Neural correlates of inter- and intra-individual saccadic reaction time differences in the gap/overlap paradigm

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Özyurt J, Greenlee MW. Neural correlates of inter- and intra-individual saccadic reaction time differences in the gap/overlap paradigm. J Neurophysiol 105: 2438–2447, 2011. First published February 23, 2011; doi:10.1152/jn.00660.2009.—To examine the neural correlates of contextually differing control mechanisms in saccade initiation, we studied 18 subjects who performed two saccade paradigms in a pseudo-random order, while their eye movements were recorded in the MRI scanner (1.5 T). In the gap task the fixation point was extinguished 200 ms before target onset, and in the overlap task the fixation point vanished 500 ms after target onset. Subjects were asked to maintain stable fixation in the fixation period and to quickly saccade to peripherally presented targets. Inter-individual variation differences were assessed using regression analyses at the second level, with mean saccadic reaction time (SRT) of subjects as a covariate. To identify brain regions varying with trial-by-trial changes in SRTs, we included SRTs as a parametric modulation regressor in the general linear model. All analyses were regions of interest based on previous findings. For the gap paradigm, we did not obtain activation in regions previously shown to be involved in preparatory processes with much longer gap periods. Interestingly, both inter- and intra-individual variability analyses revealed a positive correlation of activation in frontoparietal eye-movement regions with SRTs, indicating that slower saccade performance is possibly associated with higher cortical control. For the overlap paradigm, the trial-by-trial variability analysis revealed a positive correlation of activation in the right opercular inferior frontal gyrus with SRTs, possibly linked to fixation-related processes that have to be overcome to perform a speeded saccade in presence of a fixation point.

oculomotor control; functional magnetic resonance imaging; express saccades; trial-by-trial variability

PERCEPTION OF THE VISUAL WORLD requires an intact, context-sensitive, and highly adaptive interplay between gaze-shifting and gaze-holding mechanisms. Neuronal mechanisms conveying signals to shift or hold gaze are located in a number of brain areas along the neuraxis. These interconnected and dynamically interacting brain areas involve regions of the frontal and parietal cortex, nuclei of the basal ganglia and the thalamus, the superior colliculus (SC), and the brain stem reticular formation (Baker et al. 2006; Findlay and Walker 1999; Leigh and Zee 2006; McDowell et al. 2008). In the midbrain, the SC is known to play a critical role in the control of visual fixation and saccadic eye movements, with neuronal circuits that directly act on the brain stem saccade generator. Discharge rates of distinct neuronal populations in the intermediate layer are well correlated with fixation periods and saccadic eye movements, respectively, showing a reciprocal activation pattern (Munoz and Fecteau 2002; Munoz and Wurtz 1992, 1995). Oculomotor areas of frontoparietal cortex and the basal ganglia are assumed to exert higher-order strategic control on the SC modulating the influence of external stimulus conditions according to current needs and goals. With recordings from single caudate neurons of monkeys during the pretarget period of an antisaccade task (in a gap as well as in an overlap condition), Watanabe and Munoz (2010) recently provided evidence for the involvement of this area in both voluntary and reflexive saccade generation.

The current study aimed to probe cortical and striatal contributions to saccade initiation in the gap/overlap paradigm where minor variations in fixation offset time with respect to target onset time induce a dramatic change in saccadic behavior. In the gap task a period without visual stimulation (e.g., 100–400 ms) is introduced between the offset of the fixation target and the onset of a saccade target, resulting in a marked reduction of mean saccadic latencies, known as the gap effect (Kingstone and Klein 1993a; Pare and Munoz 1996; Saslow 1967). Additionally a proportion of saccades with very short reaction times may occur (express saccades), with latencies as low as 80 to 130 ms (Fischer 1986). In the overlap task presentation of the fixation target continues after target onset (e.g., for 500 ms), thus fixation point and saccadic target overlap in time, resulting in prolonged saccadic latencies.

Like other saccades performed in accordance with predefined rules, task-related reflexive saccades in the gap task have been proposed to be controlled by both volitional (internally driven) and reflexive (sensory driven) commands (Watanabe et al. 2010). Performance in the gap task requires cognitive control to maintain central fixation during the gap period, when no fixation target is present. In line with this, fixation neurons have been identified in frontal eye fields (FEF) and lateral intraparietal area (LIP) that maintained or increased their activity after the disappearance of a foveal fixation point or specifically responded during active fixation in the gap interval when the fixation point was absent (Ben Hamed and Duhamel 2002; Izawa et al. 2009; Sommer and Wurtz 2000). Performance in gap tasks with a constant gap period furthermore enables subjects to anticipate the time of target presentation to enhance saccade initiation. In addition to more low-level processes of ocular fixation release triggered by the vanishing fixation point in the SC (Dorris and Munoz 1995), pretarget processes that serve motor preparation have been assumed to be an essential determinant of the reduction of saccade latencies in the gap paradigm (Kingstone et al. 1995;
Neural correlates of motor preparation processes in the FEF have been detailed by studies using monkey electrophysiology, showing that greater pretarget activity of saccade-related neurons in the FEF is correlated with shorter saccadic reaction times (SRTs) (Everling and Munoz 2000), similar to findings obtained for the SC (Dorris et al. 1997). Based on evidence from studies showing variations in activation patterns of SC neurons with different cognitive states (e.g., spatial attention, motor preparation), it has been hypothesized that pretarget activity in the FEF is one source of express saccade generation by increasing the excitation of SC neurons (Everling and Munoz 2000; Sparks 1999). Neural correlates of advanced motor preparation upstream from the SC have also been shown with fMRI in fronto-parietal eye-movement regions of human subjects (Connolly et al. 2005; Connolly et al. 2002; Cornelissen et al. 2002; Gagnon et al. 2002). Moreover, in line with its role in both initiation and inhibition of saccades, lesions of the frontal eye fields have been reported to both increase (Braun et al. 1992) and to decrease (Rivaud et al. 1994) the express-saccade rate in humans.

With regards to performance in the overlap task, more effort and volition seems to be required for saccade initiation to overcome the ocular fixation reflex induced by the fixation point when a saccade target is flashed in the periphery. Fixation is an active process, either triggered automatically by environmental cues or subject to volitional control. Stimulation studies of the FEF (Goldberg et al. 1986) and the SC (Schiller and Sandell 1983) demonstrated in monkeys an elevated threshold for eliciting saccades and reduced saccadic amplitudes during steady fixation. Investigating eye movement control in patients with a small lesion affecting the left FEF, Rivaud et al. (1994) found increased latencies in an overlap task hypothesizing that the FEF play a crucial role in the disengagement of fixation. Currently, there is no single imaging study explicitly investigating saccade initiation to visual targets in the presence of a foveal fixation point.

The task design and analyses we introduce account for the effects of the sweeping of the fixation point image over the retina during a saccade in the overlap task. Ongoing presentation of a fixation point during saccade performance may have an additional influence on the visual responsive neurons in oculomotor cortical areas and therefore on hemodynamic response patterns, owing to the fact that two dots (fixation and target) are present on the display during the eye movement. Such a regional specific enhancement of activation in the overlap but not the gap paradigm would render the comparison between these conditions meaningless. Accordingly we focused on correlation effects, hypothesizing that shorter mean saccadic latencies in the gap task indicate a more efficient use of timing information, leading to enhanced motor preparation and thus increased activation in fronto-parietal eye movement regions. Based on findings of previous studies with monkey electrophysiology (Hikosaka et al. 2000), we further hypothesized that shorter mean saccadic latencies in the overlap task indicate a more efficient release of subjects’ ocular fixation, inducing increased activation in the FEF and the caudate nucleus.

METHODS

Preparation. Before scanning, a large sample of 67 subjects was trained in one or two sessions with the experimental paradigm to select those with a high proportion (>30%) of express saccades in the gap paradigm. Express saccades are extremely fast saccadic eye movements with a mean around 100 ms (Fischer 1986), which may form a first fast mode of a multimodal SRT distribution in the gap paradigm, especially in trained subjects. Their exact latency range is not precisely defined, and descriptions mostly vary within a range between 80 and 140 ms (Fischer and Ramsperger 1986, 1984; Gezeck and Timmer 1998). In our study, express saccades were considered to be those with latency equal to or less than 130 ms, assumed to indicate an efficient utilization of the timing information in the gap paradigm. Additional inclusion criteria for our subjects were a relatively low percentage of error trials (<10%) and the ability to hold gaze during the fixation period of the experimental tasks.

Subjects. Twenty subjects (24 ± 3 yr; mean ± SD; 15 females; 18 right handed) fulfilled the inclusion criteria and participated at one single scanning session consisting of six experimental runs. They all had normal or corrected to normal vision and reported no history of psychiatric or neurological disorders. Informed consent was obtained from all participants before the training and the scanning sessions according to procedures approved by the Ethics Committee of the University of Oldenburg. The data of two participants (1 female) were excluded from further analyses (1 due to technical reasons, the other due to a marked right ventricle enlargement), leaving a total dataset of 18 subjects for statistical analyses.

Stimuli and procedure. Visual stimulation was created on a VSG2/5 visual stimulus generator (Cambridge Research Systems, Rochester, England). Stimuli were presented via a projector (D-ILA, type DLA-G15E; JVC; Victor Company of Japan) positioned outside the scanner room onto a back projection screen in the bore of the MR scanner. Subjects lay supine and viewed the projected stimuli through a coil-mounted mirror. They performed visually guided saccades in the two different, pseudo-randomized oculomotor tasks (gap and overlap) depicted in Fig. 1. Each trial started with a fixation period lasting 5,800 ms (gap task) and 6,000 ms (overlap task), respectively, with a variable time period (jitter, 30–120 ms) added to the fixed fixation period. During the fixation phase a red square [fixation point (FP); 0.3°] was continuously projected in the center of the display. Subjects were instructed to maintain stable fixation on the FP until the eccentric target became visible. In the gap task the FP was extinguished 200 ms before peripheral target onset. Subjects were asked to maintain central fixation during the gap period and to initiate a speeded saccade to the target only after they detected it. The gap period of 200 ms was chosen due to the fact that this interval seems to be most effective to invoke the shortest saccadic reaction times in the gap paradigm (Dorris and Munoz 1995; Krauzlis and Miles 1996; Opris et al. 2001; Saslow 1967). In the overlap paradigm FP offset occurred 500 ms after target onset. The time period of 500 ms for the overlap between FP and target stimulus was combined with a response deadline of 450 ms to ensure equal stimulus conditions for all saccades performed in this task condition. Saccade targets (green squares, 0.3°) were presented pseudo-randomly left or right of FP with an eccentricity of 10° for the duration of 3,000 ms. After target offset, the FP reappeared in the center of the screen and subjects were requested to saccade back to this location. Subjects performed six runs, each lasting 373.3 s. During one experimental run 20 gap and 20 overlap trials were presented in a pseudo-randomized manner, each trial lasting for ~9 s.

Apparatus. Event-related fMRI was performed with a 1.5 Tesla scanner (Sonata Syngo; Siemens, Erlangen, Germany) in combination with a standard one-channel head coil. Functional data were obtained using T2*-weighted gradient echo-planar imaging (EPI; field of view = 192 × 192 cm; 64 × 64 matrix; voxel dimensions of 3°×3°×3 mm; TE = 54 ms; TR = 3.06 s; interleaved acquisition). During the
stimulation protocol for a single experimental run, 122 volumes were obtained, each with 21 axial slices (interslice gap = 20%) covering the frontal and parietal lobe, thalamus, and the striatum. Additionally, a T1-weighted scan [magnetization prepared rapid-acquisition gradient echo (MPRAGE)] was acquired. The effects of the gradient noises were reduced by earplugs and sound-dampening headphones. To minimize head motion subjects were stabilized by the use of foam padding.

During the training sessions outside the scanner and the experimental session in the MR scanner horizontal eye movements were recorded using the MR-Eyetracker, a fiber-optic limbus tracking device, which we have described previously (Kimig et al. 1999). Before each run of the experiment, the subjects’ eye movements were calibrated by fixing five targets with known displacements. In-house software was used to acquire and display the signals derived from the MR-Eyetracker. The sampling frequency of the eye-tracker signal was 1,000 Hz; the spatial resolution was 0.2°.

fMRI preprocessing. The time series of each voxel was temporally realigned to the acquisition time of the middle slice to correct for acquisition time differences between slices. Functional images were spatially realigned and unwarped to compensate for head motion during data acquisition. After spatial registration of the structural T₁-weighted volume with a mean image of the EPI data, all volumes were spatially normalized to the MNI reference brain (Montreal Neurological Institute, Quebec, Canada). The EPI data were then spatially smoothed with a three-dimensional Gaussian kernel of 10 mm full-with-half-maximum to increase signal-to-noise ratio. The size of the kernel was selected to accommodate inter-individual anatomical variability, which may be quite distinctive, e.g., in the frontal or supplementary eye fields (Grossbras et al. 1999; Luna et al. 1998).

fMRI data analysis. For statistical analyses of the fMRI data the hemodynamic response function was fitted for each event type using a general linear model as implemented in SPM2 (www.fil.ion.ucl.ac.uk/spm). At the single-subject level, data were high-pass filtered with a cut-off of 128 s to account for nonphysiological slow drifts in the measured signal and modeled for temporal autocorrelation across scans with an AR(1) model. Three regressors were defined, two for gap and overlap tasks, respectively (events of interest), and one for error trials (event of no interest). To estimate changes in hemodynamic response, time-locked with event onset, gap-onset times for gap trials, and stimulus-onset times for overlap trials were determined (basic model for the single subject analyses). The slow event-related design with long inter-trial intervals allowed for a separate estimation of the blood oxygen level dependent (BOLD) response evoked by each of the oculomotor tasks. For group analyses, contrast estimates for the regressors of interest, resulting from the single subject analyses, were taken to compute random effects models (one-sample t-tests), thus permitting generalization of results obtained from a given sample to the whole population.

General region of interest determination. To ensure a largely independent approach, half of the data (odd runs: 1, 3, 5) was used for region of interest (ROI) determination, and the other half (even runs: 2, 4, 6) for ROI analyses (Vul et al. 2009), by using the Marsbar ROI toolbox for SPM (http://marsbar.sourceforge.net). ROI determination in odd runs was carried out within a binary mask, composed of activation obtained for both the gap and overlap tasks (FWE-corrected cluster size threshold for a P = 0.05 cluster-defining threshold, using CorteClusTh.m; see http://www.sph.umich.edu/~nichols/JohnsGems2.html). Because only a small part of the caudate nucleus was covered by the mask, we adjoined an anatomically defined mask of this region (Tzourio-Mazoyer et al. 2002) to test our hypotheses. Clusters revealing the correlation of interest at a lenient threshold (P = 0.01, uncorrected) were extracted as ROIs, given that the cluster sizes comprised not less than 10 voxels for the regression analysis and 30 voxels for the parametric analysis.

Regression analysis. Contrast estimates for gap and overlap, resulting from the single subject analyses (basic model), were taken to perform random effects models. ROIs obtained with regression analyses in odd runs were used for the ROI-based regression analyses in even runs to test for the hypothesized correlations of subjects’ mean SRTs with activation strength. Subjects’ mean saccadic reaction times (SRTs) in odd and even runs, respectively, were used as predictors, both for activation in gap and overlap conditions.

Parametric modulation with SRT. To identify within-subjects performance effects on a trial-by-trial basis, we computed a second general linear model for each subject, by adding two additional parametric modulation regressors to the basic model that in itself comprised three regressors (gap, overlap, errors). The additional regressors parametrically modulated the hemodynamic response function (HRF; model of the BOLD response) with the mean corrected SRT on the corresponding trial, using a linear term. As a consequence, the height of the modulated HRF in each trial was linearly related specifically to the mean corrected SRT obtained in that trial. For the group analyses, contrast images for the parametric regressors, resulting from this single subject analysis, were taken to perform random effects models for the gap and overlap task separately. ROIs obtained with parametric modulation analyses in odd runs were used for the ROI-based parametric analyses in even runs.

All results for the regression and the parametric modulation analyses were reported with a threshold level of P < 0.05. Bonferroni-corrected for comparisons of multiple ROIs. Peak activation voxels for gap clusters extracted for the ROI analyses were reported in MNI coordinates (Table 1 and Table 2).

Eye movement data analysis. Using an algorithm developed in our laboratory we could analyze the resulting eye traces offline and extract saccades from other spurious events like eye blinks. SRTs were computed using a velocity threshold of 50°/s. Each trial was examined by the experimenter to ensure that the software was extracting the correct measurements. In-scanner monitoring of eye movements together with the event-related design enabled us to discard error trials,
thus ensuring an adequate task performance in every single trial used for further analysis and increasing the sensitivity and accuracy of the design. Trials with instable fixation between stimulus onset and saccade initiation (fixation failure), anticipations (latencies > 80 ms), omission errors (no response or latencies > 450 ms), and saccades made in the wrong direction (direction errors) were excluded from analyses. To estimate test-retest reliability of SRT performance across experimental runs in the MR scanner, the six runs were partitioned in the same way as used for specification ROIs for functional data. Thus correlations between averaged SRTs for odd and even runs were calculated by using Pearson’s correlation coefficient.

RESULTS

Eye movement data. Subjects required significantly (*t*17 = 16.71, *P* < 0.001) more time to perform saccades in the overlap (mean latency 238 ± 33 ms, mean ± SD) compared with the gap condition (mean latency 121 ± 13 ms). As depicted in Fig. 2, this gap effect is obvious in every single subject. In the gap condition, subjects exhibited significantly more express saccades (70.5%) than in the overlap condition (7.8%), where most of the subjects had either no express saccades (*N* = 5) or an express proportion less than 5%. In the experiment, the proportion of express saccades for the gap task varied considerably across subjects (17.5% to 100%). Remarkably, two of the participants performed an unusual high proportion of express saccades in the overlap condition (27.4% and 38.7%, respectively). These subjects had short mean latencies both in the gap and the overlap condition.

Error rates were 5.4% in the gap task and 2.7% in the overlap task. The prevalent error type in the gap task was related to anticipatory saccades (latency > 80 ms), facilitated by the gap period before target onset (4.5% in the gap, 0.7% in overlap). In the experiment, the proportion of express saccades for the gap task varied considerably across subjects (17.5% to 100%). Remarkably, two of the participants performed an unusual high proportion of express saccades in the overlap condition (27.4% and 38.7%, respectively). These subjects had short mean latencies both in the gap and the overlap condition.

Table 1. Simple regression analysis: correlation of mean activation strength in regions of interest for gap and overlap paradigms with subjects’ mean saccadic reaction time performance in the respective eye-movement task

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Side</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Voxels</th>
<th>P Uncorrected</th>
<th>P Corrected &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative correlation with mean reaction time</td>
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<tr>
<td>Overlap task</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal IFJ (PCG, IFG, MFG)</td>
<td>R</td>
<td>44</td>
<td>4</td>
<td>36</td>
<td>10</td>
<td>0.004</td>
<td>*</td>
</tr>
<tr>
<td>IFJ (PCG, IFG)</td>
<td>L</td>
<td>−40</td>
<td>0</td>
<td>30</td>
<td>52</td>
<td>0.002</td>
<td>*</td>
</tr>
<tr>
<td>IFG (pars triangularis)</td>
<td>L</td>
<td>−32</td>
<td>26</td>
<td>16</td>
<td>57</td>
<td>0.292</td>
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<tr>
<td>Striatum</td>
<td></td>
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<tr>
<td>Caudate nucleus (head)</td>
<td>R</td>
<td>8</td>
<td>10</td>
<td>4</td>
<td>26</td>
<td>0.001</td>
<td>*</td>
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<tr>
<td>Caudate nucleus (head)</td>
<td>L</td>
<td>−10</td>
<td>10</td>
<td>0</td>
<td>55</td>
<td>0.04</td>
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</tr>
<tr>
<td>Caudate nucleus (head)</td>
<td>L</td>
<td>−10</td>
<td>0</td>
<td>12</td>
<td>20</td>
<td>0.015</td>
<td>†</td>
</tr>
<tr>
<td>Putamen</td>
<td>L</td>
<td>−20</td>
<td>−6</td>
<td>8</td>
<td>28</td>
<td>0.368</td>
<td></td>
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<tr>
<td>Gap task</td>
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<tr>
<td>Supramarginal gyrus</td>
<td>L</td>
<td>−58</td>
<td>−32</td>
<td>32</td>
<td>71</td>
<td>0.21</td>
<td></td>
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<tr>
<td>Insula</td>
<td>R</td>
<td>36</td>
<td>6</td>
<td>−4</td>
<td>36</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Positive correlation with mean reaction time</td>
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<td>Overlap task</td>
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</tr>
<tr>
<td>Frontal FEF</td>
<td>R</td>
<td>42</td>
<td>−4</td>
<td>62</td>
<td>22</td>
<td>0.007</td>
<td>*</td>
</tr>
<tr>
<td>FEF</td>
<td>L</td>
<td>−44</td>
<td>−2</td>
<td>58</td>
<td>29</td>
<td>0.025</td>
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<tr>
<td>SFG/MedFG</td>
<td>R</td>
<td>12</td>
<td>12</td>
<td>52</td>
<td>67</td>
<td>0.354</td>
<td></td>
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<tr>
<td>Parietal SPL</td>
<td>R</td>
<td>20</td>
<td>−66</td>
<td>68</td>
<td>10</td>
<td>0.002</td>
<td>*</td>
</tr>
<tr>
<td>SPL</td>
<td>L</td>
<td>−16</td>
<td>−74</td>
<td>58</td>
<td>63</td>
<td>&lt; 0.001</td>
<td>*</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>R</td>
<td>14</td>
<td>−4</td>
<td>22</td>
<td>20</td>
<td>0.772</td>
<td></td>
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</tbody>
</table>

IFJ, inferior frontal junction; PCG, precentral gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; FEF, frontal eye field; SFG, superior frontal gyrus; MedFG, medial frontal gyrus; SPL, superior parietal lobe. *A significant effect: *P* < 0.05, corrected for multiple comparisons; †*P* value < 0.1.

Table 2. Parametric modulation analysis: regions in which mean activation strength is associated with longer reaction times (positive correlation)

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Side</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Voxels</th>
<th>P Uncorrected</th>
<th>P Corrected &lt; 0.05</th>
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<tbody>
<tr>
<td>Positive correlation with mean reaction time</td>
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<td>Overlap task</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IFG (pars opercularis)</td>
<td>R</td>
<td>54</td>
<td>12</td>
<td>8</td>
<td>40</td>
<td>0.002</td>
<td>*</td>
</tr>
<tr>
<td>Precuneus</td>
<td>R/L</td>
<td>6</td>
<td>−48</td>
<td>52</td>
<td>160</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Gap Task</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEF (medial)</td>
<td>R</td>
<td>18</td>
<td>−2</td>
<td>70</td>
<td>48</td>
<td>0.015</td>
<td>†</td>
</tr>
<tr>
<td>DLPFC</td>
<td>R</td>
<td>38</td>
<td>48</td>
<td>30</td>
<td>33</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>PCG</td>
<td>R</td>
<td>40</td>
<td>−2</td>
<td>46</td>
<td>70</td>
<td>0.163</td>
<td></td>
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<tr>
<td>SPL/precuneus</td>
<td>L</td>
<td>−10</td>
<td>−66</td>
<td>60</td>
<td>46</td>
<td>0.005</td>
<td>*</td>
</tr>
<tr>
<td>IPL</td>
<td>R</td>
<td>64</td>
<td>−42</td>
<td>34</td>
<td>294</td>
<td>0.021</td>
<td></td>
</tr>
</tbody>
</table>

DLPFC, dorsolateral prefrontal cortex; IPL, intraparietal lobe. *A significant effect: *P* < 0.05, corrected for multiple comparisons; †*P* value < 0.1.
the overlap condition). The direction of these saccades was completely random, indicating that they had been initiated before target processing was completed. Further errors mainly comprised fixation failures both in the gap and the overlap task, and few omissions and direction errors (altogether 0.9% in the gap, 2.0% in the overlap condition). Only a small proportion of direction errors has been found in the gap paradigm (0.2%), most of them clearly beneath our latency criteria for express saccades. Estimating stability of eye-movement performance (odd vs. even runs), we were able to find a high test-retest correlation (gap task: $r^2 = 0.83$, $P < 0.01$; overlap task: $r^2 = 0.88$, $P < 0.01$).

**fMRI analyses.** Both the simple regression analyses and the parametric modulation analyses reported here were ROI-based and separately calculated for gap and overlap conditions, respectively. ROIs were all determined with data obtained in odd runs, whereas results for the ROIs were calculated on data obtained in even runs ($P < 0.05$, Bonferroni-corrected for multiple ROIs compared; see METHODS).

**Simple regression analyses.** Simple regression analyses within SPM2 were performed with the mean SRTs of each subject as a covariate of interest. Results of these analyses are shown in Table 1 and Fig. 3.

**Gap paradigm: negative correlation with mean SRTs.** We had asked whether subjects with shorter mean SRTs in the gap task would also show a more pronounced activation of cortical and striatal areas assumed to be involved in saccade initiation in presence of foveal fixation. ROIs obtained with odd runs comprised clusters in bilateral inferior frontal junction (IFJ) and activation clusters in the head of the caudate nucleus of both hemispheres. Clusters identified as right and left IFJ lie well within the core region identified for this area ($x$ between $±30$ and $±47$, $y$ between $−1$ and $10$, and $z$ between $±27$ and $±40$ mm in Talairach space) (Derrfuss et al. 2009). Additionally, we obtained an activation cluster in the left inferior frontal gyrus and right putamen. Results of the ROI analysis revealed a significant negative correlation between mean SRTs of subjects and mean cluster activation in bilateral IFJ and in the head of the right caudate nucleus (see Fig. 3B). For the two ROIs in the caudate nucleus of the left hemisphere, significant activation was only obtained when not correcting for multiple ROIs. Please note that contrast values for the subjects cover a range from negative to positive values, which is not uncommon in fMRI studies investigating inter-individual differences.

**Overlap paradigm: positive correlation with SRTs.** No activated clusters were found in data obtained from odd runs that could be extracted for further ROI analyses.

**Parametric modulation analysis.** To identify activation in predefined ROIs associated with within-subjects performance effects on a trial-by-trial basis we parametrically modulated the height of the HRF with the mean corrected SRT, using a linear term. Results of these analyses are shown in Table 2 and Fig. 4.

**Gap paradigm: positive correlation with mean SRTs.** Clusters extracted for ROI analysis from the parametric modulation analysis of the three odd runs comprised ROIs located in the right premotor cortex (FEF and ventral premotor), the right prefrontal cortex [dorsolateral prefrontal cortex (DLPFC)], and in the posterior parietal cortex (precuneus/SPL and IPL). The ROI-based parametric modulation analysis performed with data of the three even runs revealed that slower saccades in the gap task were associated with significantly increased activation in the precuneus/SPL ROI. A similar tendency was obtained for the ROI in the right medial FEF for which we obtained significant results at the uncorrected level, but not when corrected for the five ROIs used in the analyses ($P = 0.07$). The peak voxel of the FEF cluster was located at its dorsal boarder ($z = 70$) and extended more ventrally.

**Overlap paradigm: positive correlation with mean SRTs.** Clusters obtained for ROI analysis from the three odd runs comprised one ROI located in the opercular part of the right inferior frontal gyrus and a second ROI located bilateral in the more anterior part of the precuneus. The ROI-based parametric modulation analysis performed with data from the three even runs revealed that slower saccades in the overlap task were associated with significantly increased activation in the inferior frontal gyrus (IFG) ROI.

No activated clusters were found with faster saccades in the overlap and gap paradigm, respectively, when using the data obtained from odd runs for ROI determination.
DISCUSSION

The main findings of the present experiment are twofold. First, both in the parametric modulation analysis and the regression analysis, we found activation in the FEF and precuneus/SPL to be positively correlated with saccadic latency in the gap paradigm. This finding may imply heightened cortically mediated suppressive influences on saccade generation with longer SRTs. Second, the parametric analysis computed for the overlap paradigm revealed a cluster in the right posterior IFG (pars opercularum) to be positively correlated with SRTs. Because the IFG in the right hemisphere is well known to be involved in response inhibition (Aron and Poldrack 2006; Bunge et al. 2002; Hirose et al. 2009; Rubia et al. 2005) and active fixation processes (Anderson et al. 1994; Petit et al. 1999), we tentatively assume that fast saccadic reacting in the presence of a fixation point requires the saccadic system to overcome cortically mediated inhibitory processes. In the following we will first briefly discuss the behavioral results partly used as covariates in our regression analyses. Afterward the findings of the fMRI study will be discussed in more detail in the context of previous findings related to saccade initiation.

Behavioral data. As expected from the literature (Kingstone and Klein 1993a, b; Reuter-Lorenz et al. 1991; Reuter-Lorenz et al. 1995; Saslow 1967), subjects required significantly less time to perform saccades in the gap compared with the overlap condition. In the gap task, ocular fixation is more automatically released by central fixation offset before peripheral target onset. Additionally, disappearance of the fixation point indicates that the target will appear in a short while. For trained subjects in particular, this serves as a powerful warning signal inducing neuronal changes related to advanced motor preparation, hence speeding response latencies (Fecteau and Munoz 2007). Performance in the overlap task, on the other hand, may

![Fig. 3: A: simple regression between mean SRT and blood oxygen level dependent (BOLD) response amplitude in the gap paradigm. Regions of interest (ROIs) in bilateral frontal eye fields (FEF) and the superior parietal lobe (SPL) are shown in red. B: simple regression between mean saccadic reaction times and BOLD response amplitude in the overlap paradigm. ROIs of bilateral inferior fronto junction (IFJ) and the caudate nucleus are shown in green. Scatter plots depict the correlation between each individual subject’s mean activation in each of these ROIs and their respective mean SRT latency. Note that ROIs depicted here were all determined with data obtained in odd runs, whereas results for the ROIs were calculated with a regression analysis on data obtained in even runs (P < 0.05, Bonferroni-corrected for multiple ROIs compared; see METHODS). *Significant correlations: *P < 0.05, corrected for multiple comparisons. L, left; R, right.)
require an active, voluntarily triggered and thus time-consuming ocular disengagement after peripheral target onset. On the behavioral level, these different neuronal processes are reflected in marked differences in mean latencies (see Fig. 2) and latency distributions, with significantly reduced saccadic reaction times and a high proportion of express saccades in the gap task. The overall small proportion of direction errors in the gap paradigm (0.2%) clearly confirms our latency criteria for anticipatory saccades and indicates that virtually all saccades classified as express saccades are driven by the onset of the target stimulus.

fMRI data: gap paradigm: negative correlation with SRT. With respect to saccadic performance in the gap paradigm, we had hypothesized that subjects with short SRTs in the gap paradigm, usually associated with a higher express rate, would show more activation in regions known to code for advanced motor preparation. Timing information provided by the gap period is thought to be one component that contributes to reduced latencies in the gap task. Advanced knowledge of target-presentation time evokes preparatory motor processes, and this heightened readiness to respond is referred to as preparatory set (Connolly et al. 2002). For subjects in the present experiment, offset of the fixation point was a reliable cue, carrying timing information about upcoming target presentation. Well experienced with the task before the fMRI session, it is likely that the subjects were able to estimate the duration of the fixed time interval of 200 ms accurately. Even so, with both parametric and regression analyses in the present study, we could not obtain significant effects associated with a preparatory set. With much longer gap periods (2 and 4 s), Connolly and colleagues (Connolly et al. 2007; Connolly et al. 2005; Connolly et al. 2002) were able to demonstrate that advanced motor preparation was associated with heightened activation in FEF as well as in the supplementary eye field and in the putative human homologue of the monkey lateral intraparietal area (Connolly et al. 2007). Notably, the FEF activation was shown to increase linearly with increasing gap interval (Curtis and Connolly 2008). The lack of significant results in our study may indicate that preparatory processes within short time scales are less suitable for examination with fMRI, due to a limit on temporal resolution. Alternatively, it could be assumed that in our study almost all saccades in the gap paradigm are in a latency range that is influenced by preparatory processes in a similar way and hence do not essentially differ with respect to the associated activation.

fMRI data: gap paradigm: positive correlation with SRT. For the parametric analysis, longer SRTs in the gap paradigm were shown to be positively correlated with the activation of ROIs in the right medial FEF ($P = 0.07$, when corrected for multiple ROIs) and left precuneus/SPL in the posterior parietal cortex (Table 2). Notably, we yielded similar results in our regression analysis, where activation of the right FEF and clusters in bilateral superior parietal lobe were found to be positively correlated with mean SRTs of subjects (Table 1, Fig. 3A). This result bears some resemblance with findings of a study of Neggers et al. (2005), who parametrically modulated combined activation obtained in a gap and step task with the respective SRTs. They found significantly more right FEF and left SEF activation with longer SRTs and more activation in the superior colliculus (not included in our study) with shorter SRTs, hypothesizing a role for the FEF/SEF complex in mainly...
conveying inhibitory signals to the eye-movement system when generating goal-directed saccades. Even though we do not share their assumption in this general fashion, their results together with ours point to the possibility that suppressive signals from cortical regions may indeed be involved in longer SRTs in the gap paradigm. Saccadic latencies differed considerably between subjects, and there were clear differences for the subjects’ ability to perform saccades in the very low latency range (express saccades). With regard to the intra-individual differences obtained in the regression analyses we speculate that higher-level processes that serve to prevent premature saccades in the gap paradigm might have been engaged to a different degree by subjects performing in the mixed gap/overlap paradigm, being particularly efficient when the fixation point offset indicated a gap trial. We tentatively assume that such higher processes specifically modulate the activity of those fixation neurons in the prefrontal and parietal eye-movement related areas that were shown to be active during the gap period and assumed to be related to the motor act of ocular fixation (Ben Hamed and Duhamel 2002; Izawa et al. 2009). Activation of these neurons seems to ensure correct task-related behavior in preventing anticipatory, premature saccades in the pretarget epoch of the gap task, when no foveal fixation target is present. With respect to the trial-to-trial differences it is therefore conceivable that these kinds of fixation neurons reduce their activation later in trials with longer compared with trials with shorter SRTs across pre- and possibly post-target periods, which has not been tested yet.

An alternative explanation for our finding of increased activation in FEF and precuneus/SPL with slower SRTs is also conceivable. The longer the SRT in a trial, the more activation will be accumulated for visual-motor neurons that discharge in the presaccade period after target appearance, and this might cause a stronger BOLD response. But note that this effect would also be expectable for the overlap paradigm where a much broader distribution of SRTs was found. On the contrary, an effect of increased activation in FEF and posterior parietal cortex with longer SRTs was not obvious for the overlap condition, neither for the regression nor for the parametric modulation analyses.

fMRI data: overlap paradigm: negative correlation with SRT. In speeded saccade tasks, saccade-initiation time is modulated by the behavioral state of the organism. This was demonstrated in studies with nonhuman primate electrophysiology showing that elevated threshold currents were needed to elicit saccades by FEF stimulation when the monkeys were in a state of active fixation (Goldberg et al. 1986; Schiller and Sandell 1983). Obviously, the oculomotor system is less susceptible to cortical signals related to gaze shifting when monkeys attempt to keep their eyes on target. Based on these findings, we assumed that more cortico-striatal resources are required for speeded saccade initiation in the overlap paradigm to overcome active fixation. Because shorter mean SRTs may indicate a more efficient saccade initiation in face of ongoing fixation-point presentation, they were expected to be associated with increased activation in fronto-striatal regions involved in saccade control.

In line with our hypothesis, we obtained a significant negative correlation of mean SRTs with mean activation of ROIs in the caudate nucleus in our regression analysis. Significant effects for the left caudate were only obtained when they were not corrected for multiple ROIs. Contrary to this finding, no significant activation increases were found in eye movement-related cortical areas but bilateral in a region termed IFJ according to its location at the junction of the inferior frontal and the inferior precentral sulcus. The IFJ frontal junction is assumed to be part of a cognitive control network (Brass et al. 2005; Cole and Schneider 2007). This area has been shown to play a major role in task switching and set shifting, both requiring activation of task representations. It has also been shown to be part of a fronto-parietal network involved in updating working memory, including new information from sensory stimuli (Roth and Courtney 2007). Whereas subjects faced with a vanishing fixation point indicating a gap trial may be able to prepare their response and react more reflexively in time with the upcoming target stimulus, the appearance of a visual target in presence of the fixation point seems to be related to a greater cognitive control effort to perform a speeded response. Efficient responding in the latter case is possibly related to the ability to quickly activate the task set associated with the stimulus-response rules of the overlap task. This especially holds for overlap trials preceded by a gap trial, but due to the long inter-trial intervals a need to reactivate the relevant task set in nonswitch trials (gap - gap or overlap - overlap) is also possible. It is conceivable that the IFJ modulates the state of the caudate nucleus, which is also known to be crucially involved in generating saccades (Gerardin et al. 2003; Kori et al. 1995). Anatomical connections between the striatum and several regions of the inferior frontal cortex have been shown in a study using diffusion tensor imaging and axonal tracking (Lehericy et al. 2004). Furthermore, a functional connection between the IFJ and the caudate nucleus was shown during the maintenance phase of a working memory task (Landau et al. 2009). In this study activation in the IFJ correlated with caudate dopamine function and task accuracy, indicating that the IFJ is involved in the integration of to-be-remembered information needed for motor response preparation.

Surprisingly, no activated regions were found to be correlated with faster SRTs in the parametric analysis. To test whether activation differences between subjects in the regression analysis are confounded by differences in the vasculature, we compared BOLD signal increases in a ROI obtained from the peak activation voxel of the right FEF in the contrast overlap > rest (8-mm sphere). Raw data were extracted and mean corrected by using the mean activation value of the respective session. We then calculated every subject’s mean activation in an intermediate SRT range (216 to 267 ms) using the combined activation values of the first and second scan after target onset. Activation level of all subjects was within two standard deviations of the overall mean, suggesting that any coarse differences in the vasculature cannot explain our findings. Thus the findings of the regression analysis seem to be valid, suggesting that subjects may differ in their ability to quickly update the current task set in the overlap task according to recent relevant environmental information to fulfill task requirements, leading to overall shorter SRT.

fMRI data: overlap paradigm: positive correlation with SRT. Trial-by-trial analysis revealed more activation in a ROI located in the posterior part of the right ventral IFG (pars opercularis) with longer SRTs in the overlap task. Although not assumed to be one of the core eye-movement regions, the
posterior IFG (pIFG) has been shown in several fMRI studies to be involved in corrective saccades (Haller et al. 2008) and in memory-guided saccades (Brown et al. 2004; Ozyurt et al. 2006). In addition, it is well known that the right IFG area plays a crucial role in response inhibition across response modalities (Chikazoe et al. 2007) including inhibition of eye movements in the antisaccade (Ettinger et al. 2008) and the go/nogo paradigm (Brown et al. 2008). In line with a potential role in oculomotor control, involvement of the IFG in foveal fixation has been shown in two studies with positron emission tomography where activation during stable central fixation was compared with either saccade performance (Anderson et al. 1994) or a rest condition (eyes open in total darkness) (Anderson et al. 1994; Petit et al. 1999), the latter study additionally showing more activation in the FEF and the intraparietal sulcus. Gaze-holding signals with monkey electrophysiology have mostly been examined in the FEF (Hanes et al. 1998; Izawa et al. 2009; Sommer and Wurtz 2000). With a countermarking task, where subjects had to withhold their saccade in case a stop-signal was presented after target presentation, Hanes et al. (1998) were able to show that fixation- and saccade-related activity after the presentation of the stop-signal clearly differentiated between execution and inhibition of sac- cade eye movements. Cells with fixation-related activity have been further recorded in the LIP (Ben Hamed and Duhamel 2002) and the DLPFC (Bon and Lucchetti 1992) among other cortical areas, but, to our knowledge, activity related to central fixation has not been examined yet in the monkey homolog of the posterior inferior frontal cortex (F5). A possible explanation for stronger IFG activation with longer SRTs in the overlap condition in our task is that subjects needed much more time to release central fixation to make a speeded targeting saccade. The finding of a higher activation level in the right inferior frontal operculum with slower saccades in the overlap paradigm is striking but it is unknown yet which processes induce the heightened activation within this area and how oculomotor regions of the brain may interact to decrease activation for a more speeded responding in the overlap condition.

Conclusion

To our knowledge, this is the first imaging study to explicitly investigate cortico-striatal contributions to saccade initiation in presence of foveal fixation. Notably, the type of analyses used together with a response deadline ensuring all saccades in the overlap task to be performed under the same condition enabled us to obviate confounding effects of fixation point sweeping over the retina during saccade performance. Interestingly, parametrically modulating activation by trial-by-trial variability in SRTs, a ROI in the right opercular part of the IFG was found to be more active with slower saccades in the overlap task. This finding is possibly related to a heightened influence of foveal fixation processes that may interact with saccade generation in presence of a foveal fixation point. Results of both inter- and intra-individual analyses for the gap paradigm revealed that slower saccades were associated with more activation of frontal and parietal eye movement-related areas, possibly indicating suppressive influences on saccade generation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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