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Relationship between saccadic eye movements and cortical activity as measured by fMRI: quantitative and qualitative aspects

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Abstract We investigated the quantitative relationship between saccadic activity (as reflected in frequency of occurrence and amplitude of saccades) and blood oxygenation level dependent (BOLD) changes in the cerebral cortex using functional magnetic resonance imaging (fMRI). Furthermore, we investigated quantitative changes in cortical activity associated with qualitative changes in the saccade task for comparable levels of saccadic activity. All experiments required the simultaneous acquisition of eye movement and fMRI data. For this purpose we used a new high-resolution limb-tracking technique for recording eye movements in the magnetic resonance tomograph. In the first two experimental series we varied both frequency and amplitude of saccade stimuli (target jumps). In the third series we varied task difficulty; subjects performed either pro-saccades or anti-saccades. The brain volume investigated comprised the frontal and supplementary eye fields, parietal as well as striate cortex, and the motion sensitive area of the parieto-occipital cortex. All these regions showed saccade-related BOLD responses. The responses in these regions were highly correlated with saccade frequency, indicating that repeated processing of saccades is integrated over time in the BOLD response. In contrast, there was no comparable BOLD change with variation of saccade amplitude. This finding speaks for a topological rather than activity-dependent coding of saccade amplitudes in most cortical regions. In the experiments comparing provs anti-saccades we found higher BOLD activation in the “anti” task than in the “pro” task. A comparison of saccade parameters revealed that saccade frequency and cumulative amplitude were comparable between the two

tasks, whereas reaction times were longer in the “anti” task than the pro task. The latter finding is taken to indicate a more demanding cortical processing in the “anti” task than the “pro” task, which could explain the observed difference in BOLD activation. We hold that a quantitative analysis of saccade parameters (especially saccade frequency and latency) is important for the interpretation of the BOLD changes observed with visual stimuli in fMRI.

Keywords Functional brain imaging · BOLD effect · Saccades · Eye movement recordings · Antisaccades

Introduction

Saccadic eye movements serve to bring a visual object of interest to the foveal region of the eye. Saccades are fast eye movements, which are both voluntary and ballistic in nature. The latter fact indicates that the brain preprograms most processing steps before the neural command signals are sent to the oculomotor nuclei in the brainstem for saccade execution. Several processing steps are usually performed before a saccade is released. These include the disengagement of attention from a previously attended target, the target selection, the reallocation of attention to the new target, the calculation of the spatial coordinates of the new target, and the decision process when to execute the saccade (Fischer et al. 1995).

Single-unit recording studies in animals and clinical observations in patients with focal cerebral lesions revealed the contribution of several cortical and subcortical regions to the generation of saccades. Among these regions are the frontal eye field (FEF; Bruce and Goldberg 1985), the dorsolateral prefrontal cortex (DLPC; Funahashi et al. 1989, 1991; Pierrot-Deseilligny et al. 1991), the supplementary eye field (SEF; Schlag and Schlag-Rey 1987; Fried et al. 1991), the posterior parietal cortex (PPC; Gnadt and Andersen 1988; Barash et al. 1991a, 1991b; Pierrot-Deseilligny et al. 1991), the primary visual cortex (Brodmann area BA 17, corre-

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sponding to V1; Schiller 1977), the basal ganglia (Hikosaka and Wurtz 1985a, 1985b; Lasker et al. 1988; Crawford et al. 1989) and the superior colliculus (SC; Schiller et al. 1980).

With the development of new imaging techniques – like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) – it has become possible to visualize the activity in saccade-related brain areas of healthy human subjects and to corroborate the findings of animal and clinical studies (Petit et al. 1993; Luna et al. 1998; Darby et al. 1996; Bodis-Wollner et al. 1997; Anderson et al. 1994; Paus et al. 1995; Sweeney et al. 1996).

So far, however, there have been hardly any attempts to correlate behavioral visuo-oculomotor data to the corresponding blood oxygenation level dependent (BOLD) responses. Such measurements are required if one wants to distinguish general task-related activity from the activity related to premotor saccade programming, especially since the temporal resolution of the imaging techniques does not allow for such a distinction. Due to the lack of a precise eye movement measurement system for fMRI, some researchers resorted to the measurement of eye movements before or after the imaging session outside the scanner. Others obtained estimates of oculomotor activity with an electro-oculography technique (cf. Felblinger et al. 1996). However, the rather poor spatial resolution of the latter method suggests that low amplitude saccades or smooth eye movements were not always detected. The purpose of these measurements was primarily to assess the reliability of task performance rather than performing a quantitative analysis of the eye movements. Therefore, the exact pattern and the metrics of eye movements contributing to the cortical activity during imaging remained mostly undetermined in these studies, so that direct relationships to the cortical activity, as measured by fMRI, could not be established. Knowing the effects of saccadic amplitude and frequency, for instance, might turn out to be highly relevant for future fMRI studies concerning the design of the experimental paradigms that include eye movements to visual stimuli.

fMRI is a technique used to non-invasively map hemodynamic responses to sensorimotor and cognitive stimulation in the human brain. T2*-weighted imaging reveals changes in blood oxygenation in cortical areas involved in neural processing (Kwong et al. 1992; Ogawa et al. 1990, 1993; Turner et al. 1993). We intended to assess quantitatively cortical activity related to saccadic eye movements with fMRI, by varying the visuo-oculomotor task, such that either the number of target jumps per time interval or target amplitude was selectively modified. In these two experimental series we explored whether the changes in saccadic activity lead to measurable changes in the BOLD contrast. Furthermore, we analyzed whether the involved cortical regions are differentially influenced for a given level of saccadic activity.

Conceivably it would be desirable in many studies to be able to differentiate between cortical BOLD effects

related to premotor saccade preparation (saccade metrics) and those related to other preparatory activity, such as the effort of target selection. As a first step towards this goal, we measured the BOLD effect across two different tasks for comparable levels of saccadic activity in a third experimental series. In this series we chose the pro-saccade versus anti-saccade paradigm. The tasks were to perform either a saccade towards a suddenly appearing visual target (pro-saccade) or to suppress this saccade to the target and, instead, execute a corresponding saccade in the opposite direction, i.e., to a “virtual target location” in a mirror-symmetric contralateral position (anti-saccade). This paradigm was selected because it is simple and has been extensively used in both basic research and clinical studies. The pro-saccade and anti-saccade tasks we used were identical with respect to predictability of timing and target location. They differed mainly with respect to two functions, the internal transformation of target location and the suppression of a reflexive saccade (in the anti-saccade task).

Previous work on the pro- versus anti-saccade paradigm which has focused mainly on the role of the FEF does not give an unequivocal picture yet. Studies in monkey and man showed that a lesion/inactivation of the FEF or adjacent regions impairs the suppression of reflexive (pro-) saccades, thereby increasing the error rate (Braun et al. 1992; Burman and Bruce 1997; Guitton et al. 1985; Sommer and Tehovnik 1997). In the study by Pierrot-Deseilligny et al. (1991), lesions, which produced such increased error rates, were located in the dorsolateral prefrontal rather than in the FEF region. In the PET studies which investigated this task, the majority reported higher FEF activation with anti-saccades than with pro-saccades (Doricchi et al. 1997; O’Driscoll et al. 1995; Sweeney et al. 1996). However, the PET study of Paus et al. (1993) and a recent fMRI study (Muri et al. 1998) were unable to detect significant differences in FEF activity between these two tasks. Furthermore, with respect to laterality, the left FEF did not appear to be crucial for saccadic suppression (Rivaud et al. 1994; Gaymard et al. 1999). In view of the rather long acquisition times in such neuroimaging studies we consider it especially important to carefully control for saccade parameters (frequency of occurrence, amplitudes, reaction times) when trying to relate the metabolic changes to performance aspects and to compare across different studies with the same objective.

Materials and methods

MR-Eyetracker

For eye movement recordings we used the MR-Eyetracker, a fiberoptic limbus tracking device, which we have described previously (Kimmig et al. 1999). A multichannel computer program (LabVIEW, National Instruments, Austin, TX) was used to acquire and display the signals derived from the MR-Eyetracker. The sampling frequency was 1000 Hz, the spatial resolution was less than 0.2°. Additional signals, which documented the stimulus position, were recorded and displayed. The MR scanner provided a TTL

pulse at the beginning of each volume acquisition. This pulse was used to trigger both our stimulation and the eye movement acquisition programs.

Magnetic resonance imaging

Magnetic resonance imaging was performed with a 1.5-Tesla clinical scanner (Magnetom Vision, Siemens, Erlangen, Germany) equipped with an echo-planar imaging (EPI) booster for fast gradient switching and a full-head radiofrequency (RF) receive-transmit headcoil. High-resolution, sagittal T1-weighted images were acquired with the MP-RAGE (magnetization prepared rapid acquisition gradient echo) sequence to obtain a 3D anatomical scan of the head and brain. We defined the anterior-posterior commissural (AC-PC) plane (Talairach and Tournoux 1988) and report all findings in this coordinate system. Shimming was performed for the entire brain using an auto-shim routine for magnetic field homogeneity.

Functional imaging was performed with T2*-weighted gradient recalled EPI. The technical data for the functional measurements were TE=66 ms, TR=4 s, flip angle = 90°, field of view = 256 mm, matrix = 128×128, resulting in a voxel size of 2×2×4 mm. The stimulation protocol for each experimental run consisted of twelve 32-s intervals with six alternating periods of rest (Off) and stimulation (On). This protocol yielded 96 echo-planar volumes. To increase the temporal resolution of the MR signals, we limited the acquisition volume to 16 contiguous slices. Therefore, certain areas in the prefrontal cortex could not be assessed in this study.

To minimize head motion, the subject's head was fixed with a vacuum cap. Despite these precautions, residual head motion was still evident in some of the image data. In-plane motion could be corrected by applying an image alignment algorithm (Cox 1996). The effects of the gradient noise were reduced by sound-dampening headphones.

Visual stimulation

The subjects viewed the stimuli through a mirror that was adjusted to allow an overhead view into the scanner gantry. The stimuli were created on a Visual Stimulus Generator graphics card (Cambridge Research Systems Ltd., Rochester, UK) and projected (LCD projector, Panasonic, Osaka, Japan) onto a translucent screen which was mounted at the back of the gantry. The image subtended 30° × 30° of visual angle (800×600 pixels) at a viewing distance of 1.3 m.

The stimulus presentation started by continuously displaying a bright-red square (0.5°; fixation point FP) in the center of a uniform background for a duration of 32 s. Subjects were instructed to fixate FP during the "fixation period." During the following "saccade period" (duration 32 s), FP was extinguished after 1000–1500 ms. For a temporal gap of 200 ms the screen was blanked before a peripheral (randomized left or right) target appeared for a duration of 3000 ms. With target offset, FP reappeared for the next trial. The subject was asked to make a saccade as quickly as possible to the target location. For each experimental run, fixation and saccade periods were repeated 6 times. In the experiments that investigated the effect of amplitude (amplitude series), subjects performed three runs with target amplitudes of 2°, 6° and 10°, with the runs being conducted in random order. During a 32-s saccade period, 14 target jumps occurred, yielding 7 centrifugal and consecutively 7 centripetal gaze shifts. Thus, the stimulus repetition rate (frequency) was constant at 0.44 Hz. Since we used a block design with alternating periods of fixation and stimulation, the direction selectivity of cortical regions could not be tested. As a consequence, we randomized rightward and leftward centrifugal saccades during the saccade period. For investigating the effect of saccade frequency (frequency series), the amplitude was kept constant at 10°. Subjects performed three runs with target frequencies of 0.06, 0.44, and 1.25 Hz (corresponding to 2, 14, and 40 target

jumps in the 32-s saccade period). In the third set of experiments subjects performed one run in a pro-saccade task, and one in an anti-saccade task (frequency 0.44 Hz, amplitude 10°). The order of runs was randomized between subjects for each experimental series.

Data analysis

The data were analyzed and visualized using BrainTools developed by Dr. K. Singh (<http://www.liv.ac.uk/mariarc/software.html#BRAINTOOLS>). The motion-corrected data were processed using a correlation method based on techniques established by Bandettini et al. (1992) and Friston et al. (1995). The time course of the BOLD response profile was correlated with the phase-shifted On/Off cycle of visual stimulation, yielding a correlation coefficient r . The SD of the T2* signal (in arbitrary intensity units) was multiplied by the correlation coefficient r after normalization ($r' = \ln(1+r/1-r)$); the first metric reflects the overall correlated activity. It is monotonically related to the Z-score). To reduce noise, spatial smoothing of the functional signal within each slice was performed by convolution with a 2D gaussian function (Friston et al. 1995) with a standard deviation of 1.7 mm. The time course of each voxel was correlated with a smoothed periodic function (square wave convolved with a gaussian; time constant = 6 s; cf. Friston et al. 1995). The time course of each voxel was also smoothed with a gaussian (time constant = 6 s). A region of interest (ROI) analysis was performed by calculating the mean activity of all voxels in a 6×6-voxel grid centered on the most activated voxels within a given region. Visual inspection confirmed that the ROI was positioned near the respective anatomical landmarks. Once the grid position was determined it remained constant over conditions. Mean ROI activation was calculated without a threshold, i.e., all 36 voxels contributed to the mean value. Results were superimposed on the 3D MP-RAGE data set, both being mapped in Talairach coordinates. The coordinates of the center of the ROI were determined and assigned to specific cortical subregions described in the literature. The BOLD values for each subject were normalized across activated regions to their own maximum BOLD effect (Normalized BOLD, ranging from 0 to 100%). Values for each subject were entered into a statistical analysis program for group analysis of variance.

Eye movement data were analyzed by an interactive computer program. Saccade detection was performed by a velocity threshold algorithm (velocity threshold 50°/s). The algorithm detected saccades greater than 0.75°. Saccades smaller than 0.75° were determined interactively. Saccade detection below the noise level of 0.2° was not performed. Artifacts like drifts or blinks were identified by visual analysis and removed.

The program yielded estimates of reaction time, duration, peak velocity and amplitude of each saccade. We then calculated the mean amplitude of gaze shifts which occurred during the six fixation periods and compared this mean value with that of the six saccade periods. To investigate the effect of saccade amplitude on BOLD effect, we also calculated the cumulative saccade amplitude over the six saccade periods. We furthermore counted the number of saccades during the six fixation and six saccade periods, respectively. In the pro-saccade and anti-saccade tasks we analyzed the mean saccadic reaction times (SRT), investigated the frequency distributions of SRT, and performed further analysis on SRT subpopulations (such as express saccades and fast regular saccades; cf. Fischer et al. 1993).

Subjects

After giving their informed consent, 15 volunteers participated in the study, which was approved by the local Ethics Committee. The subjects' age ranged from 20 to 37 years (mean 27 years). One volunteer was left handed, the others were right handed. Five subjects participated in the saccade amplitude and frequency series; the other ten subjects participated in the third series with the pro-saccade and anti-saccade tasks.

Results

Saccade frequency and amplitude series

Analysis of the eye movement data from the frequency and amplitude series showed that some spontaneous saccades occurred during the fixation periods, but they were rare and had small amplitudes (open circles in Fig. 1). With stimulation in the *frequency series*, total gaze amplitude (amplitude of primary and corrective saccades) corresponded closely to stimulus amplitude (target dis-

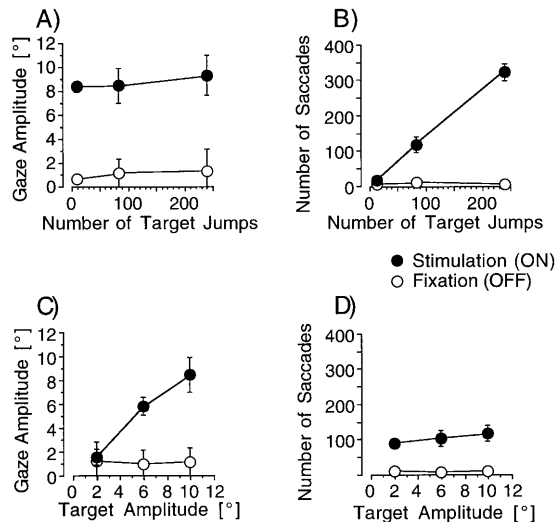


Fig. 1A–D Saccade parameters obtained for the frequency and amplitude series. **A, B** Frequency series. Mean gaze amplitude per target jump (**A**) and number of saccades during the total acquisition time of 192 s (6 periods of 32 s each; **B**) are plotted as a function of the number of target jumps ($n=12$, 84 and 240, corresponding to frequencies of 0.06, 0.44 and 1.25 Hz). Target amplitude remained constant at 10° . Subjects' compliance to the task is documented by the fact that mean saccade amplitude approximated 10° and saccade frequency linearly increased with target jump frequency. **C, D** Amplitude series. Mean gaze amplitude increased almost linearly with target amplitude (**C**) whereas the number of saccades remained essentially constant ($n=84$; frequency 0.44 Hz; **D**). Filled circles give mean data during ON (stimulation) periods (error bars 95% confidence intervals). Open circles show corresponding Off (fixation) periods

placement), which was constant (10° ; Fig. 1A). The total number of saccades occurring during the 192 s of stimulation (six periods of 32 s each; saccade frequency) closely covaried with the number of target jumps per 192 s (stimulus frequency; Fig. 1B). Similarly, in the *amplitude series* total gaze amplitude rose as a function of stimulus amplitude (Fig. 1C) and total number of saccades (saccade frequency) remained essentially constant, proportional to stimulus frequency (Fig. 1D).

When comparing the average BOLD contrast of the stimulation periods with those of the corresponding fixation periods for each subject, a highly significant effect of saccadic activity was found in the ROIs, whose locations corresponded to FEF, SEF, parietal Brodmann areas BA7, BA19, to V1 and the motion sensitive area V5/V5A (corresponding to the junction of BA19 and BA37). We termed our ROIs according to these well-known cortical subregions although we could not fully exclude that other, unknown functional subregions were contained in the ROIs as well. The number of subjects (total, $n=5$) showing an activation in these regions is given in Table 1 together with the corresponding Z-scores and the mean Talairach coordinates, separately for the right and left hemisphere. Statistically we found no difference of the BOLD effect between hemispheres ($P=0.9$) with our stimulations, which covered both visual hemifields and saccade directions. Also, no significant interaction between the factors “Hemisphere” and “Area” was found ($P=0.6$). In the following the data for right and left hemispheric activations were pooled for corresponding areas.

Examples of the obtained BOLD effects are given in Fig. 2. This figure focuses on the BOLD effect in the FEF on the right side of one subject. The functional images are overlaid on the corresponding anatomical data after transformation in Talairach space. The three horizontal rows in Fig. 2A give the responses for the three stimulus frequencies, with the crosshairs always at the same coordinates ($x=41$, $y=-7$, $z=49$ mm) to ease comparison. Note that the increase in stimulus frequency is associated with an increase in the number of activated voxels in FEF as well as with some increase in signal intensity (red $z>3.0$; orange $z>4.0$; yellow $z>5.0$; a voxel was highlighted here only if its time course was highly

Table 1 Talairach coordinates (means \pm SD) of ROIs and corresponding Z-scores across the five subjects performing the saccade frequency and amplitude series (n number of subjects showing

significant activation in a given region in at least one of the frequencies and amplitudes tested)

Region of interest	Right hemisphere								Left hemisphere							
	n	Z-score	x	SD	y	SD	z	SD	n	Z-score	x	SD	y	SD	z	SD
FEF	5	3.4	36	9	-11	8	49	5	5	3.9	41	9	-14	7	45	6
SEF	3	2.6	2	1	-7	4	52	3	4	2.2	7	1	-8	6	51	2
SPL	4	2.8	26	8	-72	13	52	9	4	2.5	31	9	-71	9	53	11
PCU	2	3.6	15	2	-83	2	49	1	2	3.7	18	11	-79	2	50	3
V1	5	3.3	6	3	-86	9	1	7	5	4.3	11	2	-84	7	1	3
V5/V5A	5	3.9	44	6	-71	6	-1	5	5	3.9	47	4	-78	4	-3	9
BA19	3	3.3	27	9	-95	1	23	1	2	3.8	17	5	-94	1	27	6

Fig. 2A, B Representative examples of fMRI data from one subject (frequency series). **A** Functional images overlaid on the corresponding anatomical data, showing the axial, sagittal and coronal planes with crosshairs centered in the right FEF (Talairach coordinates as indicated). Data are shown for the three different frequencies used: 0.06, 0.44, and 1.25 Hz (number of target jumps $n=12, 84, 240$). **B** Percentage BOLD signal change over time in the right FEF of the same subject, corresponding to the target frequencies given in **A**. We define 0 as the mean value across the entire scan period and deviations from this mean value as positive or negative deviations in percent

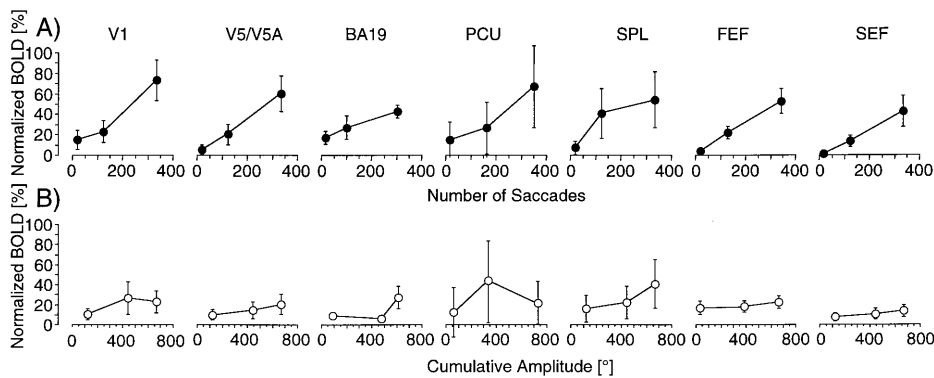
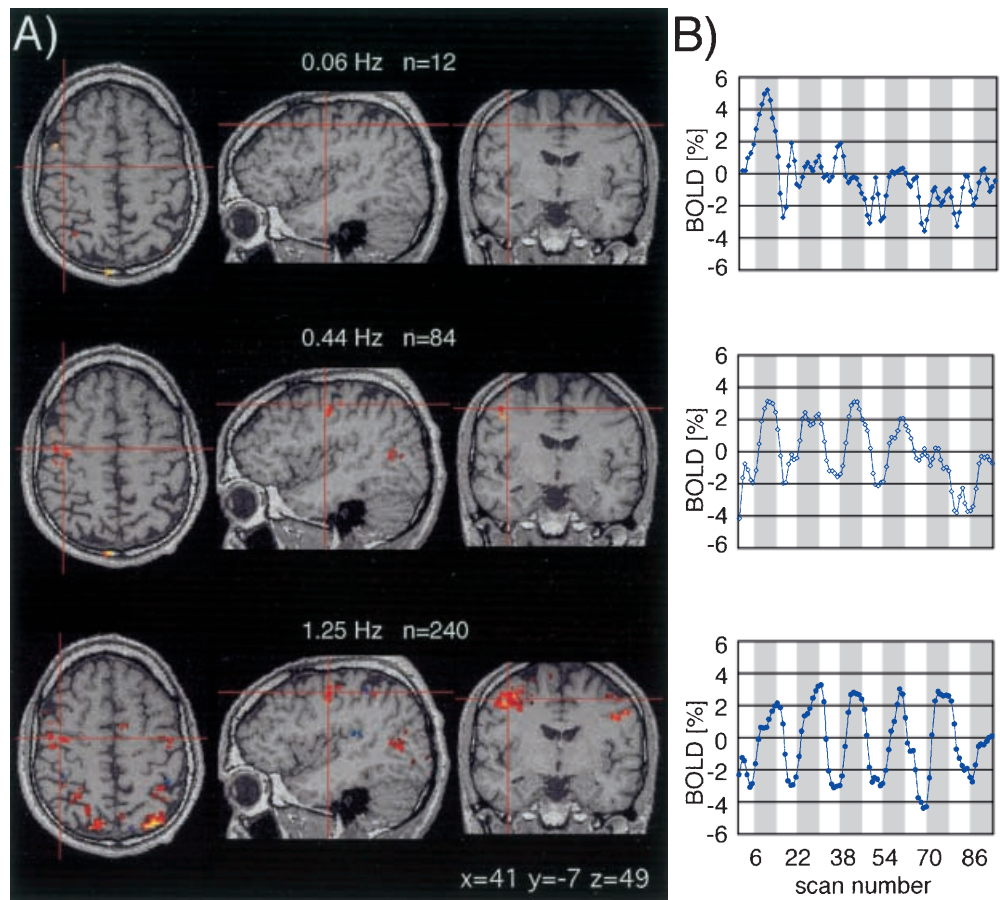


Fig. 3 Normalized BOLD effect in the frequency (**A**) and amplitude (**B**) series. Mean values (%) are shown separately for the identified cortical regions V1, V5/V5A, BA19, PCU, SPL, FEF, and SEF as a function of the number of saccades performed during the time period of 192 s at a constant target amplitude of 10° (**A**) and as a function of cumulative saccade amplitude at a constant frequency of 0.44 Hz (**B**). Small variations in the number of saccades and the cumulative amplitude across regions (see *abscissas*) depend on the number of subjects showing activation in a given region. The number of subjects (n) was the same for all frequencies and amplitudes tested in a given region (*error bars* 95% confidence intervals). Note that the BOLD response clearly covaries with saccade frequency, unlike with cumulative saccade amplitude

correlated [$r=0.5$] with that of a phase retarded smoothed stimulus version; cf. “Materials and methods”). Figure 2B shows the corresponding change of the BOLD contrast over time (as a percentage), calculated for a ROI of 6×6 voxels centered around the crosshairs. Note that the activation, reflected by the difference between saccade periods (shaded) and fixation periods (non-shaded), increases with stimulus frequency.

This frequency dependent BOLD effect in the FEF was obtained in all five subjects. Furthermore, the overall effect (average across all identified cortical areas and all subjects) consisted of a clear increase with increasing saccade frequency [$F_{(2,144)}=43.2$; $P=0.0001$]. This increase was found with each region, although with con-

siderable variations across regions [$F_{(6,144)}=3.9$; $P=0.0012$]. Consistent changes of the BOLD effect over time within a given experiment, i.e., repetition effects across the six pairs of rest-stimulation (Dejardin et al. 1998), were not observed. Figure 3A displays the BOLD effects as a function of the number of saccades (saccade frequency) for the subjects shown in Table 1. Noticeably, the increase in BOLD contrast with saccade frequency was similar across all regions (statistically, there was no significant interaction between factors “Region” and “Number of saccades”, $P=0.48$). As to the factor “Subjects”, the BOLD contrast varied in magnitude considerably among subjects [$F_{(4,177)}=33.7$; $P=0.0001$], as did the increase in the BOLD contrast with saccade frequency [$F_{(8,177)}=8.0$; $P=0.0001$]. Taken together, these results show that the cortical activity of all these regions is related to the number of saccades performed per time interval, although with some interindividual variation (concerning the amount of activation).

In the *amplitude series* (Fig. 3B) there was again no overall difference in BOLD contrast between hemispheres ($P=0.8$) and no significant interaction between the factors “Hemisphere” and “Region” ($P=0.7$). The mean cortical activity across all identified cortical regions and all subjects showed a slight increase with increasing saccadic amplitude [$F_{(2,144)}=4.6$; $P=0.012$]. However, when analyzed separately for each cortical region, the level of statistical significance was not reached. The BOLD contrast differed significantly across regions [$F_{(6,144)}=5.9$; $P=0.0001$], but the interaction between factors “Region” and “Cumulative amplitude” was not significant ($P=0.7$). These findings are in contrast to those obtained in the frequency series where the BOLD contrast showed a clear increase with saccade frequency.

The lack of a clear-cut effect of saccade amplitude on BOLD contrast may not appear surprising, since a coding of saccade amplitude by the amount of neuron firing frequency is found essentially only in immediate premotor neurons at brainstem level (e.g., burst neurons), while at cortical levels it is coded mainly topologically, as in the superior colliculus (where neurons close to the foveal representation are involved in the generation of small foveating saccades and neurons far from the foveal representation in large ones; e.g., Lee et al. 1988). This consideration led us to investigate whether there would be a shift of cortical activation across the saccades of different amplitude. This investigation was restricted to the FEF, where a “robust” BOLD contrast was observed in all subjects. The analysis was performed in two ways, with a different approach as before. Using BrainTools, the ROI was now placed separately for each of the three amplitudes in single subjects, and the coordinates of the center of the ROI were then analyzed. In the second approach (Statistical Parametric Mapping, SPM, Wellcome Department of Cognitive Neurology, London, UK), we used the peak activated voxel in FEF, separately for each amplitude and each subject. No major differences were obtained with either approach, however.

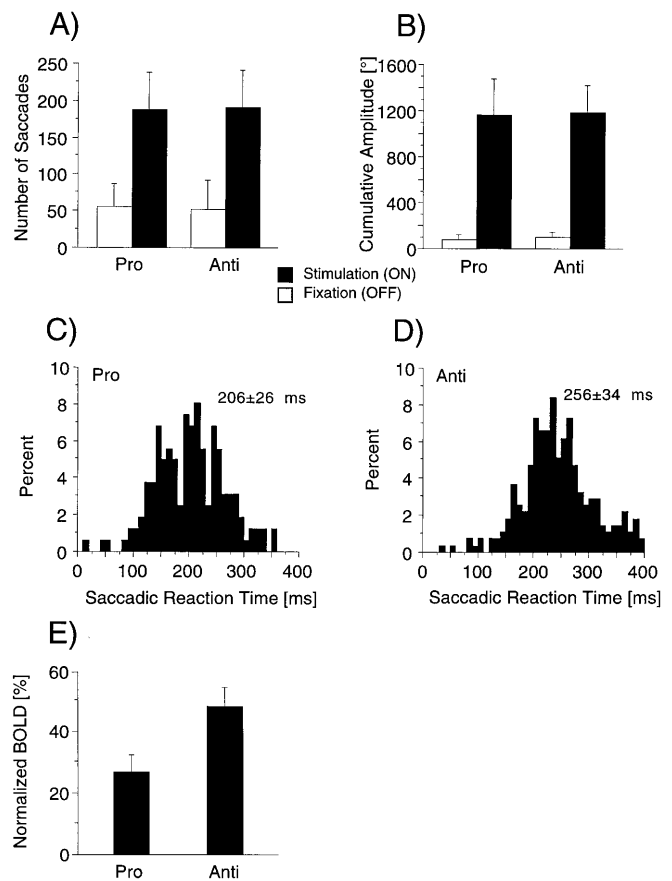


Fig. 4 Saccade parameters (A–D) and BOLD effects (E) in the “pro” versus the “anti” task. **A** Number of saccades and **B** cumulative amplitude. Mean values of six fixation periods (white bars) and six stimulation periods (black bars) in the “pro” and “anti” task. **C**, **D** Frequency distributions of saccadic reaction times of correctly performed pro- (**C**) and anti-saccades (**D**). Note that anticipatory saccades in **C** and **D** are rare. Binwidth 10 ms. Numbers in the graphs indicate mean reaction time (\pm SD). **E** Normalized BOLD effect (averaged across all identified cortical regions) separately for the “pro” and “anti” task (error bars in **A**, **B** and **E** 95% confidence intervals)

Pro-saccade versus anti-saccade series

The evaluation of oculomotor activity in the fixation (Off) periods of this series showed that saccadic activity was small and comparable across “pro” and “anti” tasks, in terms of both number of saccades and cumulative amplitude (Fig. 4A, B, white bars). In the stimulation periods (On), the number of saccades as well as the cumulative amplitude (Fig. 4A, B black bars) were highly increased as compared to the fixation periods, and this by comparable amounts for the “pro” and the “anti” task. Concerning the number of saccades, there was no statistically significant difference for the factor “Task” (“pro” vs “anti”; $P=0.9$). In contrast, there was a highly significant difference for the factor “Off/On” (fixation vs stimulation; [$F_{(1,28)}=52.8$; $P=0.0001$]), but no significant effect for the interaction between factors “Task” and “Off/On” ($P=0.8$). Similar results were obtained for cumulative am-

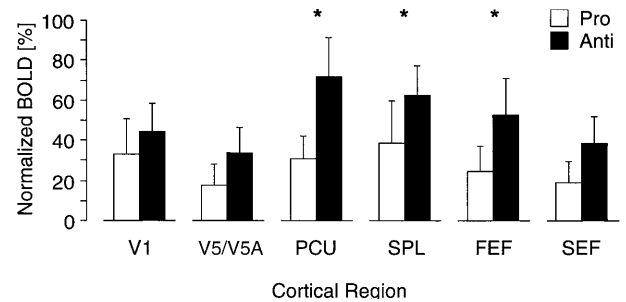
Table 2 Talairach coordinates (means \pm SD) of ROIs and corresponding Z-scores across the ten subjects performing the “pro” and “anti” task (n number of subjects showing significant activation in a given region)

Region of interest	Right hemisphere								Left hemisphere							
	n	Z-score	x	SD	y	SD	z	SD	n	Z-score	x	SD	y	SD	z	SD
FEF	7	3.6	41	9	-4	8	49	10	8	3.5	45	4	-7	7	45	6
SEF	5	3.2	2	3	-1	1	57	2	9	3.2	4	3	-1	7	53	4
SPL	7	3.8	28	10	-64	10	49	4	8	3.9	29	8	-68	10	49	4
PCU	5	3.6	9	7	-78	9	47	6	4	4.0	15	5	-78	8	46	4
V1	9	3.2	10	9	-92	7	-2	13	9	3.5	13	9	-92	7	-5	10
V5/V5A	10	3.0	44	5	-72	7	1	6	10	3.4	49	3	-74	6	0	7

plitude (factor “Task” $P=0.8$; factor “Off/On” [$F_{(1,28)}=173.9$; $P=0.0001$]; interaction between factors “Task” and “Off/On” $P=0.9$). Note that in this analysis all saccades were considered, i.e., also directional errors with subsequent corrective saccades. A separate analysis of directional errors revealed that subjects produced more errors in the anti-saccade task as compared to the “pro” task; error rate amounted to 1% of all trials (range 0–6%) for the “pro” task and 18% (3–29%) for the “anti” task. However, these direction errors hardly affected the saccade parameters “number of saccades” and “cumulative amplitude” in the two tasks. The analysis of saccadic reaction times (SRT) of centrifugal, stimulus triggered primary saccades revealed that, on average, the SRT in the “pro” task was lower than in the “anti” task by about 50 ms (difference statistically significant, $P=0.01$). Further analysis of the frequency distributions of SRT (Fig. 4C, D) showed that this increase in SRT in the “anti” task was mainly due to a reduction of short latency saccades (such as express saccades and fast regular saccades). The latter two saccade populations (range 90–180 ms) amounted to about 35% of all saccades in the “pro” task, but only to 11% in the “anti” task ($P=0.02$).

Figure 4E gives the corresponding normalized BOLD contrast averaged across all subjects and all cortical regions identified. We found no significant difference between hemispheres ($P=0.4$) and no significant interaction between the factors “Hemisphere” and “Region” ($P=0.4$); therefore, the data for right and left hemispheric activations were pooled for corresponding regions. The normalized BOLD effect in the “anti” task was almost twice as high as that in the “pro” task. This effect was statistically significant [$F_{(1,136)}=29.9$; $P=0.0001$]. Saccade-related cortical activation was found in the ROIs whose location corresponded well to the following regions: FEF, SEF, superior parietal lobule (SPL), precuneus (PCU), V1 and V5/V5A. The mean values of the ROI coordinates in Talairach space, the corresponding Z-scores as well as the number of subjects who showed activation in this region are given in Table 2, separately for the right and left hemisphere.

Changes in the BOLD effect over time, i.e., repetition effects across the six pairs of rest stimulation, were not observed, either in the “pro” or in the “anti” task. Figure 5 shows the BOLD effect separately for these regions. The BOLD effect differed across regions, showing

**Fig. 5** Normalized BOLD effect in the “pro” and “anti” tasks. The effects are shown separately for the cortical regions V1, V5/V5A, PCU, SPL, FEF and SEF (error bars 95% confidence intervals, asterisks statistically significant difference between tasks)

highest values in the parietal regions [$F_{(5,136)}=4.1$; $P=0.002$]. The activation was always higher during the “anti” task than during the “pro” task. The change of activation across tasks differed somewhat across regions; the largest increase in activation from the “pro” to the “anti” task was seen in PCU ($P=0.003$), SPL ($P=0.02$) and FEF ($P=0.002$).

Discussion

Saccade frequency and amplitude

Our data demonstrate a graded relationship between saccadic eye movement activity and cortical activity as measured by fMRI. The relationship consists of an essentially linear increase in BOLD effect with increase in saccade frequency. Interestingly, cumulative saccade amplitude showed only a marginal effect on the BOLD contrast. These findings applied to all cortical sites within the investigated brain volume, which showed changes in BOLD contrast with saccadic eye movements, i.e., V1, V5/V5A, BA19, PCU, SPL, FEF, and SEF. In the following we relate these findings to previous neuroimaging data as well as to electrophysiological data on the neuronal processing of saccades, as revealed by single cell studies in animals. Furthermore, we try to explain how changes in the neuronal activity are transformed into changes in the level of blood oxygenation.

Given the BOLD contrast represents a global (with respect to overall energy consumption) measure of cortical activity, the question arises as to how this effect relates to neuronal processing that occurs during saccade preparation. Saccades are known to represent mainly preprogrammed eye movements, i.e., most processing steps are performed in advance to saccade execution. To give a highly simplified survey, four major steps are taking place: (1) the visual stimulus on the retina evokes a discharge of neurons in the visual cortices (Schiller 1977), (2) at higher levels of processing, attentional processes select one of several stimuli, (3) a calculation of coordinates is performed, e.g., in parietal cortex (for review see Colby and Goldberg 1999), and (4) the decision to allow for a saccade is made in the frontal cortex (see Schall 1997). There exists an intimate interconnection between these cortical regions prior to the execution of each saccade. Conceivably, performing n saccades per time interval requires n times the processing/discharge of neurons in the above-mentioned regions (note that the tasks were not overtrained and that directions were randomized, enforcing reactions to the individual stimuli). Given the amount of neuronal activity increases with the number of saccades, one would expect a corresponding increase in regional cerebral blood flow (rCBF; Raichle et al. 1976; Fox and Raichle 1986; Fox et al. 1988), which manifests itself in the blood oxygenation level by a washing out of deoxygenated blood (Ogawa et al. 1990). Our results indicate that this relationship is rather robust; the frequency effect was evident in all saccade-related cortical regions found.

The present findings seem to be in conflict with a previous PET study of Paus et al. (1995), who found a decrease in rCBF in V1, V2 and parietal cortex with increasing saccade frequency. However, these authors investigated self-paced, stereotyped saccades (of estimated 45° amplitude) in complete darkness, the generation of which would not require visual and visuospatial processing. An increase in frequency in such a paradigm may actually lead to an automated performance with a shift of activity to subcortical structures. This notion would be compatible with further findings of the previous authors, showing that rCBF is increased with this paradigm in FEF, SC and cerebellar vermis, i.e., in saccade generating brain structures that are close to premotor mechanisms. A similar interpretation holds for the task repetition effect across repeated pairs of rest stimulation within a given experiment (Dejardin et al. 1998), which was not consistently seen in our tasks.

Less intuitive is our observation that there was only very little change in BOLD contrast with increase in saccade amplitude. In particular, if one focuses on the regions where the BOLD effects were most consistent (showing the least variability), i.e., on V5/V5A, BA19, FEF, and SEF, there was no statistically significant effect, but one might suspect from the curves shown in Fig. 3 (lower panel) a very slight increase with increase in cumulative saccade amplitude. This notion of a slight increase was confirmed by a significant increase in BOLD effect with increasing cumulative amplitude when averaging across all saccade regions investigated. In the fol-

lowing we consider first possible reasons for the mainly negative finding, before speculating on the small effect.

It is known that the neural representation of visuomotor signals in the primary visual or striate cortex (V1) is coded retinotopically, thus in a spatial rather than a magnitude domain (Schiller 1977). This principle is also found at higher level visual areas such as V2, V3, V4 or V5, although the topological representation may not be as specific as in V1. The decreasing topological specificity is accompanied by an increase in receptive field size. Compared to V1, the receptive field size in V5, for instance, is about two orders of magnitude larger, and the receptive fields in V5A are even larger. They are comparable to those of neurons in the parietal cortex for which only a crude topological arrangement has been found (Felleman and Van Essen 1991; Gattass and Gross 1981; Sereno and Allman 1991; Van Essen et al. 1981). More detailed information exists for FEF neurons in monkeys. Many neurons in this region show a topological pattern, with small saccade amplitudes being represented laterally in the arcuate sulcus and large amplitudes being represented more medially. The fact that most saccade-related cortical regions code saccade amplitude on a neuronal level by locally distributed neuron assemblies explains the mainly negative dependency of BOLD contrast on saccade amplitude.

We have attempted to disclose a topological shift of BOLD contrast in the FEF with saccade amplitude, but could not demonstrate it. First, the range of saccadic amplitudes investigated here was rather small, due to the limited visual field within the scanner gantry. Second, the resolution of our fMRI at 1.5 T (6×6 -voxel grid for the ROI analysis) is rather coarse and might have prevented a mapping of small topological differences. Despite these methodological limitations, we favor a further explanation. There is some overlap of the amplitude responses between neighboring cells of the topological representations (Bruce and Goldberg 1985), which likely causes a blurring of the local peak of activation. The situation in SEF appears to be even worse in this respect; neurons coding for certain amplitudes are intermingled such that no clear topology in terms of direction and amplitude results (Schlag and Schlag-Rey 1987; Russo and Bruce 1993).

The observed tendency for a very slight increase in BOLD contrast with saccade amplitude can possibly be related to the fact that in cortical regions involved in saccade preparation, some neurons (movement neurons) do show a burst of firing frequency that is related to saccade amplitude, as it has been demonstrated for the FEF for instance (Bruce and Goldberg 1985). An alternative explanation in terms of an effect related to attentional effort appears very unlikely to us; upon retrospective request, our subjects considered the effort to perform the largest saccades (10°) to be less than that for the small saccades.

Anti- versus pro-saccade task

As mentioned before, the visual stimuli in the “pro” and “anti” tasks were predictable with respect to eccentricity

and timing, but not to direction. Planning of the saccade goal required a spatial transformation in the “anti” task, unlike in the “pro” task, which made the former more demanding. Given comparable numbers of saccades in the two tasks, as in our experiment, differences in BOLD response in saccade-related areas might mainly reflect differences in information processing (e.g., coordinate transformation, suppression of pro-saccades) and/or in effort of performance (e.g., higher attentional load) between the two tasks.

The main finding with these tasks was that the BOLD contrast was significantly higher in the “anti” than the “pro” task. There was a tendency for this effect in all saccade-related regions, but significance level was reached only in PCU, SPL, and FEF. We therefore concentrate in the following on discussion of the latter three regions, but mention also the SEF, since previous work indicates an important role of this region for the “anti” task.

Parietal cortex (SPL)

An increase in SPL activation during anti-saccades has previously been reported in a number of PET studies (Doricchi et al. 1997; O’Driscoll et al. 1995; Paus et al. 1993; Sweeney et al. 1996). The PET activation in SPL has been associated, at least in part, with the control of spatial visual attention (Corbetta et al. 1993), for which there is a higher demand during the “anti” than during the “pro” task. Adjacent to SPL, there is a well-studied region in the monkey in the inferior parietal lobule within the lateral bank of the intraparietal sulcus (LIP). LIP neurons have been shown to participate in the internal mapping of sensory representations (Andersen et al. 1997; Duhamel et al. 1992), the location of visual cues (Gottlieb and Goldberg 1999), and spatial attention (Powell and Goldberg 2000). The human homologue of LIP is not clearly defined as yet, but is presumably located outside SPL, in the intraparietal sulcus as in monkeys.

Precuneus

Another parietal region that is known to be activated during saccade tasks (e.g., Luna et al. 1998) showed significantly higher BOLD activation in the “anti” than in the “pro” task. Little is known so far about the functional role of this region; it has been related to “topokinetic memory” (Berthoz 1997) and “setting up spatial attributes” (Ogiso et al. 2000), among others.

Frontal eye fields

Our evidence for an increase in FEF activity in the “anti” as compared to the “pro” task requires more detailed consideration, since the current literature is controversial in this respect. Increased activity during an anti-saccade task has been previously reported in some PET studies

(Doricchi et al. 1997; O’Driscoll et al. 1995; Sweeney et al. 1996). In contrast, the PET study by Paus et al. (1993) and the fMRI study by Muri et al. (1998) reported similar activations in FEF for the “anti” and “pro” tasks (a slight trend towards higher activations in the “anti” task can be seen in the latter study, though). There exist considerable differences in the experimental paradigms used, but it is difficult to estimate the role of these differences, which concern: randomization of target location, “gap” duration between fixation point extinction and target appearance, stimulus amplitude and target presentation time. Paus et al. (1993) used a regularly alternating stimulus in the “pro” task versus a direction-randomized one in the “anti” task (a fact which hampers the comparison already in their experiments, because the former is predictable, unlike the latter), while Muri et al. (1998) used randomized stimulus directions during both tasks, as in our study. On the other hand, both Sweeney et al. (1996) and Muri et al. (1998) used no “gap” (0 ms), yet the former found an increase in FEF activation in the “anti” task (similar to our results; “gap” = 200 ms), while the latter study found no significant effect. Stimulus amplitude alone does not appear to represent a decisive factor either, since increased FEF activities were found with amplitudes of 5° and 10° (Doricchi et al. 1997; Sweeney et al. 1996) as well as with 15° (O’Driscoll et al. 1995). The same applies to target presentation time; while this time amounted to 3000 ms in our study, it was 700 ms in the study by Muri et al. (1998); yet an increase in FEF activation in the “anti” task was reported even for very short target presentation times (100 ms; O’Driscoll et al. 1995).

Since comparison with the literature is problematic, we focus in the following on the present findings on BOLD effects and relate these to the behavioral data we obtained. In our experiments not only the number of saccades, but also cumulative saccade amplitude was comparable between the two tasks. However, there was a difference concerning saccadic reaction times, which was mainly due to the relatively small number of short latency saccades (<180 ms) in the “anti” task (see Fig. 4D). Furthermore, error rate was higher in the “anti” than in the “pro” task. We take these differences as indicating a more complex signal processing in the “anti” as compared to the “pro” task and relate our observation of a larger BOLD response in the former to this more elaborate processing. In two previous studies investigating patients with very small lesions restricted to the left FEF, the percentage of errors in the “anti” task was normal while latencies were also increased (Rivaud et al. 1994; Gaymard et al. 1999). Effects of laterality could, however, not be tested with our block-design experiment, which always included saccades in two directions within one block (to the target and back to the center).

Noticeably, in the neuroimaging studies so far (including our own), the “anti” and “pro” tasks were presented in separate experimental sessions and comparisons were made between sessions. This is different from studies in which the task was varied from trial to trial,

for instance in the study by Everling and Munoz (2000), where a cue (e.g., changes in color of the fixation spot) announced the task (requiring a decision process in each trial). These authors compared FEF neuronal activity in monkey between the tasks and report that neurons, which project to the superior colliculus, show a higher activity for short latency correct pro-saccades than for late pro-saccades, direction errors and anti-saccades. We hold that these findings are difficult to compare with the present ones, because of the difference in the tasks. Also, we conceive of the possibility that FEF neurons might be inhibited with the anti-task and functional imaging might record this inhibitory activity in terms of an increased metabolism (which represents a highly speculative assumption so far, however).

Supplementary eye fields

An increased SEF activation in anti-saccade trials similar to that in our data was found in several functional imaging studies (PET: Doricchi et al. 1997; O'Driscoll et al. 1995; Paus et al. 1993; Sweeney et al. 1996). Interestingly, SEF neurons in monkey also showed an increased discharge in anti- vs pro-saccade trials (Schlag-Rey et al. 1997). This would be in line with the generally accepted notion that the SEF plays a major role in motor planning and internally guided behavior (Schall 1991).

Conclusions

We demonstrated that the BOLD response as a measure of cortical activity in saccade-related regions is closely correlated with saccade frequency. There was no such relationship for saccade amplitude. Furthermore, for comparable amounts of saccade frequency we demonstrated changes in cortical activation for different saccade tasks; we found the BOLD response with the anti-saccade task increased as compared to a pro-saccade task in essentially all cortical regions involved in saccade processing. We hold that an accurate quantitative assessment of behavioral correlates (here saccade parameters) enhances the significance of findings from human neuroimaging studies and helps to compare these with electrophysiological data.

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