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Published in:
NeuroReport

DOI:
[10.1097/WNR.0b013e32805868ba](https://doi.org/10.1097/WNR.0b013e32805868ba)

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Recommended citation(APA):

Baumann, O., Frank, G., Rutschmann, R. M., & Greenlee, M. W. (2007). Cortical activation during sequences of memory-guided saccades: A functional MRI study. *NeuroReport*, 18(5), 451-5.
<https://doi.org/10.1097/WNR.0b013e32805868ba>

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Cortical activation during sequences of memory-guided saccades: a functional MRI study

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Keywords: brain imaging; dorsolateral prefrontal cortex; functional magnetic resonance imaging; oculomotor control; saccade sequences; working memory

Abstract

Blood oxygenation-level dependent changes in the cerebral cortex were measured using event-related functional magnetic resonance imaging in participants while they performed triple-step memory-guided saccades. To explore the role of dorsolateral prefrontal cortex in the manipulation of the contents of working memory, the sequence of saccade targets in the memory-guided task was either constant or was manipulated using coloured cues. The dorsolateral prefrontal cortex was significantly activated only during the period when participants had to reorder the locations of the saccade targets and not during the maintenance of spatial locations. This finding suggests that dorsolateral prefrontal cortex is primarily involved in the manipulation, and to a lesser extent, in the maintenance of the contents of working memory.

Introduction

Saccadic eye movements serve to bring a visual target into the foveal region of the retina. In memory-guided, multistep paradigms, the individual is instructed to maintain, for a brief period of time, the relative locations of the saccade targets and, following a retention period, to execute these saccades in the predetermined order. In a functional MRI (fMRI) block-design study, Heide and colleagues [1] explored triple-step saccades to visual targets and reported several saccade-related activations in parietal and prefrontal cortex. Interestingly, in the memory-guided triple-step saccade task, the dorsolateral prefrontal cortex was not activated. Heide *et al.* [1] speculated that the retention period used in their study (0.5 s) was too short to activate memory processes underlying the maintenance of visuospatial information.

Although it is generally accepted that the dorsolateral prefrontal cortex is a substantial component of the neural network, which is the basis for working memory processes, its exact function in humans is still unclear and remains controversial. Levy and Goldman-Rakic [2] suggest a 'domain-specific' model, according to which the dorsolateral prefrontal cortex (Brodmann area 9/46) is specialized for visuospatial processing, whereas the ventrolateral prefrontal cortex (Brodmann area 45/47) is specialized for nonspatial visual processing (e.g. objects, faces). In contrast, 'process-specific' theories suggest the hypothesis that the ventrolateral prefrontal cortex is responsible for the active maintenance of memory contents, whereas the dorsolateral prefrontal cortex is activated during executive processing only if a manipulation and a monitoring of the information held in working memory is necessary [3,4].

In this study, we introduce a new experimental manipulation that requires individuals to reorder the remembered saccade locations with the help of a colour-coded sequence, indicating in which order the saccadic sequence has to be performed. This new approach allowed us to isolate endogenous processes related to the manipulation of the contents of visual working memory, while keeping the sensory and motor components of the task constant.

Materials and methods

Study participants

After giving informed consent to procedures approved by the University of Regensburg ethics committee, 13 right-handed volunteers (six women) participated in the study. The participants' ages ranged from 20 to 28 years (mean 24.5 ± 2.1 years). None of the participants had a history of neurological or psychiatric disorders.

Prescanning training of saccade tasks

Before participation in the main experiments, all participants took part in three training sessions, which were performed in an oculomotor laboratory. Here the participants were familiarized with the visual stimuli, eye-movement recordings and tasks to be performed in the main experiment.

Visual stimulation

The participants viewed the stimuli with a mirror that reflected the image from the projection screen placed behind the head of the individual in the back of the scanner gantry. The stimuli were created using the software package 'Presentation' (Version 9.20; Neurobehavioral Systems, USA) and projected through a radiofrequency waveguide with a liquid-crystal display projector (JVC; model name D-ILA_915 E, Victor Company of Japan, Ltd., Yokohama, Japan) located outside of the scanner room. The image subtended $36.5 \times 28.0^\circ$ of visual angle (1024×768 pixels) at a viewing distance of 70 cm.

Three conditions were applied: baseline fixation, memory-guided saccade task, and the colour-coded memory-guided saccade task. Each condition consisted of 42 consecutive trials. The sequence of conditions was pseudo-randomized over participants. Each trial started with a fixation period during which a white dot (0.8° ; fixation point) was continuously projected to the centre of the display. Participants were instructed to maintain stable fixation on the fixation point. In the fixation task, the white fixation spot was replaced by a series of three differently coloured dots for 1 s each (red, yellow, green, in random sequence). The participants were instructed to attend to the central fixation and to note the colour sequence presented on each trial. No further behavioural task was required during the fixation condition. In the memory-guided saccade task, the central fixation spot remained visible when each differently coloured saccade target was presented at one of four possible locations: $\pm 9^\circ$, $\pm 18^\circ$ (negative values indicate positions to the left of central fixation), for 1 s each in sequence. After a retention period of either 2 or 5.5 s, the fixation spot was extinguished and the participants performed saccades to the remembered location in the original order and timing (one saccade per second, independent of the colour of each target). Finally, in the colour-coded memory-guided saccade task, the participants first viewed the colour and location of the three saccade targets while maintaining central fixation as in the memory-guided saccade condition. The central white dot was then replaced by a colour sequence (e.g. red, green, yellow); each colour was shown for 1 s. This new sequence

indicated to the participants in which order the saccades should be executed. For example the original order (yellow 18° right of central fixation, green 18° left of central fixation, red 9° right of central fixation) had to be reordered according to the colour sequence (green first, yellow second, red third), which implies that the sequence to be performed on that trial was green 18° left of central fixation, yellow 18° right of central fixation, and red 9° right of central fixation. The actual colour sequence on each trial was pseudo-randomly determined. As in the memory-guided saccade condition after a fixation period of either 2 or 5.5 s the fixation spot was extinguished and participants performed three saccades with 1-s intervals to the colour-instructed locations. Participants were instructed to time their responses on the basis of the preceding stimulus intervals.

In-scanner recordings of eye movements

Eye movements were recorded using the MR-Eyetracker, (Cambridge Research Systems Ltd., Rochester, Kent, England) a fibre-optic limbus-tracking device, which we have described previously [5]. The sampling frequency of the eye-tracker signal was 1000 Hz and the spatial resolution was 0.1°. Before the experiment, the Eyetracker was calibrated to the four eccentricities (−9, −18, +9, +18° visual angle), which were used in the experiment as target locations. Using a Matlab (Version 6.5)-based computer program, developed in our laboratory, we could analyze the resulting eye traces offline and were able to extract the onsets of saccades and to determine their directions and amplitudes.

MRI

MRI was performed with a 1.5 T clinical scanner (Magnetom Sonata, Siemens, Erlangen, Germany) equipped with an echo-planar imaging booster for fast gradient switching and an eight-channel, phased-array radio frequency receive–transmit headcoil (MRI-Devices, Orlando, Florida, USA). Functional imaging was performed with T2*-weighted gradient echo-planar imaging. The time to echo was 60 ms, total scan repetition time was 2.9 s and the flip angle was 90°. We used a field of view equal to 192 mm, with a voxel matrix of 64×64, resulting in a voxel size of 3 mm³. Volumes with 30 contiguous slices (no gap) were acquired in interleaved mode. Acquisition jitter was accomplished by choosing trial intervals that were not divisible by the total scan repetition time.

Data analysis

The data were preprocessed, analyzed and visualized using SPM2 (www.fil.ion.ucl.ac.uk/spm), a software package for the analysis of brain imaging data sequences. After slice timing and motion correction, the functional images were coregistered to the anatomical volume. Then functional and anatomical images were normalized to the Montreal Neurological Institute-template [6]. Functional images were resliced to 2×2×2 mm voxels and smoothed with a 3D-Gaussian (full width at half maximum=8 mm).

Analysis using the general linear model [7] was conducted, including high-pass filtering (cut-off, 128 s) and serial correlations. In an event-related design analysis, responses during specified epochs of each trial were modelled using the haemodynamic response function. Visual events represented by the onsets of the saccade targets in the memory-guided saccade

condition and the colour-coded memory-guided saccade task, as well as the central colour sequence in the fixation and colour-coded memory-guided saccade conditions, were modelled using four regressors with 126 1-s epochs (42 trials with three onsets each). Saccadic events in the memory-guided saccade and colour-coded memory-guided saccade conditions were modelled as events using the exact time of saccade execution using two regressors. Finally, we modelled the last second of the retention period as a 1-s epoch in the memory-guided saccade and colour-coded memory-guided saccade condition separately for the 2- and 5.5-s retention intervals using four regressors. This approach was used to keep the condition models comparable and because we expected differences in the end rather than the beginning of the retention periods, as the initial 2 s are the same for both retention periods. We chose the 3-s colour-sequence fixation period in the fixation condition for comparisons with activation during saccade execution. This yields a constant-duration task epoch for all saccade conditions and can account partly for the visual input and other task-related activity.

For population inference statistics, a nonparametric random-effects group analysis was performed with SnPM2 [8,9]. Clusters surpassing a defining threshold of pseudo- $t=3.00$ voxelwise and a cluster-size threshold of $P=0.05$ (corrected for multiple comparisons) were identified as activated.

Results

Eye movement data

By comparing the eye traces with the data of the calibration recordings and with regard to the onset times of the visual stimuli, we could determine the exact time points, directions and amplitudes of all executed saccades. Saccades were judged as correct if the final eye position fell within an interval of $\pm 3^\circ$, centred on the correct target position. Participants required slightly more time to execute the initial saccade of the triple-step sequence in the colour-coded memory-guided saccade condition (mean latency: memory-guided saccade condition 420 ms; colour-coded memory-guided saccade condition 452 ms), compared with the memory-guided saccade condition. As instructed, participants were able to maintain the 1-s rhythm of the target presentation. Mean intervals between the first and second, and second and third saccade were 954 and 983 ms for the memory-guided saccade and 943 and 930 ms for the colour-coded memory-guided saccade condition, respectively. Saccades to erroneous target locations occurred only in 2.6 and 4.9% of all cases for the memory-guided saccade and colour-coded memory-guided saccade conditions, respectively.

Functional MRI data

The different triple-step saccadic tasks evoked a robust pattern of activation in occipital, parietal and prefrontal cortex.

Memory-guided saccades vs. fixation

Regions of maximal activation were located in the posterior parietal cortex, including locations that correspond to the human homologue of the lateral intraparietal area of primates [10]. A prominent activation in the frontal eye field was seen in the right hemisphere and in the medial supplementary eye field in Brodmann area 6. Prefrontal cortex anterior to the frontal eye field is not strongly activated in this task.

Colour-coded memory-guided saccades vs. fixation

The colour-coded memory-guided condition was associated with a much broader activation pattern than in the simple memory-guided saccade condition with additional bilateral foci around the precuneus/cuneus gyri and in the posterior part of the anterior cingulate cortex.

Effect of the duration of the retention period

In the memory-guided saccade tasks, participants were required to retain the visual and spatial information over a retention period that was either 2 or 5.5 s in duration. The results for the contrasts, which compares the activity arising during the last second of the short retention period with that measured for the last second of the long retention period, for the colour-coded memory-guided saccade condition are shown in Fig. 1a and Table 1. They indicate that for the short (2-s) retention period, bilateral clusters in posterior parietal cortex and another expansive bilateral activation extending from the cuneus up into the occipitoparietal region were significantly more activated than for the long retention period (5.5 s).

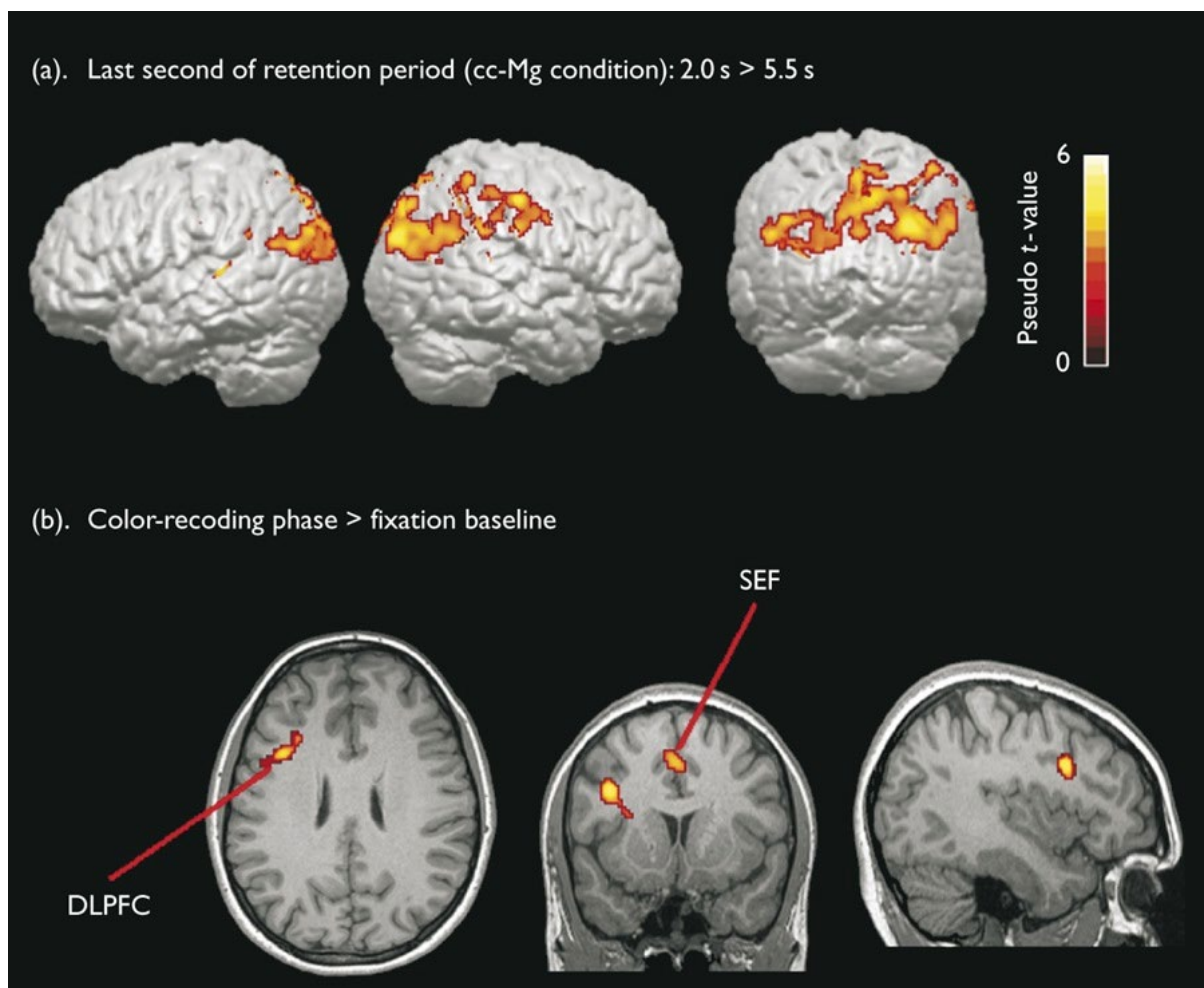


Fig. 1 (a) Group activation map illustrating significant activity associated with the comparison between the last second of the short (2 s) and the long (5.5 s) retention period during the colour-coded memory-guided task. (b) Group activation map illustrating significant activity associated with manipulation of the contents of working memory in the colour-coded memory-guided (cc-MG) task compared with central fixation in the baseline condition. Transverse (Talairach z-coordinate=27), coronal (Talairach y-coordinate=12) and sagittal (Talairach x-coordinate=-39) sections showing regions of interest located in the DLPFC and in the SEF. DLPFC, left dorsolateral prefrontal cortex; SEF, supplementary eye field.

Effect of manipulation in working memory

Table 2 and Figure 1b show the results of the comparisons of the period during which the participant had to reorder the saccade sequence in the colour-coded memory-guided saccade condition, compared with the fixation period in the baseline condition (i.e. the 3-s colour sequence). The colour-coding phase of the colour-coded memory-guided saccade task (while viewing the three-colour sequence) evoked more activity in dorsolateral prefrontal cortex, the supplementary eye field and the precuneus. Apparently, the additional cognitive demands of reordering the sequence, with which the saccades should be executed later on in the trial, led to activations in these areas.

Table 1 Significant BOLD-cluster associated with the last second of the two different retention periods in the colour-coded memory-guided saccade condition (2.0>5.5 s).

Region	Hemisphere	Brodmann area	Talairach coordinates			Pseudo-t-values of maxima (cluster size in number of voxels)
			x	y	z	
MOG/MTG/SOG/Cuneus/AG/SMG/CiG/IPL/Prec	R/L	7/18/19/23/31/39/40	28	-86	30	4.90 (3336)
PrCeG/IPL/PoCeG	R	1/2/3/4/6/40	51	-17	45	4.65 (492)
IPL/Prec/SPL	R	7/40	42	-44	57	3.98 (234)
HeG/Insula/STG/Nuc. Caud.	L	13/29/41	-30	-35	9	4.22 (150)

AG, angular gyrus; CiG, cingulate gyrus; HeG, Heschel's gyrus; IPL, inferior parietal lobule; MOG, middle occipital gyrus; MTG, middle temporal gyrus; Nuc. Caud., caudate nucleus; PoCeG, posterior central gyrus; Prec, precuneus; PrCeG, precentral gyrus; SMG, supramarginal gyrus; SOG, superior occipital gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus.

Table 2 Significant BOLD-cluster associated with the manipulation of the saccadic target locations in the colour-coded memory-guided saccade condition (colour-recoding phase > fixation baseline).

Region	Hemisphere	Brodmann area	Talairach coordinates			Pseudo-t-values of maxima (cluster size in number of voxels)
			x	y	z	
CiG/MFG	R/L	6/8/9/32	0	20	41	4.70 (209)
Prec/IPL	L	7	-6	-65	60	5.37 (171)
IFG/MFG	L	9	-38	13	27	5.20 (160)

CiG, cingulate gyrus; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; Prec, precuneus.

Discussion

Cortical activation during memory guided triple-step saccades

Our results indicate that an extensive network of regions in the posterior parietal cortex and in the frontal and supplementary eye fields, which are located in premotor cortex, is active during the planning stage for triple-step saccades. The novel result of this study, presented in Fig. 1b and Table 2, is that the dorsolateral prefrontal cortex is only activated when the participants are required to perform a manipulation of the information stored about the colour and the position of the saccade targets. The extent and amplitude of this activation are in good agreement with earlier studies [3].

Cortical activation during the retention period of memory-guided triple-step saccades

The comparison of the results for short (2-s) and long (5.5-s) retention periods indicates that focal areas in the precuneus and cingulate cortex were more active during the short retention period (Fig. 1a). The lack of activations related to the retention period in the dorsolateral prefrontal cortex runs contrary to the notion that this cortical area plays a critical role in the maintenance of the contents of working memory, as suggested by single-unit recordings [11] and inactivation studies in monkeys [2,12].

Our findings indicate that the lack of dorsolateral prefrontal cortex activation is not related to inadequately short retention periods, as suggested by Heide *et al.* [1]. In contrast, less activity was evident for the long retention period than for the short one (Fig. 1a). Our findings suggest that dorsolateral prefrontal cortex in human cortex is selectively activated by tasks that demand the manipulation of the contents of working memory irrespective of the subsequent duration of the retention period (Fig. 1b). This conclusion is in line with the process-specific model.

In our experiment, the posterior parietal cortex was robustly activated by both the memory-guided tasks performed here (Table 1). Activation of the posterior parietal cortex has also been reported by our group and by others in a recent comparison between simple visually and memory-guided saccade tasks [13-15]. These findings point to the vital role of the posterior parietal cortex in the retention of object-related and spatial information in delayed response paradigms.

Conclusion

The present results provide additional support for the process-specific model of dorsolateral prefrontal cortex in spatial working memory [16]. Our findings support a role of the human dorsolateral prefrontal cortex in the executive functions related to the manipulation and task-dependent reorganization of visuospatial information in working memory. The posterior parietal cortex and precuneus/cuneus appear to support the maintenance of visuospatial information.

Acknowledgement

This work was funded in part by the Bayerische Forschungsförderung (BayernBrain 3T).

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