J., & Schlag-Rey, M. (1987). Evidence for a supplementary eye field. *Journal of Neurophysiology, 57,* 179–200.

Schlag-Rey, M., Amador, N., Sanchez, H., & Schlag, J. (1997). Antisaccade performance predicted by neuronal activity in the supplementary eye field. *Nature, 390,* 398–401.

Shima, K., Mushiake, H., Saito, N., & Tanji, J. (1996). Role for cells in the presupplementary motor area in updating motor plans. *Proceedings of the National Academy of Sciences, U.S.A., 93,* 8694–8698.

Shook, B. L., Schlagrey, M., & Schlag, J. (1988). Direct projection from the supplementary eye field to the nucleus raphe interpositus. *Experimental Brain Research, 73,* 215–218.

Sweeney, J. A., Mintun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenberg, D. R., & Carl, J. R. (1996). Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *Journal of Neurophysiology, 75,* 454–468.

Ullsperger, M., & von Cramon, D. Y. (2001). Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage, 14,* 1387–1401.

Worsley, K. J., & Friston, K. J. (1995). Analysis of fMRI time-series revisited—again. *Neuroimage, 2,* 173–181.

Yantis, S., & Jonides, J. (1984). Abrupt visual onsets and selective attention: Evidence from visual search. *Journal of Experimental Psychology: Human Perception and Performance, 10,* 601–621.

Zarahn, E., Aguirre, G., & D'Esposito, M. (1997). A trial-based experimental design for fMRI. *Neuroimage, 6,* 122–138.