Success and Failure Suppressing Reflexive Behavior

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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 prepontency 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
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

**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.
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 antisaccade 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 $p s < .008$). 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 $t s > 4.11$ and all $p s < .002$). 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, $t(11) = 10.79, p > .0000004$;
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.
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 readsies 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

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.
has been shown to be more prominent prior to correct antisaccades than before prosaccades and reflexive pro-
saccade 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 anti-
saccade 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 move-
ment-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 deter-
mines, 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 specifi-
cally designed to better address differential contribu-
tions 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 oculomo-
tor 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, Slaghrey, &
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 oculo-
motor 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 intercon-
ected 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, pre-
venting 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 organ-
zizing 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 paramentral 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 comparisons) 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 these analyses, 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.

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The data reported in this experiment have been deposited in The fMRI Data Center (http://www.fmridc.org). The accession number is 2-2003-113E7.

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