Distinct Neural Correlates for Volitional Generation and Inhibition of Saccades

Benedikt Reuter, Christian Kaufmann, Julia Bender, Thomas Pinkpank, and Norbert Kathmann

Abstract

The antisaccade task has proven highly useful in basic and clinical neuroscience, and the neural structures involved are well documented. However, the cognitive and neural mechanisms that mediate task performance are not yet understood. An event-related fMRI study was designed to dissociate the neural correlates of two putative key functions, volitional saccade generation and inhibition of reflexive saccades, and to investigate their interaction. Nineteen healthy volunteers performed a task that required (a) to initiate saccades volitionally, either with or without a simultaneous demand to inhibit a reflexive saccade; and (b) to inhibit a reflexive saccade, either with or without a simultaneous demand to initiate a saccade volitionally. Analysis of blood oxygen level-dependent signal changes confirmed a major role of the frontal eye fields and the supplementary eye fields in volitional saccade generation. Inhibition-related activation of a specific fronto-parietal network was highly consistent with previous evidence involved in inhibitory processes. Unexpectedly, there was little evidence of specific brain activation during combined generation and inhibition demands, suggesting that the neural processing of generation and inhibition in antisaccades is independent to a large extent.

INTRODUCTION

The antisaccade task has become an important tool in neuroscience, providing insight into well-defined brain functions based on cell recordings, lesion studies, and functional neuroimaging (Munoz & Everling, 2004). In standard paradigms, subjects have to fixate a central visual stimulus. Then, a peripheral stimulus is presented, and subjects have to look immediately to its mirror position. Because task performance is most sensitive to neuropsychiatric conditions like schizophrenia (Hutton & Ettinger, 2006), insight into the neurocognitive functions involved will prepare the ground for better understanding of pathological brain function.

Most studies on the neural correlates of antisaccade performance used control conditions where subjects had to look immediately toward sudden-onset visual stimuli (pro-saccades). A number of neuroimaging studies showed that typical antisaccade tasks evoke greater activation in a wide network of brain areas including the FEFs, the supplementary eye fields (SEFs), the intraparietal sulcus (IPS), the dorsolateral prefrontal cortex (DLPFC), the ACC, and the ventrolateral prefrontal cortex (VLPFC; Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Ford, Goltz, Brown, & Everling, 2005; Curtis & D’Esposito, 2003; Desouza, Menon, & Everling, 2003; Connolly, Goodale, Menon, & Munoz, 2002; Sweeney et al., 1996; O’Driscoll et al., 1995). The functional significance of these activations is not clear yet because pro- and antisaccades differ in at least two aspects. First, antisaccades but not prosaccades require the inhibition of unwanted reflexive saccades toward a new stimulus. Second, antisaccades require volitional saccade generation, that is, the rule-based computation and initiation of a saccade. In contrast, prosaccade tasks allow to follow a motor signal that is induced by the onset of a visual stimulus.

A recent fMRI study (Ettinger et al., 2008) aimed to isolate the specific components of antisaccades by employing delayed pro- and antisaccade tasks (Reuter, Jager, Bottlender, & Kathmann, 2007). Like standard antisaccades, these tasks require to inhibit a reflexive saccade when a peripheral visual stimulus is presented. However, the demand to generate a volitional saccade is delayed for a few seconds. The study by Ettinger et al. (2008) confirmed multimehood evidence of the FEFs and the IPS being involved in saccade generation (Grosbras, Laird, & Paus, 2005; Hanes & Schall, 1996; Rivaud, Muri, Gaymard, Vermesch, & Pierrot-Deseilligny, 1994; Bruce & Goldberg, 1985), whereas inhibition in the delayed tasks was associated with activation in the right supramarginal gyrus (SMG) and in the lateral FEF.

Specific correlates of saccade inhibition were also found when pro- and antisaccades were randomly interleaved with no-go trials and subjects had to continue central fixation after onset of peripheral stimulus (Brown, Vilis, & Everling, 2008; Brown, Goltz, Vilis, Ford, & Everling, 2006). No-go trials were consistently associated with activation in the right SMG. Other correlates of no-go inhibition varied across studies. When no-go trials were interleaved with equally frequent pro- and antisaccades, the no-go...
condition was also associated with activation in the superior frontal sulcus and the posterior cingulate sulcus (Brown et al., 2006). When the need for response inhibition was increased by interleaving no-go trials with twice as many prosaccade trials, response inhibition on no-go trials was additionally associated with activation in the SEF, the ACC, and the VLPFC (Brown et al., 2008). Thus, there is some evidence of independent neural correlates of saccade generation and inhibition. However, brain activation associated with inhibition has not been fully consistent across studies, which may reflect variations of inhibitory demands. In the study by Ettinger et al. (2008), the inhibition phase was contrasted with the generation phase, and only the inhibition phase contained the additional demand to decide whether to make a saccade or not. In contrast, Brown et al. (2008) employed a cue that informed subjects on the forthcoming prosaccade, antisaccade, or no-go demand. Hence, inhibition on no-go trials was not confounded with additional task selection processes. However, precuing allowed for task-specific preparation, so that both brain activation and performance were largely determined by preparatory processes.

With regard to antisaccades, a critical unresolved issue refers to the interaction of volitional saccade generation and inhibition. Dissociable neural correlates were shown on isolated conditions for each component. However, it is not yet clear whether brain activation upon simultaneous generation and inhibition, as required in typical antisaccades, simply reflects the sum of brain activations on isolated generation and inhibition conditions. Alternatively, the effect of simultaneous demands may be larger or smaller than the sum of effects of isolated demands, or simultaneousness activates brain areas that are not active on isolated conditions.

The present fMRI study investigated the BOLD response to isolated and simultaneous saccade generation and inhibition when both the preparatory activation and the task selection demand were identical on each condition. The task first required to fixate the same central dot in all trials (Figure 1). The dot was then replaced by an arrow instructing the generation of a saccade to the left or right or by an arrowlike stimulus without direction information, instructing to continue central fixation. Both stimuli types were sometimes accompanied by a peripheral visual stimulus, which served as a distractor on fixation trials and when a saccade to the opposite side was required. This allowed us to test for the effects of volitional saccade generation (generation vs. fixation), inhibition (distracter vs. no distracter), and interaction of both on otherwise identical conditions.

We expected volitional saccade generation to be associated with fronto-parietal activation, most probably including the FEF and the IPS. Inhibition was expected to activate a fronto-parietal network, most probably including the right SMG. With regard to possible interactions, a priori information was sparse. Theoretical considerations suggest that efficient generation of intended saccades may contribute to successful inhibition of reflexive saccades toward a distracter (Kristjansson, 2007; Hunt, Olk, von Muhlenen, & Kingstone, 2004; Massen, 2004; Reuter & Kathmann, 2004). Facing a distracter, the possibility to commit a reflexive error might thus evoke a strengthening of saccade-related brain activation on generation conditions as compared with generation conditions without inhibition.

**Figure 1.** Stimulus timing and task design. (A) Succession and duration of stimuli. The initial fixation point (central filled circle) was identical on all trials. Only the subsequent imperative stimuli varied across conditions. The figure illustrates imperative stimuli of Condition 2 (central arrow) and Condition 3 (neutral symbol, peripheral filled circle). In the experiment, fixation point and imperative stimuli were yellow. (B) Imperative stimuli of Conditions 1–4 (examples), representing the combined levels of the factors volitional saccade generation and inhibition. (C) Imperative stimuli of Condition 5 (visually supported saccade generation).
METHODS

Participants

Twenty-two students performed saccade tasks in the scanner and received €20 for participation. Subjects with self-reported signs of neurological diseases or mental disorders (as assessed by the Structured Clinical Interview for the DSM-IV; First, Spitzer, Gibbon, & Williams, 1995), drug use in the last three months, or contraindications toward MRI scanning, were not included. Because in three subjects FMRI data quality was insufficient due to excessive head motion, only the remaining 19 subjects (mean age = 24.9 years, SD = 3.2) were included in the analyses of group data. Seventeen of them were right-handed, two were left-handed.

The study protocol was approved by a local ethics committee and was in accordance with the ethical standards of the revised declaration of Helsinki (Edinburgh, October 2000). After complete description of the study to the subjects, written informed consent was obtained.

Apparatus and Data Acquisition

BOLD signal was acquired using a 1.5-T scanner (Siemens Sonata, Erlangen, Germany) with the Siemens Magnetom Sonata (circular polarized) standard head coil. A total of 869 volumes lasting for 27 min 5 sec (T2*-weighted single-shot gradient EPI sequence) were acquired using the following parameters: repetition time = 1870 msec, echo time = 40 msec, 33 consecutive slices, 3 × 3 × 3.5 mm voxel, flip angle = 90°, field of view = 192 mm, 64 × 64 matrix, AC-PC orientation (oblique). Before functional runs, 176 anatomical, three-dimensional, modified derived equilibrium Fourier transform slices (Deichmann, Schwarzbauer, & Turner, 2004) were acquired (spatial resolution 1 × 1 × 1 mm, repetition time = 12.24 msec, echo time = 3.56 msec, flip angle = 23°, 256 × 224 matrix). Stabilization and movement prevention were achieved through cushioning of the head, the arms, and the legs. Subjects wore earplugs for auditory protection and earphones for communication with the scanner control room.

Stimuli were generated by a computer, using Presentation software (Neurobehavaioral Systems, Albany, CA), and presented with an LCD projector onto a 13 × 9.75-cm milk glass screen attached to the head coil, mounted approximately 14.5 cm above the subjects’ eyes.

Movements of the right eye were recorded at a sampling rate of 50 Hz using MEyeTrack-LR (SensoMotoric Instruments, Teltow, Germany), a video-based eye tracking system with a camera installed inside the scanner room recording the infrared illuminated eyes via a mirror. The system provides a tracking resolution of 0.1° and a gaze position accuracy of 0.5°–1°. Before the experiment, a five-point calibration of the tracking system was performed, and after each experimental block of 20 trials, a drift correction was carried out.

Saccade Tasks and Stimuli

All stimuli were presented within three adjacent square frames with thin gray sidelines (side length 8.5°, line thickness < 0.1°; Figure 1). In the beginning of each trial, subjects were instructed to fixate a filled yellow circle (diameter 1.5°) presented in the center of the middle square. After 3.74 sec, the circle was replaced by an arrow (height 1.5°, width 2°) directing toward the left or the right square or an arrowlike neutral symbol (equal dimensions) without direction information. Subjects were instructed to look into the middle of the square the arrow directed to or to continue central fixation in case of an arrowlike symbol. The central change was sometimes accompanied by the onset of another filled yellow circle (diameter 1.5°) in the middle of the left or the right square. There were five different conditions: (1) arrow with a circle opposite to the arrow direction; (2) only the arrow, no circle; (3) neutral symbol with a circle in the left or right frame; (4) only neutral symbol; (5) arrow with a circle in arrow direction.

On all conditions, all stimuli were extinguished after 1.87 sec. Only the frame remained present during the intertrial interval, which was pseudorandomly varied and had one of the following durations: 7.48 sec, 8.42 sec, 9.35 sec, 10.29 sec, 11.22 sec, 12.16 sec, 13.08 sec or 14.03 sec. There were 20 test trials of each condition, which were pseudorandomly interleaved within one run of 100 trials. After every 20 trials, the intertrial interval was extended to 43 sec to provide a short rest period. On Conditions 1, 2, and 5, the arrow pointed equally often to the left and to the right. On Conditions 1 and 3, the circle appeared equally often in the left and the right frame. Before the scanning session, subjects received detailed instructions about each condition and performed 20 practice trials (four of each condition) outside the scanner.

Experimental Design

Conditions 1 and 2 required volitional saccade generation either with (Condition 1) or without (Condition 2) concurrent inhibition of a reflexive saccade to the distracter (Figure 1). They contrasted to Conditions 3 and 4, which required fixation on otherwise identical conditions. Conditions 1 and 3 required inhibition of a reflexive saccade with (Condition 1) and without (Condition 3) volitional saccade generation. They contrasted to Conditions 2 and 4, which did not require inhibition on otherwise identical conditions. Condition 5 was included to ensure that subjects considered the circle as a potential saccade target, which was expected to increase the inhibitory demands on the distracter conditions. The onset of a dot at the target position of the saccade is likely to facilitate saccade generation, so that these saccades are considered to be more reflexive than the purely volitional saccades in Conditions 1 and 2. It was therefore not included in the evaluation of neural correlates of volitional saccade generation.
**Data Analysis**

**Behavioral Data**

Saccades were detected based on minimum amplitude (>3°) and velocity (>50° per second) using BrainVision Analyzer software (Brain Products, Munich, Germany). The data point after the saccade exceeded a velocity of 30° per second was defined as saccade onset. Only the initial saccade after onset of the imperative signal was used to evaluate performance. The 0.4% of all trials were classified as invalid because the initial saccade was anticipatory as defined by a latency of less than 80 msec after onset of the imperative signal (Fischer et al., 1993; Wenban-Smith & Findlay, 1991). Another 3.0% of all trials were invalid because data loss (due to failures to detect the pupil) or technical artifacts prevented unequivocal evaluation of trial performance. The remaining valid trials were classified as correct if the arrow was answered by a saccade in the correct direction or if the neutral symbol was answered by constant fixation until the end of the trial. For each arrow condition (Conditions 1, 2, and 5), we calculated the median latency of correct saccades as individual performance measure. For inhibition conditions (Conditions 1 and 3), we calculated the proportion of direction errors (saccades in the direction of the circle) relative to all valid trials as individual measure of inhibitory performance. Condition effects on latencies were evaluated using one-way ANOVA for repeated measures with condition (Conditions 1, 2, and 5) as within-subjects factor and subsequent t test for paired samples. Paired-samples t tests were also used to test for different inhibitory performance in the two inhibition conditions. The alpha level for these tests was set to .05 (two tailed).

**fMRI Data**

fMRI data were analyzed with SPM5 (Statistical Parametric Mapping; Friston et al., 1994). To avoid nonsteady state effects caused by T1 saturation, the first five volumes of each functional time series were excluded from further analysis. Images were then slice-time corrected, and the anterior and the posterior commissural lines were defined for each subject. By realigning all images to the mean volume to adjust for head movements, a motion correction estimation was computed for all subjects. Head movement or rotation exceeding 2 mm in any dimension was not accepted and led to exclusion of the subject.

The acquired anatomical data were coregistered with the mean T2* EPI image. The high-resolution anatomical image was then segmented into gray matter, white matter, and cerebrospinal fluid. Image segmentation included an automated spatial transformation (12-parameter affine transformation followed by nonlinear iterations using 7 × 8 × 7 basis functions) onto a T1 template provided by the Montreal Neurological Institute (MNI template). The resulting normalization parameters were applied to the T2* scans, with a downsampling to a resolution of 2 × 2 × 2 mm voxel size. Finally, the data were smoothed by an FWHM isotropic Gaussian kernel of 8 mm to get a locally weighted average of the surrounding pixels.

Further analysis of fMRI data was restricted to trials with correctly executed saccades. On the single-subject level, each event of interest was convolved with the canonical hemodynamic response function. Events of interests were modeled separately for the five different conditions and involved the onsets of the respective imperative stimuli (i.e., the arrows or arrow-like symbols with or without peripheral

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**Table 1. Brain Areas with Significant Main Effects of Saccade Generation**

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Brodmann’s area</th>
<th>Label</th>
<th>MNI Coordinates</th>
<th>kE</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipito-parietal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuneus, lingual gyrus, posterior cingulate</td>
<td>17, 18, 19, 30</td>
<td></td>
<td>−14 −64 6 sub</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>6</td>
<td>FEF</td>
<td>−26 −6 56</td>
<td>426</td>
<td>4.78</td>
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<tr>
<td>Middle frontal gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>6</td>
<td>FEF</td>
<td>18 4 62</td>
<td>337</td>
<td>4.47</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
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<td>1024</td>
<td>4.19</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>6</td>
<td>SEF</td>
<td>6 −10 72</td>
<td>64</td>
<td>4.07</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claustrum</td>
<td>−</td>
<td></td>
<td>38 0 6</td>
<td>59</td>
<td>4.79</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>39</td>
<td></td>
<td>−46 −76 24</td>
<td>42</td>
<td>3.25</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>2</td>
<td></td>
<td>58 −22 30</td>
<td>29</td>
<td>3.16</td>
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<tr>
<td>Insula</td>
<td>13</td>
<td></td>
<td>46 12 4</td>
<td>29</td>
<td>3.02</td>
</tr>
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</table>

Sub = subcluster.
stimulus). Temporal smoothing was done with a high-pass filter cutoff set to 128 sec. Univariate regression analysis was used to calculate estimates for the following contrasts of interest: main effect of saccade generation (Conditions 1 and 2 > Conditions 3 and 4), main effect of inhibition (Conditions 1 and 3 > Conditions 2 and 4), and the interactions of generation and inhibition (condition 2 and 3 > 1 and 4, and 1 and 4 > 2 and 3). In addition, we contrasted Conditions 2 and 5 (Conditions 2 > 5; volitional saccade generation vs. visually guided saccade generation).

Single-subject contrast images were then combined at the group level (random effects analysis) to produce statistical parametric maps of group activation using one-sample t tests. The significance level was set to $q < .05$ [p values corrected with false discovery rate (FDR); minimum cluster size set to 25 voxels]. As regards main effects, there were significant activations for the main effect of generation but not for the main effect of inhibition, implying distinct conclusions for generation (see Discussion). Insignificant results for inhibition impeded the validation of brain areas involved in inhibition but would not justify denying inhibition-related neural activation. Given previous evidence of inhibition-related activation (Brown et al., 2006, 2008), we also explored for activations at a less conservative significance level of uncorrected $p < .005$.

Results were localized according to the Talairach Daemon (Lancaster et al., 2000) and were defined by Talairach coordinates (Talairach & Tournoux, 1988). Clusters that were mainly white matter according to Talairach Daemon localization were not included. Subclusters of at least 30% of the original cluster size that were gray matter clusters were taken into the results. MNI coordinates of the contrast images were transformed into Talairach coordinates using a tool provided by Matthew Brett (http://www.fil.ion.ucl.ac.uk/spm, access date July 5, 2006).

**RESULTS**

**Behavioral Data**

Latencies of correct saccades showed a significant main effect of condition, $F(2) = 53.86, p < .001$. Latencies on Condition 1 (arrow with distracter, $M = 519$ msec, $SD = 87$ msec) were longer than on Condition 2 (only arrow, $M = 490$ sec, $SD = 70$ sec; $t = 3.70, p = .002$) and on Condition 5 (arrow directing toward dot, $M = 460$, $SD = 78$; $t = 7.61, p < .001$). The difference between Conditions 2 and 5 was also significant ($t = −5.29, p < .001$). Hence, latencies were longest when volitional saccade generation was accompanied by inhibitory requirements, intermediate when only volitional saccade generation was required, and shortest when volitional generation was supported by the onset of a visual saccade target.

Direction errors were more frequent on Condition 3 (fixation with distracter, $M = 12.5\%$, $SD = 13.4\%$) than on Condition 1 (generation with distracter, $M = 4.8\%$, $SD = 5.68\%$). The difference between conditions was significant ($t = −2.31, df = 18, p = .033$). The occurrence of errors was restricted to 16 subjects on condition 3 and 11 subjects on condition 1. Mean latencies for these subgroups were $375$ msec (condition 3; $SD = 75$) and $299$ msec (condition 1; $SD = 108$). Also, for those who made errors on both conditions ($N = 9$), the mean latencies appeared to be longer on condition 3 ($M = 347$ msec; $SD = 66$) than on condition 1 ($M = 294$ msec; $SD = 110$). The difference was not significant (Wilcoxon test, $Z = −1.48, p = .14$). Because error latencies rely on very few trials per subject, their reliability is questionable and interpretation should be very cautious.

**fMRI Data**

Table 1 shows brain areas that had a significant ($p < .05$, FDR corrected) main effect of volitional saccade generation. Beyond expected bilateral activation in FEF and SEF, activation included a large cluster of connected bilateral activations in occipital and parietal areas, including the IPS (Figure 2A). Further bilateral activation referred to the insula/claustrum region (with somewhat different activation peaks in the left and the right cortex) and the cerebellum. Unilateral activation was found in the left middle temporal gyrus and in the right precentral and postcentral gyri.

Inhibition did not yield significant main effects on the a-priori defined significance level. At the more liberal level of $p < .005$ (uncorrected), right hemisphere activations were found in the cuneus, the precentral gyrus, the SMG, and the superior frontal gyrus (Table 2, Figure 2B). Left hemisphere activation was seen in the parahippocampal gyrus, the precuneus, the superior temporal gyrus, and the cerebellum.

The first interaction (condition 2 and 3 > 1 and 4) was significant for the occipital gyrus and the cuneus ($p < .05$, FDR-corrected) (Table 3). The effect on occipital gyrus activation implied that volitional saccade generation was associated with a reduced BOLD activation on conditions with distracter, whereas there was no such effect on conditions without distracter (Figure 2C). In contrast, the effect on cuneus activation implied that volitional saccade generation was associated with an increased BOLD activation signal on conditions with distracter, whereas there

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**Figure 2.** Statistical parametric maps and contrast estimates of BOLD activation in selected brain areas. Note: Bar graphs depict BOLD contrast estimates for selected peak activations on the four different combinations of the generation and the inhibition factor: G+ = generation, G− = no generation, I+ = inhibition, I− = no inhibition. (A) Selected brain areas with a significant main effect of generation ($P_{FDR-corrected} < .05$, $k = 25$ voxels). (B) Selected brain areas with a significant main effect of inhibition ($P_{uncorrected} < .005, k = 25$ voxels). (C) Selected brain areas with a significant interaction effect ($P_{FDR-corrected} < .05, k = 25$ voxels).

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was no such effect on conditions without distracter. The second interaction (condition 1 and 4 > 2 and 3) was not significant for any brain area.

The contrast between Conditions 2 and 5 did not yield any significant effect on the BOLD activation.

DISCUSSION

Saccade Generation

Volitional saccade generation was associated with activation in several brain areas that have repeatedly been found to be associated with antisaccade performance. Especially, the FEFs and the SEFs were reliably activated in previous studies that compared antisaccades with prosaccades or fixation conditions (Ettinger et al., 2008; Curtis & D’Esposito, 2003; Connolly et al., 2002). The present results confirm the assumption that these areas are especially important for the generation component of the antisaccade task.

FEF involvement in saccade generation has been documented in numerous neuroimaging and lesion studies and in cell recordings (Mort et al., 2003; Pierrot-Deseilligny, Ploner, Muri, Gaymard, & Rivaud-Pechoux, 2002; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000; Paus, 1996; Henik, Rafal, & Rhodes, 1994; Bruce & Goldberg, 1985). A recent fMRI study revealed that latencies of antisaccades were shorter the more the FEF contralateral to saccade direction was activated, corroborating a functional relationship between FEF activation and saccade generation (Connolly, Goodale, Goltz, & Munoz, 2005). Another fMRI study compared centrally cued saccades and visually guided saccades and suggested greater FEF activation in volitional saccade generation (Mort et al., 2003).

As regards the SEF, evidence from nonhuman primates suggest some functional overlap with the FEF during saccade generation (Stuphorn & Schall, 2002). Neurons of both areas are responsive to visual stimulation and discharge in relation to saccades (Schall, 1991; Schlag & Schlag-Rey, 1987). However, the SEF was also shown to serve specific functions in the executive control of eye movements (Schall & Boucher, 2007). Both human neuroimaging studies and nonhuman cell recordings showed greater activation of SEF or specific SEF neurons in antisaccades compared with visually guided saccades (Amador, Schlag-Rey, & Schlag, 2004; Curtis & D’Esposito, 2003; Schlag-Rey, Amador, Sanchez, & Schlag, 1997; O’Driscoll et al., 1995), which has been attributed to the inhibitory component of antisaccades (Curtis & D’Esposito, 2003). The present study does not support this attribution, as SEF activation was not associated with inhibition of reflexive saccades. SEF activation in our study may nevertheless relate to executive control, as it was found on conditions of volitional saccade generation. There is some evidence that the SEF is particularly involved when saccade generation is not guided by a visual target stimulus (Carpenter, 2004; Schall, 1991).

Both FEF and SEF activations are considered to be particularly involved in the preparation rather than the execution of saccades (Ford et al., 2005; Curtis & D’Esposito, 2003; Desouza et al., 2003). It has even been suggested that

Table 2. Brain Areas with Main Effects of Inhibition*

<table>
<thead>
<tr>
<th>Anatomical Region</th>
<th>Brodmann’s area</th>
<th>Label</th>
<th>MNI Coordinates</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>x   y   z   kE  Z</td>
</tr>
<tr>
<td>Precentral gyrus/inferior frontal</td>
<td>44/45</td>
<td>VLPFC</td>
<td>46  16  8  95  3.97</td>
</tr>
<tr>
<td>gyrus</td>
<td></td>
<td></td>
<td>50  −42 30  92  3.82</td>
</tr>
<tr>
<td>SMG</td>
<td>40</td>
<td></td>
<td>−10 −8 −16 215 3.74</td>
</tr>
<tr>
<td>Parahippocampal gyrus</td>
<td>34</td>
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<td>−2 −62 20 121 3.59</td>
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<tr>
<td>Cerebellum</td>
<td>7</td>
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<td>−2 −52 54 92  3.56</td>
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<tr>
<td>Superior temporal gyrus</td>
<td>39</td>
<td></td>
<td>−46 −50 6 26  3.52</td>
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<tr>
<td>Cuneus</td>
<td>17</td>
<td>Visual cortex</td>
<td>−8 −80 4 77  4.05</td>
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*p<.005.

Table 3. Brain Areas with Significant Effects of Generation by Inhibition Interaction

<table>
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<tr>
<th>Anatomical Region</th>
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<th>Label</th>
<th>MNI Coordinates</th>
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<tr>
<td></td>
<td></td>
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<td>x   y   z   kE  Z</td>
</tr>
<tr>
<td>Middle occipital gyrus</td>
<td>18</td>
<td>Visual cortex</td>
<td>26 −93 5 1887 4.96</td>
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<tr>
<td>Middle occipital gyrus</td>
<td>18</td>
<td>Visual cortex</td>
<td>−34 −91 5 1220 4.61</td>
</tr>
<tr>
<td>Cuneus</td>
<td>7</td>
<td></td>
<td>18 −78 30 236 3.83</td>
</tr>
</tbody>
</table>
that the observation of BOLD effects for the execution period represents a carryover from preparatory activation (Ford et al., 2005; Desouza et al., 2003). The present study revealed a BOLD effect for generation albeit preparation was equal in generation and no-generation conditions, suggesting that beyond its undoubted meaning for saccade preparation, FEF and SEF activities play an independent role in the execution of saccades.

Beyond the activation of FEF and SEF, the generation conditions were associated with a large cluster of occipitoparietal activation. This included bilateral activation of the medial wall of the IPS and the adjacent superior parietal lobule. This region is considered a putative human equivalent of the lateral intraparietal areas in monkeys (Grefkes & Fink, 2005). It was shown to be involved in saccade generation and may reflect the processing of visuospatial information (Ettinger et al., 2008; Brown et al., 2006; Grosbras et al., 2005; Pierrot-Deseilligny, Mlea, & Muri, 2004). In previous studies, the IPS was more active during antisaccades compared with prosaccades (Ettinger et al., 2008; Brown et al., 2006; Curtis & D’Esposito, 2003; Kimmig et al., 2001), possibly reflecting more demanding visuospatial processing such as vector inversion, that is, the translation of a visual location code into a mirror image location code for a saccade target (Nyffeler, Rivaud-Pechoux, Pierrot-Deseilligny, Diallo, & Gaymard, 2007). The saccades in the present study did not require vector inversion nor the simple perception of peripheral information (as in typical prosaccades) but the computation of peripheral oculomotor target locations based on centrally presented cues. IPS activation on this condition is in line with the view that the IPS is involved in coding target locations of saccades (Medendorp, Goltz, & Vils, 2005).

As regards the remaining parieto-occipital activations (lingual gyrus, precuneus, and cuneus, including the extrastriate visual cortex), similar activations were shown to be associated with antisaccades and other saccade generation conditions (Grosbras et al., 2005), but their functional meaning has rarely been addressed. Note that visual stimulation of our generation and no-generation conditions was nearly identical (Figure 1), ruling out explanations by visual and attentional processing of new environmental stimuli. However, only the generation conditions were associated with a forthcoming shift of the visual image on the retina. Such shifts are compensated by neuronal remapping in which classical receptive fields shift to future spatial locations before the onset of a saccade (Duhamel, Colby, & Goldberg, 1992). Remapping is considered to preserve the perception of a stable visual scene and probably takes place in a number of cortical areas including the parietal cortex and extrastriate visual areas (Merriam, Genovese, & Colby, 2007).

So far we discussed the effects of volitional saccade generation, collapsing saccades away from peripheral stimuli and those without sudden-onset peripheral stimuli. Such saccades are considered volitional because their initiation is completely rule based and not triggered by the onset of a saccade target. The saccades in Condition 5 were based on the same rule (“Look into arrow direction!”). However, here the rule was fully compatible with the reflexive tendency to look toward a new stimulus, suggesting a reflexive component in saccade generation. In support of this assumption, these saccades had shorter latencies than the fully volitional saccades. However, the contrast between these “prosaccades” and the other saccade generation conditions did not yield significant differences in brain activation. By contrast, Mort et al. (2005) found greater activation in FEF and IPS in centrally cued saccades compared to typical prosaccades toward peripheral stimuli. In the present study, due to the central cueing of all saccades, the prosaccades (toward peripheral stimuli) may have been less reflexive than those in Mort et al. (2003), so that their volitional component did not differ as much from purely volitional saccades. It is possible that our experimental design did not provide enough power to detect neural correlates of this rather subtle difference between centrally cued saccade generation with and without visual stimulation of the saccade target.

Saccade Inhibition

Using the same statistical threshold as for the generation contrast, the inhibition contrast did not yield any significant effect, suggesting that the neural correlates of saccade inhibition are not as distinct as the correlates of saccade generation. However, given previous evidence of inhibition-related brain activation in similar saccade tasks and the relatively high probability of type II errors, the failure to find significant effects would not justify denying inhibition-related brain activation. Lowering the statistical threshold to explore for smaller than a priori expected effects, we found evidence of closely circumscribed inhibition-related activation in a number of cortical and subcortical areas. The activations in the right SMG and the VLPFC are consistent with previous evidence of inhibition-related brain activation.

Right SMG activation was associated with the inhibition of reflexive saccades in different oculomotor tasks (Brown et al., 2006, 2008; Ettinger et al., 2008; Chikazoe et al., 2007; Matsuda et al., 2004). Similar activation of the inferior parietal lobe including the SMG or the neighboring inferior parietal lobule was reliably associated with response inhibition in manual go/no-go tasks (Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Rubia et al., 2001), suggesting a supramodal role in response inhibition. Yet, the SMG was also found to be involved in covert attention shifts toward visual stimuli (Perry & Zeki, 2000; Corbetta et al., 1998) and may mediate stimulus detection or alerting other areas to the appearance of a salient stimulus (Perry & Zeki, 2000). These functions may be triggered automatically by the distracters in the inhibition conditions of the present study, providing a different explanation of SMG activation. Future research will have to dissociate attentional and inhibitory components in the response to distracters.
Activation of the right VLPFC was repeatedly found to be associated with inhibition in manual go/no-go and stop tasks (Chikazoe et al., 2007; Aron & Poldrack, 2006; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Liddle, Kiehl, & Smith, 2001; Rubia et al., 2001) but not in typical antisaccade tasks. This difference between task types may reflect a difference in how inhibition is implemented. Although no-go and stop tasks require the inhibition of prepotent responses under minimal preparatory set, typical antisaccades allow to prepare the task set before antisaccade execution and may require less inhibition at the time of peripheral stimulus onset (Chikazoe et al., 2007). In line with this assumption, the right VLPFC was active in antisaccades when inhibitory demands were increased by interleaving pro- and antisaccades and preventing task-specific preparation (Chikazoe et al., 2007). As task-specific preparation was also prevented in the current study, activation of the right IFG might actually reflect inhibitory processes that start when the unwanted prepotent response is triggered.

The remaining brain areas with main effects of inhibition at the lower significance level in the present study have not been suggested to serve inhibitory functions in previous studies. Activation of the extrastriate visual cortex may be due to visual processing of the distracter whose sudden occurrence distinguished between inhibitory and noninhibitory conditions of the present study. Other areas (precuneus, superior temporal gyrus, and cerebellum) were previously shown to be generally involved in oculomotor tasks and spatial attention (Grosbras et al., 2005; Gitelman, Parrish, Friston, & Mesulam, 2002; Corbetta et al., 1998), so that their activation may not directly reflect inhibitory processes either. In general, the effects of inhibition in the present study appear to be somewhat weaker compared to recent studies on other oculomotor tasks addressing inhibitory functions (Brown et al., 2006; Brown et al., 2008; Ettinger et al., 2008). This might reflect our efforts to minimize the cognitive and behavioral differences between inhibitory and non-inhibitory conditions. In previous studies inhibition was typically modeled as a difference between explicitly different tasks (e.g. go task vs. nogo task), which typically implied complex functional differences (e.g., during preparation and response period). In contrast, in the present study inhibition is modeled as a difference within basically equal tasks, i.e. within the task of looking into arrow direction and within the task to continue fixation. Moreover, the main effect of inhibition reflects the commonalities of inhibition on different boundary conditions (i.e., fixation and saccade generation). Altogether, our inhibition contrast addressed a very circumscribed function whose neural correlates might be rather subtle. This might explain why whole brain analysis yielded significant effects only with a relatively liberal statistical threshold.

One might be surprised that inhibition was not associated with activation of the DLPFC although lesion studies repeatedly showed that damage to this structure results in increased error rates in antisaccade tasks (Ploner, Gaymard, Rivaud-Pechoux, & Pierrot-Deseilligny, 2005; Fukushima, Fukushima, Miyasaka, & Yamashita, 1994; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991). Several other FMRI studies revealed activation of the DLPFC on antisaccades compared to prosaccades or fixation control conditions (Desouza et al., 2003; Ettinger et al., 2008; McDowell et al., 2002), which has sometimes been attributed to the inhibitory component of antisaccades. However, DLPFC activation is probably related to the preparation of antisaccades (Everling & Desouza, 2005) and recent studies suggested that DLPFC activation is more likely to reflect greater demands in the activation and maintenance of task rules or in response selection (Ettinger et al., 2008; Dyckman, Camchong, Clementz, & McDowell, 2007). In the present study the same task rules had to be maintained throughout the experiment and specific preparation for the different conditions was impossible. It is thus likely that the DLPFC was similarly active throughout the experiment.

**Interaction of Generation and Inhibition**

We expected that on distracter conditions the likelihood to commit a reflexive error might strengthen saccade-related brain activation. Although there were indeed significant generation by inhibition interactions, their pattern did not match our hypothesis. The interactions referred to occipital brain areas that are unlikely to be involved in saccade generation per se. Regarding the visual cortex, the interaction effect indicated that on conditions with distracter, saccade generation was associated with reduced brain activation, whereas on conditions without distracter, there was no generation effect. This could reflect the suppression of visual processing before saccade onset (Vallines & Greenlee, 2006; Kleiser, Seitz, & Krekelberg, 2004; Ross, Morrone, Goldberg, & Burr, 2001), which might be restricted to conditions with salient extrafoveal visual stimulation. The interaction effect of brain activation in the cuneus implied greater activation upon saccade generation compared with fixation on inhibition conditions, which is in line with the proposed involvement of the cuneus in presaccadic remapping processes (see above). It remains undiscovered why this effect did not show up on noninhibitory conditions.

**Conclusions**

The present study confirmed a major role of FEF and SEF in volitional saccade generation. These areas did not show effects of inhibition or generation by inhibition interactions, suggesting that their involvement in antisaccades is due to the component of volitional saccade generation rather than the inhibition component. Other neural correlates of volitional saccade generation involved the IPS and a widely distributed network of occipito-parietal activation, probably reflecting the coding of saccade target locations and presaccadic remapping. The neural correlates of inhibiting reflexive saccades appear to be less distinct. However, moderate activation of VLPFC and SMG was highly
consistent with previous evidence of a specific frontoparietal network involved in inhibitory processes. The neural correlates of saccade generation differed between inhibitory and noninhibitory conditions, but these differences probably referred to visual processing rather than saccade production. Otherwise, there was no evidence of specific interactions between volitional saccade generation and inhibition.

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Reprint requests should be sent to Benedikt Reuter, Institut für Psychologie, Lehrstuhl für Klinische Psychologie, Humboldt-Universität zu Berlin, Rudower Chaussee 18, 12489 Berlin, Germany, or via e-mail: reuter@psychologie.hu-berlin.de.

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