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Topographic Maps in Human Frontal Cortex Revealed in Memory-Guided Saccade and Spatial Working-Memory Tasks

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Kastner S, DeSimone K, Konen CS, Szczepanski SM, Weiner KS, Schneider KA. Topographic maps in human frontal cortex revealed in memory-guided saccade and spatial working-memory tasks. *J Neurophysiol* 97: 3494–3507, 2007. First published March 14, 2007; doi:10.1152/jn.00010.2007. We used fMRI at 3 Tesla and improved spatial resolution ($2 \times 2 \times 2 \text{ mm}^3$) to investigate topographic organization in human frontal cortex using memory-guided response tasks performed at 8 or 12 peripheral locations arranged clockwise around a central fixation point. The tasks required the location of a peripheral target to be remembered for several seconds after which the subjects either made a saccade to the remembered location (memory-guided saccade task) or judged whether a test stimulus appeared in the same or a slightly different location by button press (spatial working-memory task). With these tasks, we found two topographic maps in each hemisphere, one in the superior branch of precentral cortex and caudalmost part of the superior frontal sulcus, in the region of the human frontal eye field, and a second in the inferior branch of precentral cortex and caudalmost part of the inferior frontal sulcus, both of which greatly overlapped with activations evoked by visually guided saccades. In each map, activated voxels coded for saccade directions and memorized locations predominantly in the contralateral hemifield with neighboring saccade directions and memorized locations represented in adjacent locations of the map. Particular saccade directions or memorized locations were often represented in multiple locations of the map. The topographic activation patterns showed individual variability from subject to subject but were reproducible within subjects. Notably, only saccade-related activation, but no topographic organization, was found in the region of the human supplementary eye field in dorsomedial prefrontal cortex. Together these results show that topographic organization can be revealed outside sensory cortical areas using more complex behavioral tasks.

INTRODUCTION

The human visual system contains a multitude of topographic maps, as revealed by functional magnetic resonance imaging (fMRI) in recent years. Each visual map provides a point-by-point representation of the contralateral hemifield in retinotopic coordinates (Brewer et al. 2005; DeYoe et al. 1996; Engel et al. 1997; Schneider et al. 2004; Sereno et al. 1995; Tootell et al. 1997). The degree of detail provided by these maps depends on physiological parameters such as the receptive field (RF) size of neurons in a given area (Kastner et al. 2001) and on technical limitations of the functional magnetic resonance imaging (fMRI) technique such as spatial resolution. The retinotopic organization of visual areas has been the basis for delineating different areas and probing response properties

at the population level in each area (e.g., Heeger and Ress 2002; Kastner et al. 1998). In contrast, it has proven difficult to identify higher-order cortical areas outside visual cortex based on topographic criteria. Using a cognitive mapping approach, three different retinotopic maps related to memory-guided saccades and the spatial allocation of attention were found in the intraparietal sulcus (IPS1 and IPS2) (Schluppeck et al. 2005; Silver et al. 2005) and in the superior parietal cortex (Sereno et al. 2001). Most recently, first evidence of topographic representations of visual space has also been demonstrated in frontal and prefrontal cortex using a face working-memory task (Hagler and Sereno 2006).

Based on monkey physiology studies, at least three topographic principles of organization may be found in frontal cortex (see Moore et al. 2003; Schall 2002; Tehovnik et al. 2000 for reviews). First, in the frontal eye field (FEF), *saccade amplitude* is organized topographically such that smaller saccades are elicited by stimulating sites in its ventrolateral part and larger saccades are elicited from sites in its dorsomedial part (Bruce et al. 1985; Robinson and Fuchs 1969). Second, in the FEF and possibly also in the supplementary eye field (SEF), *saccade direction* appears to be organized in a columnar fashion with neighboring columns coding saccades in similar directions covering the complete range of contralateral saccades but representing same directions in multiple locations of the map (Bruce et al. 1985; Mott and Schaefer 1890; Russo and Bruce 2000; Wagman et al. 1961). Third, in the dorsolateral prefrontal cortex (DLPFC), a similar columnar organization has been suggested for neurons with *memory fields* coding for a particular location of the visual field during working-memory delays (Funahashi et al. 1989, 1990; Goldman-Rakic 1996; Rainer et al. 1998a; Sawaguchi 1996). However, the topography of saccade direction and memory fields in the FEF and DLPFC at the scale of a functional map has never been systematically explored in the primate brain.

The most classical task that has been used to study topography in frontal cortex is the memory-guided saccade task, during which delayed saccades are performed to peripheral spatial locations within the visual field that are held in working memory. Here we used this task to probe topographic organization of areas in human frontal cortex by using fMRI at 3 Tesla and improved spatial resolution ($2 \times 2 \times 2 \text{ mm}^3$). Topographic maps found with the memory-guided saccade task were related to activations evoked by visually guided saccades, a task that served to identify the human FEF and SEF, and also

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to a delayed response task that required a manual rather than a saccadic response. We refer to the latter task as the spatial working-memory task. Two topographic maps were found with the delayed response tasks that mainly represent saccade directions and memorized locations of the contralateral hemifield. One was found in the superior branch of precentral cortex and caudalmost part of the superior frontal sulcus, in the region of the human FEF, and the second in the inferior branch of precentral cortex and caudalmost part of the inferior frontal sulcus. Both areas were also activated by visually guided saccades. Notably, no topographic organization was found with the delayed response tasks in the region of the human SEF in dorsomedial prefrontal cortex.

METHODS

Subjects

Ten subjects (aged 20–36 yr, 6 females) participated in the study, which was approved by the Institutional Review Panel of Princeton University. All subjects were in good health with no history of psychiatric or neurological disorders and gave their informed written consent. Subjects had normal or corrected-to-normal visual acuity. All subjects participated in one scanning session in which the memory-guided saccade task was tested, and a second scanning session in which high-resolution structural images for cortical surface reconstructions were obtained. Four of the 10 subjects participated in two additional scanning sessions in which a saccade localizer task and the spatial working-memory task, which required a manual instead of a saccadic response, were probed.

Visual display

The stimuli were generated on a Macintosh G4 computer (Apple Computer, Cupertino, CA) using MATLAB software (The MathWorks, Natick, MA) and Psychophysics Toolbox functions (Brainard 1997; Pelli 1997). Stimuli were projected from a PowerLite 7250 liquid crystal display projector (Epson; Long Beach, CA) outside the scanner room onto a translucent screen located at the end of the scanner bore. Subjects viewed the screen at a total path length of 60 cm through a mirror attached to the head coil. The screen subtended 30° of visual angle in the horizontal dimension and 26° in the vertical dimension. A trigger pulse from the scanner synchronized the onset of stimulus presentation to the beginning of the image acquisition.

Visual stimuli and experimental design

Three different tasks, performed in separate scanning sessions, were tested: a memory-guided saccade task, a spatial working-memory task, and a saccade localizer task.

Memory-guided saccade task

The memory-guided saccade task was performed at 8 or 12 peripheral locations arranged clockwise around a central fixation point (see Fig. 1A). During each trial of the task, subjects ($n = 10$) maintained fixation at a central cross while a target stimulus (0.3°) was presented in one of the peripheral locations at ~10° eccentricity for 500 ms, the location of which had to be remembered, followed by distracters presented for 3 s. The distracters were 100 dots (0.3°) randomly configured within an annulus spanning 9–11° eccentricity with a new configuration displayed every 500 ms. The disappearance of the fixation point and the distracters indicated to subjects to execute a saccade to the remembered target location and then immediately back to fixation, where the fixation point reappeared after 750 ms. Subjects had another 750 ms to prepare for the next trial, which started with the

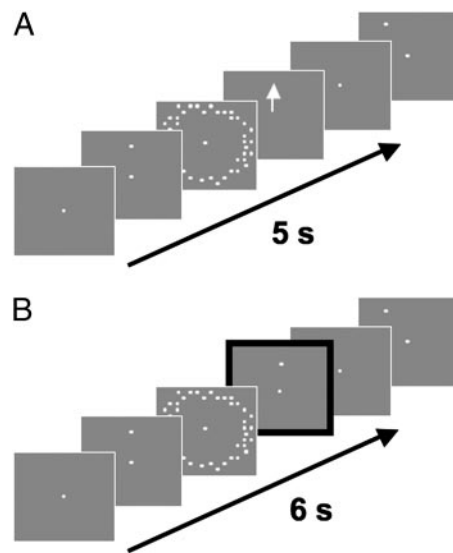


FIG. 1. Memory-guided saccade (A) and spatial working memory (B) tasks. Subjects performed the tasks at 8 or 12 different peripheral locations arranged clockwise around the fixation point. Example of a 12 o'clock trial. In both the memory-guided saccade and the spatial working-memory tasks, subjects maintained fixation throughout the trial. A target stimulus was presented at ~10° eccentricity for 1 s, the location of which subjects memorized, followed by the presentation of a ring of distracters for 3 s at similar eccentricities (working-memory delay period). In the memory-guided saccade task, subjects were prompted to saccade to the remembered target location on disappearance of the fixation point and distracters, as schematically indicated by the arrow (A). In the spatial working-memory (SWM) task, the target reappeared at the end of the trial (marked by the black frame) in the same or a slightly different location. Subjects indicated by button press whether the target reappeared at the remembered (correct), or a different (incorrect) location (B). Performance in the SWM task was individually adjusted to an ~85% correct level. Each trial lasted for 5 s in the memory-guided saccade task and for 6 s in the SWM task with 8 or 12 trials per cycle and 6–8 cycles per single scan run, respectively.

appearance of a target at a new location. An example for a 12 o'clock trial is given in Fig. 1A. Each trial at a given target location was 5 s long. The first target appeared at the right horizontal meridian and subsequent target locations were marked counterclockwise through 12 or 8 equally spaced positions. In the 12 locations version of the task (Serenio et al. 2001), the peripheral locations were arranged clockwise, whereas in the 8 locations version of the task, the 1 and 2 o'clock, 3 and 4 o'clock, 7 and 8 o'clock, and 10 and 11 o'clock positions were replaced by 1:30, 3:30, 7:30, and 10:30 o'clock positions, respectively. The 12, 3, 6, and 9 o'clock positions were common to both task versions. The position of each target was randomly jittered by $\leq 2.5^\circ$ in each direction to reduce the predictability of the task. Each 12-position run was composed of eight 60-s cycles, whereas each 8-position run was composed of eight 40-s cycles. In addition, the eight locations version of the task included 20 s of fixation at the beginning and the end of each run. Eight subjects were tested in the eight locations version, and four subjects (S1–S4) were tested in the 12 locations version. Two subjects (S3–S4) were tested with both versions of the task. And two subjects (S4–S5) were tested repeatedly in the eight locations version of the task. Studies were initially conducted with the 12-locations version of the task but then continued with the 8-locations version. The latter version of the task yielded very similar results (see Fig. 5) but had several advantages. First, the overall time of a single run was significantly shorter (6 vs. 8 min), and therefore subject's performance was less likely to decline over time. And second, a larger amount of data could be acquired within a single scan session, thereby enhancing the chances of obtaining robust functional activation maps in each subject.

Spatial working-memory task

The spatial working memory task (Fig. 1B) was identical to the 12 locations version of the memory-guided saccade task with the following differences. After the disappearance of the distracters, a test dot appeared for 750 ms at or near the location of the target stimulus (indicated by the black frame in Fig. 1B). While maintaining fixation, subjects judged whether the test dot was in the identical or a different location as the target and responded by pressing one of two buttons for matching and nonmatching locations. Subjects ($n = 4$) were required to respond within 1.5 s of the appearance of the test stimulus, or else the trial was classified as incorrect. Each trial lasted for 6 s with 12 trials per cycle and six cycles per scan. Each scan started and ended with a 10-s central fixation period. The same subjects were also tested in the 12 locations version of the memory-guided saccade task.

Prior to scanning, each subject was tested in behavioral sessions to determine the spatial deviation from the target location that yielded ~85% correct performance. This deviation was initially used during the scanning session but was monitored after each run and adjusted, if necessary, to maintain each subject's performance ~85% correct throughout the scanning session. The spatial deviation ranged from 2.5 to 4° across subjects. The behavioral data acquired during scanning sessions were used to determine memory performance fields, which were computed as the accuracy at each location averaged across all trials performed during the session. Statistical significance of behavioral performance across the visual field was assessed using repeated-measures ANOVAs with the subject as the random variable.

Saccade localizer task

The same four subjects, who participated in the 12 locations version of the memory-guided saccade task and the spatial working-memory task, were also scanned while performing visually guided saccadic eye movements alternating with a baseline fixation condition. During the eye-movement task, subjects executed saccadic eye movements toward a black dot (0.2° diam) presented on a gray background, which first appeared at a central location. During a given block of eye movements the dot jumped with a frequency of 2 Hz to different eccentric positions along one of four axes (horizontal, vertical, diagonal to the top right and the bottom left of the screen, and diagonal to the top left and the bottom right of the screen), and subjects performed saccadic eye movements to follow the dot movements in both directions (e.g., up/down, right/left etc.), which randomly ranged from 5 to 20° with an average amplitude of 12.5°. On average, 33 saccadic eye movements were performed during a block with the number of saccade directions equated across scans. During the fixation task, subjects were asked to maintain fixation at a central dot. Saccade blocks alternated with blocks of central fixation, each with a length of 16 s. Each scan started and ended with a 16-s central fixation period. Each axis of saccade directions was repeated twice during a given scan with the order of saccade axes counterbalanced across scans. Subjects performed four scans of 272 s each during a scanning session.

Data acquisition

Data were acquired with a 3T Allegra head-dedicated MRI scanner (Siemens, Erlangen, Germany) using a standard birdcage head coil. For the 12-locations version of the memory-guided saccade task and the spatial working-memory task, six series of 240 and seven series of 226 volumes each were acquired. For the eight-locations version of the memory-guided saccade task, eight series of 144 volumes were acquired. Four series of 136 volumes each were acquired for the saccade localizer task. All acquisitions used a gradient echo, echo planar sequence with a 128 square matrix (20–25 axial slices, 2 mm thick, with a 1-mm gap between slices, interleaved acquisition) leading to an in-plane resolution of $2 \times 2 \text{ mm}^2$ [field of view (FOV),

$256 \times 256 \text{ mm}^2$; repetition time (TR), 2–2.5 s; echo time (TE), 41 ms; flip angle, 90°]. A partial Fourier factor of 7/8 was used to acquire an asymmetric fraction of k -space to reduce the acquisition time. The acquisition volume was positioned to cover frontal, parietal, and dorsal occipital cortex. Echo-planar images were compared with a high-resolution anatomical scan taken at the end of each session (MPRAGE sequence, TR = 2.5 s, TE = 4.38 s, flip angle = 8°, 256×256 matrix, 1-mm³ resolution). An in-plane magnetic field map image was acquired to perform echo planar imaging undistortion (FOV = $256 \times 256 \text{ mm}$, 128 matrix, TR = 345 ms, TE = 5.06/8.06 ms, flip angle = 40°, bandwidth = 260 Hz/pixel). For cortical surface reconstructions, a high-resolution structural scan was acquired in a separate session (MPRAGE sequence, same parameters as in the preceding text, 6 acquisitions).

The subjects' heads were surrounded by foam to reduce head movements.

Data analysis

Data were analyzed using AFNI (Cox 1996) (<http://afni.nimh.nih.gov/afni/>), MATLAB, FREESURFER (Dale et al. 1999; Fischl et al. 1999) (<http://surfer.nmr.mgh.harvard.edu/>), and SUMA (<http://afni.nimh.nih.gov/afni/suma>). The functional images were motion corrected (Cox and Jesmanowicz 1999) to the image acquired closest in time to the anatomical scan and undistorted using the field map scan. Data were spatially smoothed with a Gaussian kernel size of twice the smallest dimension of the voxel size in the image set.

For the memory-guided saccade and spatial working-memory tasks, first the linear trend in the fMRI time series was subtracted for each voxel, and the time series was transformed into percent signal modulation by dividing it by its mean intensity. A mean time series for each voxel was calculated from the six to eight identical scanning runs within a session. For the 12-locations version of the memory-guided saccade task, the volumes acquired during the first cycle of stimulation were discarded to avoid transient effects of signal saturation and to allow the hemodynamics to reach a steady state, yielding a time series with 210 time points for each voxel. For the eight-locations version of the memory-guided saccade task and for the spatial working-memory task, the volumes acquired during the blank periods at the beginning and end of each run, along with the first cycle of stimulation, were discarded, yielding a time series with 128 or 180 time points for each voxel, respectively.

A Fourier analysis was used to identify voxels activated by the tasks (Bandettini et al. 1993; Engel et al. 1997). For each voxel, the amplitude and phase—the temporal delay relative to the stimulus onset—of the harmonic at the stimulus frequency was determined by a Fourier transform of the mean time series of the voxel. The correlation coefficient r , between the harmonic and time series, was computed as the amplitude of the harmonic component divided by the square root of the time series power. To correctly match the phase delay of the time series of each voxel to the phase of the saccade direction/memorized location, and thereby localize to the region of the visual field to which the underlying neurons responded best, the response phases were corrected for the hemodynamic lag (5 s). To report the Talairach coordinates, the statistical maps and structural images for each subject were transformed into Talairach space (Talairach and Tournoux 1988).

Statistical maps were thresholded at $r > 0.20$ ($P < 0.01$, uncorrected for multiple comparisons). For the purpose of this report, we restricted the analysis to frontal cortex, i.e., to brain regions located anterior to the central sulcus. Contiguous clusters of activated voxels within frontal cortex showing a systematic representation of visual space in the memory-guided saccade or spatial working-memory tasks were defined as region of interests (ROIs). Volumetric analyses of these ROIs were performed using AFNI and MATLAB. To derive a volumetric representation of the visual field the percentage of volume activated at each of the 8 or 12 memorized locations was determined

by dividing the volume at each location by the total volume of the area. The resulting data were plotted in polar coordinates for the delayed saccade and spatial working-memory tasks in each subject and averaged across subjects. Statistical significance of differences of volumetric representations across the visual field was determined using paired *t*-test.

For the saccade localizer, a multiple regression analysis was conducted where square wave functions corresponding to the time course of the experimental design were convolved with a gamma-variate function of the hemodynamic response, which were then used as regressors of interest. Additional regressors were included in the regression model to account for variance due to baseline shifts between time series, linear drifts within times series, and head motion. Brain regions responding more strongly to eye movements were identified by contrasting presentation blocks of saccade periods, regardless of the trajectory of the moving dot with blocks of central fixation. The statistical maps were thresholded at $P < 0.001$ (uncorrected for multiple comparisons) and overlaid on anatomical scans or cortical surface reconstructions. Cortical surface reconstructions were created with FREESURFER, using an average of six high-resolution anatomical scans, which were aligned to the functional data. Functional data were projected onto the surfaces using AFNI/SUMA. Activations in frontal cortex from the saccade localizer were outlined on the inflated surface reconstructions using SUMA and superimposed with the aligned topographies from the memory-guided saccade and spatial working-memory tasks, respectively. The surfaces were aligned to each of the experimental sessions using AFNI by performing a registration between the experimental session's whole-brain anatomical scan and the anatomical scan from which the surfaces were created.

Eye-movement recordings

Eye movements were monitored in 8 of 10 subjects. For two subjects participating in the eight-locations version of the memory-guided saccade task (*subjects S3 and S6*) and three subjects participating in the 12-locations version of the task (*subjects S1, S2, and S4*), eye movements were monitored in the scanner. For another four subjects participating in the eight-locations version (*subjects S4, S5, S7, and S8*), eye movements were monitored in behavioral testing sessions outside the scanner. For the eye tracking setup at the scanner, a stimulus screen was used with a hole of 1.9° in diameter located at one edge through which a subject's eye was viewed through a telephoto lens (Model 504 with Long Range Optics, Applied Science Laboratories, Bedford, MA). For the eye-tracking setup outside of the scanner, subjects' heads were secured in a chinrest (Applied Science Laboratories), and the stimuli were presented on a monitor (Mitsubishi Electronics America, Irvine, CA). The same eye-tracking apparatus was used to test subjects outside of the scanner as was used inside the scanner. With both setups, the eye position was measured at a sampling rate of 60 Hz and was displayed in real-time on a video monitor in the scanner control room, superimposed on the stimulus image. The experimenter observed the eye-position display to ensure that the subjects were alert, performing the task, and making saccades in the correct direction toward the stimulus location. Eye-position data were recorded on the stimulus computer through a serial interface with the eye-tracker control module. The eye-tracking system had a resolution of 0.14° and is able to report differences in relative eye position of $\sim 0.25^\circ$.

Ilab software (Gitelman 2002) was used to analyze the eye-movement data. The data were first processed to automatically detect and remove blinks. Eye positions were calculated relative to the mean eye position during the fixation periods of each trial. The destination of each saccade was determined as the most eccentric point along the eye-movement trajectory during each trial. Eye-movement regions (EMR) were then positioned around each of the average target locations. Each EMR was $5 \times 5^\circ$ in size to account for spatial jitter

and was centered 10° from fixation at each of the peripheral clock positions. EMR locations were kept constant across runs and subjects to provide a more objective measure of accuracy. The percentage of saccades correctly made into an EMR over an entire experimental session was then calculated for each location and each subject. Figure 9 depicts an example of the eye movements from a typical run of one subject (*S6*). The EMRs for each location are also shown.

RESULTS

Memory-guided saccade task

In the memory-guided saccade task, subjects performed delayed saccades to multiple peripheral locations arranged clockwise around a central fixation point (see Fig. 1A). The task was initially tested in four subjects in a 12-locations version similar to that used by Sereno et al. (2001). In subsequent studies, an eight-locations version of the task was used in which the 1 and 2 o'clock locations were replaced by a 1:30 o'clock location, the 3 and 4 o'clock locations by a 3:30 o'clock location, and so on (see METHODS for further details). The eight-locations version of the task yielded very similar results as compared with the 12-locations version but had several advantages (see METHODS). Eight subjects were tested in the eight-locations version of the task. For direct comparison of the two task versions, two subjects were tested in both.

Individual activation maps are shown for *subject S1*, who was tested in the 12-locations version of the task, in Fig. 2. Activated voxels the fMRI time series of which were correlated with the fundamental frequency of the saccade direction in the memory-guided saccade task, $r > 0.2$, are shown overlaid on inflated cortical surface reconstructions of the right and left hemisphere (Fig. 2A) and on four contiguous axial slices arranged from superior (S) to inferior (I); (Fig. 2B). The axial slices show only the portion of superior and inferior frontal cortex containing the activated regions depicted in Fig. 2A in an enlarged view. The color of each voxel was determined by the phase of its response and indicates the memorized location and saccade direction within the visual field to which it was most responsive, as depicted in the color legend at the top of each figure (see supplemental Fig. S1¹ for examples of time series of fMRI signals). The extent of the activation obtained with the saccade localizer for this subject is indicated by the schematic outlines (see also Fig. 6).

In *subject S1*, bilateral activations were found in the region of the superior branch of precentral cortex and superior frontal sulcus (PreCC/SFS) and in the region of the inferior branch of precentral cortex and the inferior frontal sulcus (PreCC/IFS). The right and left PreCC/IFS area showed a topographic representation that was almost exclusively confined to the contralateral hemifield. The PreCC/SFS area showed a strong bias toward the contralateral hemifield with 91% of activated voxels in the left hemisphere and 96% of activated voxels in the right hemisphere, representing saccade directions to the contralateral hemifield or along the upper and lower vertical meridian. In the right PreCC/SFS (Fig. 2, A and B), the map of memorized locations and saccade directions was arranged such that the upper visual field was represented more laterally and inferior compared with the horizontal meridian and the weakly represented lower visual field. Notably there was a systematic

¹ The online version of this article contains supplemental data.

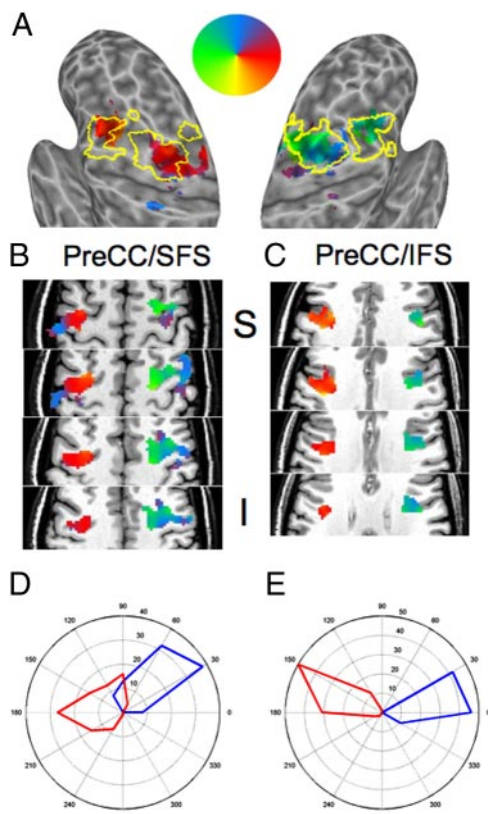


FIG. 2. Topographic maps obtained with the memory-guided saccade task. Results from *subject S1* tested with the 12 locations version of the task. **A**: bilateral activations of 2 topographic maps were found in the superior branch of precentral cortex (PreCC) encroaching into the caudalmost part of the superior frontal sulcus (SFS) and in the inferior branch of PreCC encroaching into the inferior frontal sulcus (IFS), respectively. In both areas, a spatial map of saccade directions representing predominantly the contralateral visual hemifield was found, as shown overlaid on inflated right and left hemispheres. **B** and **C**: activations in the PreCC/SFS and PreCC/IFS areas overlaid on several contiguous axial slices arranged from superior (S) to inferior (I), presented in an enlarged view of superior and inferior frontal cortex. The color code is shown for voxels the responses of which were correlated with the fundamental frequency of the saccade direction, $r > 0.20$, indicating the phase of the response. The visual field color legend in **A** labels the saccade direction within the visual field to which each voxel is most responsive. The extent of the activations found with the saccade localizer are outlined in yellow (see also Fig. 6). **D** and **E**: volumetric representations of the visual field in polar coordinates for the PreCC/SFS (**D**) and PreCC/IFS (**E**) areas. The percentage of volume activated at each of the 12 locations was plotted for the areas activated in the left (blue) and right (red) hemisphere, respectively.

progression of saccade directions with similar directions being represented in neighboring locations of the map. Particular saccade directions (e.g., the 1 o'clock position coded in dark blue) were represented in several locations of the map. These features of the spatial map can be best seen on the axial slices in Fig. 2B. A similar topographic organization was found in the left PreCC/SFS in this subject (Fig. 2, A and B; see supplemental Fig. S1A for a time series of fMRI signals in this area and subject). The topographic organization of the PreCC/IFS area was more difficult to evaluate due to the smaller activation size of this area (Fig. 2, A and C). A systematic progression of the representation of different saccade directions within the contralateral hemifield was observed in this area as well. The volumetric representations of the visual field are plotted in polar coordinates for the regions in the superior (Fig. 2D) and

inferior (Fig. 2E) branch of PreCC and for the left (blue) and right (red) hemisphere in this subject.

Individual activation maps for all other subjects projected onto inflated cortical surface reconstructions of the right and left hemispheres are shown in Fig. 3 and supplemental Fig. 2. Examples of axial slices through superior and inferior frontal cortex are shown for each subject in supplemental Fig. 3. The extent of the activations obtained with the saccade localizer for *subjects S2-S4* is indicated by the schematic outlines (Fig. 3). Bilateral activations were observed in all 10 subjects, and the activations of each area had a strong bias toward saccade directions within the contralateral hemifield. Nine of the 10 subjects had two distinct activations, one in the region of the PreCC/SFS, and the other in the region of the PreCC/IFS (Figs. 2 and 3 and supplemental Fig. 2; see also supplemental Fig. 1 for examples of fMRI time series in these areas). In *subject S2*, only the PreCC/SFS region was activated (Fig. 3). The mean Talairach coordinates for centers of mass of these activations are given in Table 1. Across subjects, the mean volume of each area activated by the memory-guided saccade task was $3,592 \pm 345 \text{ mm}^3$ for the right PreCC/SFS ($n = 10$), $4,255 \pm 501 \text{ mm}^3$ for the left PreCC/SFS ($n = 10$), $2,254 \pm 368 \text{ mm}^3$ for the right PreCC/IFS ($n = 9$), and $4,357 \pm 836 \text{ mm}^3$ for the left PreCC/IFS ($n = 9$).

As can be seen from the maps of the subjects depicted in Figs. 2 and 3 and supplemental Figs. 2 and 3, and the volumetric representations of the visual field depicted in supplemental Figs. 4 and 5 for each subject, the topographic organization of saccade directions showed highly individual activation patterns. The most common shared topographic feature was a lateral-medial progression from the upper vertical meridian (coded in blue) to the lower vertical meridian (yellow) in 13 of 18 hemispheres. In 5 of 18 hemispheres, the reversed pattern was observed with the lower vertical meridian located lateral to the upper vertical meridian. These features can be best appreciated on the axial slices shown in supplementary Fig. 3. Despite the individual differences in the topographic

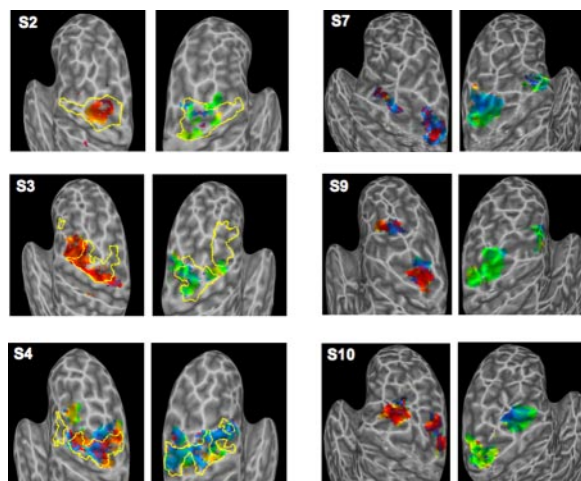


FIG. 3. Memory-guided saccade task: Topographic maps of 6 additional subjects. Activations obtained in the memory-guided saccade task in *subjects S2-S4, S7, S9* and *S10* overlaid on inflated right and left hemispheres. *Subject S2* was tested in the 12 locations version of the delayed saccade task; all other subjects were tested in the 8 locations version of the task. The extent of the activations found with the saccade localizer for the same subjects are outlined in yellow for *S2-S4* (thresholded at $P < 0.001$). All other conventions including the color legend as in Fig. 2.

TABLE 1. Talairach coordinates and activated volumes

Area	BA		x	y	z	n
<i>Memory-guided saccade task</i>						
PreCC/SFS	6	L	-36 ± 1	-12 ± 1	+49 ± 1	10
	6	R	+36 ± 2	-9 ± 1	+49 ± 2	10
	6	L	-34 ± 1	-11 ± 2	+50 ± 2	4
	6	R	+34 ± 1	-10 ± 2	+52 ± 2	4
PreCC/IFS	6/44	L	-41 ± 1	+1 ± 2	+31 ± 1	9
	6/44	R	+41 ± 2	+3 ± 1	+31 ± 1	9
	6/44	L	-42 ± 2	-1 ± 2	+30 ± 0	3
	6/44	R	+41 ± 5	0 ± 3	+28 ± 1	3
<i>Saccade localizer task</i>						
PreCC/SFS	6	L	-35 ± 1	-12 ± 2	+49 ± 2	4
	6	R	+36 ± 2	-9 ± 1	+50 ± 3	4
PreCC/IFS	6/44	L	-42 ± 4	-5 ± 2	+35 ± 2	4
	6/44	R	+42 ± 3	+1 ± 2	+32 ± 3	4
DMFC	6		+0 ± 2	-6 ± 3	+57 ± 2	4
<i>Spatial working-memory task</i>						
PreCC/SFS	6	L	-39 ± 1	-11 ± 4	+50 ± 2	4
	6	R	+32 ± 2	-10 ± 2	+49 ± 3	4
PreCC/IFS	6/44	L	-46 ± 2	-2 ± 3	+35 ± 3	3
	6/44	R	+44 ± 4	+2 ± 4	+31 ± 1	3

SEs are indicated in parentheses. Last column is number of subjects. PreCC, precentral cortex; SFS, superior frontal sulcus; IFS, inferior frontal sulcus; DMFC, dorsomedial frontal cortex; BA, Brodmann area.

representation of saccade directions, the following organizational principles appeared to be common in the PreCC/SFS and also in the PreCC/IFS area in all subjects. First, there was a strong contralateral bias. In the group of subjects, 93 and 86% of activated voxels coded for contralateral saccade directions in the left and right PreCC/SFS, respectively, and 89 and 80% of activated voxels in the left and right PreCC/IFS, respectively (PreCC/SFS: right vs. left visual field representation, $P < 0.001$; PreCC/IFS: right vs. left visual field representation, $P < 0.01$). Second, there was typically a systematic progression in the representation, where neighboring saccade directions were represented in adjacent locations of the map. For example smooth transitions from the representations of the upper ver-

tical meridian (coded in dark blue) through the left upper visual field (light blue) and the left horizontal meridian to the lower left visual field (green) and the lower vertical meridian (yellow) or from the lower vertical meridian (yellow) through the lower right visual field (orange) to the right horizontal meridian (red) and the upper right visual field (purple) were most commonly observed (see axial slices in supplementary Fig. 3).

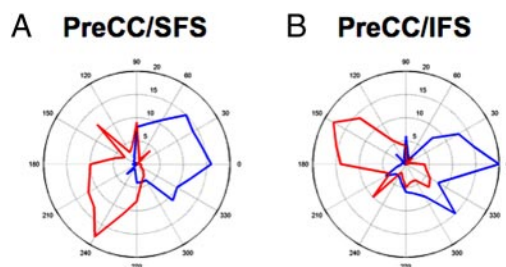


FIG. 4. Polar angle representations obtained in the memory-guided saccade task. Group analysis of volumetric representations of the visual field in polar coordinates for the regions in the PreCC/SFS (A; $n = 10$) and PreCC/IFS (B; $n = 9$) areas plotted for the left (blue) and right (red) hemisphere. The percentage of volume activated at each of the 8 or 12 locations was calculated for each subject and averaged at each location for the group of subjects. The 12, 3, 6, and 9 o'clock locations were tested in all 10 subjects. The 1, 2, 4, 5, 7, 8, 10 and 11 o'clock locations were tested in 4 subjects, and the 1:30, 3:30, 7:30 and 10:30 o'clock locations were tested in 8 subjects.

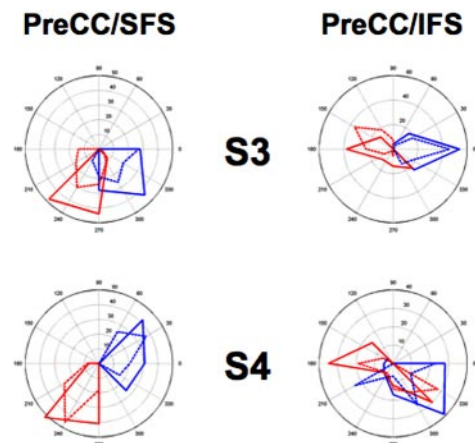


FIG. 5. Comparison of polar angle representations obtained in the 8 and 12 locations version of the memory-guided saccade task. Analysis of volumetric representations of the visual field in polar coordinates for the regions in the PreCC/SFS and PreCC/IFS areas plotted for the left (blue) and right (red) hemisphere for subjects S3 and S4, tested in both versions of the task in separate scanning sessions conducted several weeks or months apart. The percentage of volume activated at each of the 8 (solid line) or 12 (dashed line) locations was calculated for each subject.

In contrast, “jumps” in the visual field representation such as from the horizontal meridian (red) to the vertical meridian (yellow/blue) were only rarely seen (see *subject S4*'s PreCC/SFS area for such a rare occurrence on the axial slice in supplementary Fig. 3). And third, particular saccade directions were often represented in multiple locations of the map. That is, a certain saccade direction (e.g., the 11:00 position coded in light blue) could occur in several nonadjacent locations of the map.

In the group of subjects, all saccade directions were represented in both areas, as shown in the group polar plots in Fig. 4A for the PreCC/SFS ($n = 10$) and in Fig. 4B for the PreCC/IFS ($n = 9$). In the PreCC/SFS area (Fig. 4A), 8.5 and 5.5% of activated voxels represented the right and left horizontal meridian, whereas the vertical meridian was represented by 8.5% (upper) and 6% (lower) of activated voxels. The four quadrants of the visual field were represented with 22.5% (upper right = 1, 1:30, 2 o'clock positions), 10% (upper left = 10, 10:30, 11 o'clock positions), 15.5% (lower right = 4, 4:30, 5 o'clock positions), and 23.5% (lower left = 7, 7:30, 8 o'clock positions) of activated voxels, the differences of which were not significant. In the PreCC/IFS (Fig. 4B), 12 and 7.5% of activated voxels represented the right and left horizontal meridian, whereas the upper and lower vertical meridian was represented by 5 and 5.5% of activated voxels. The four quadrants of the visual field were represented with 12% (upper right), 21% (upper left), 24% (lower right), and 13.5% (lower left) of activated voxels. None of these differences were significant.

In *subjects S3* and *S4*, the 12- and 8-locations versions of the memory-guided saccade task were directly compared. As can be seen from the polar plots of the volumetric representation of the visual field in the right and left PreCC/SFS and PreCC/IFS in Fig. 5, the two versions of the task yielded very similar results. Importantly, this comparison also demonstrates the reliability of the study results, which were replicated in different scan sessions that were conducted several weeks apart from each other in the same subject. It should be noted that the asymmetric representations of saccade directions and memorized locations in the PreCC/SFS areas were replicated in both subjects.

The test-retest reliability of the results obtained with the eight-locations version of the memory-guided saccade task was investigated in *subjects S4* and *S5*, who were scanned twice with this paradigm. The scan sessions were several weeks apart from each other. The resulting frontal maps in the region of precentral cortex are shown in enhanced views in supplementary Fig. 6. The data from the first “test” scan session for these subjects can also be seen in Fig. 3 and supplementary Fig. 2 on inflated hemispheres. In *subject S4*, the extent of the activations was stronger in the test than in the re-test session. Importantly, the topographic organization of the regions that were commonly activated in both scan sessions was remarkably similar. In *S4*'s left hemisphere, the representation of the upper vertical meridian (coded in blue) was flanked by representations of saccade directions to the right visual hemifield (orange-red), whereas in the right hemisphere, the representation of the left horizontal meridian (green) was flanked by saccade directions to the upper left quadrant of the visual field (light and dark blue). This topographic organization is apparent in both maps from the two scanning sessions (supplementary Fig. 6). In *S5*'s

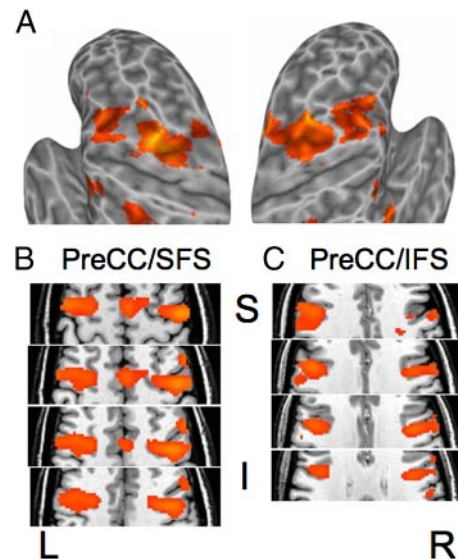


FIG. 6. Activations obtained with the saccade localizer task. Areas in frontal cortex activated by saccadic eye movements relative to fixation baseline. Results are shown for *subject S1* (same subject as in Fig. 2; $P < 0.001$). A: activations overlaid on inflated right and left hemispheres. B and C: activations overlaid on several sequential axial slices through superior and inferior frontal cortex arranged from superior (S) to inferior (I). Areas consistently activated across subjects included bilateral activations of a region in the superior branch of PreCC encroaching into the SFS (often referred to as the human frontal eye field, FEF), bilateral activations of a region in the inferior branch of PreCC encroaching into the caudalmost part of the IFS, and a region in dorsomedial prefrontal cortex (DMFC), which is apparent only on the axial slices in B (often referred to as the human supplementary eye field, SEF). Similar activations were found in the other three subjects tested with this task (see schematic outlines in Fig. 3). R, right; L, left.

left hemisphere, the extent of the activations was similar with predominant representations of the right visual field. It should be noted that small details in the map such as the representation of the 1:30 direction (purple) were observed in identical parts of the map in both sessions. In *S5*'s right hemisphere, the extent of the activation was larger in the retest session. But the topography of the commonly activated areas was similar with the upper vertical meridian (dark blue) flanked by representations of saccade directions within the left visual field (green-yellow; supplementary Fig. 6). Taken together, these data demonstrate the test-retest reliability of the complex individual topographic activation patterns obtained in human frontal cortex within single subjects.

Saccade localizer

Four of the 10 subjects were also tested in a saccade localizer task that was designed to activate regions of frontal cortex involved in the planning and execution of saccadic eye movements. This task served to identify the human FEF and SEF and to relate activations obtained with visually guided saccades to those found with memory-guided saccades. Subjects executed saccadic eye movements toward a black dot that jumped to different eccentric positions along one of four axes (horizontal, vertical, and the 2 diagonals; see METHODS). Saccade amplitudes varied randomly and were unpredictable. The eye-movement task was interleaved with a baseline fixation condition. Areas activated in frontal cortex during saccadic eye movements relative to the fixation baseline are depicted in Fig.

6 for *subject S1*. Three different activations were found. First, the most extensive activations were found bilaterally in the superior branch of PreCC (Ono et al. 1990), encroaching onto the caudalmost part of the SFS (Fig. 6, A and B). Second, bilateral activations were found in the inferior branch of PreCC, encroaching into the caudalmost part of the IFS (Fig. 6, A and C). And a third activation was found in dorsomedial prefrontal cortex (DMFC; Fig. 6B). Similar activation patterns (only schematically outlined in Fig. 3) were found in the other three subjects (*S2–S4*) tested with this task. In these subjects, activations of the superior and inferior branch of PreCC were contiguous but typically with separate peak activations in the two branches. The mean Talairach coordinates for the three areas activated in the saccade localizer are given in Table 1 and are in close agreement with several previous human fMRI studies probing saccade-related activity in frontal cortex (e.g., Beauchamp et al. 2001; Bermann et al. 1999; Brown et al. 2004; Corbetta et al. 1998; Lobel et al. 2001; Luna et al. 1998; Nobre et al. 2000; Paus 1996; Petit et al. 1997). Mean activated volumes averaged across subjects were $6,891 \pm 875$ (SE) mm^3 for the DMFC, $11,217 \pm 951$ mm^3 for the right PreCC/SFS, $10,569 \pm 1,281$ mm^3 for the left PreCC/SFS, $3,540 \pm 1,860$ mm^3 for the right PreCC/IFS, and $2,628 \pm 1,164$ mm^3 for the left PreCC/IFS. In the human fMRI literature, the activations in PreCC/SFS have typically been referred to as the human FEF, and the activations in DMFC as the SEF with the assumption that these areas are homologous to the monkey frontal oculomotor system. Interestingly, a similar saccade localizer task has indeed been shown to activate the monkey frontal oculomotor system in recent fMRI studies (Baker et al. 2006; Koyama et al. 2004). The activations in PreCC/IFS have also been referred to as “inferior FEF” (Berman et al. 1999). It is not clear how this area relates to the monkey frontal oculomotor system (see DISCUSSION).

The activations obtained in the memory-guided saccade task in the PreCC/SFS and PreCC/IFS in the same four subjects heavily overlapped with those obtained in the saccade localizer task (Figs. 2 and 3). The mean Talairach coordinates for the PreCC/SFS and PreCC/IFS regions were not different in the memory-guided saccade and saccade localizer tasks in the four subjects (Table 1). It is noteworthy that no activations were found in the DMFC region with the memory-guided saccade task. These findings suggest that superior and inferior precentral but not dorsomedial regions of the human oculomotor system contain topographically organized maps related to saccade direction and memorized location.

Spatial working-memory task

In a third study performed in the same four subjects, who also participated in the memory-guided saccade and saccade localizer tasks, we asked whether the topographically organized activity in the PreCC/SFS and PreCC/IFS areas depended on the execution of the saccade or whether topographic organization in these areas could be revealed by a delayed response task that required a manual response instead of an oculomotor response. The delayed response task that we devised was identical to the memory-guided saccade task in most respects with the exception that, following the memory delay period, a test dot was shown at or near the location of the target, and subjects pressed one of two buttons to indicate

whether or not the test dot matched the memorized location. We will refer to this task as the spatial working-memory task. Because the memory-guided saccade task and the spatial working-memory task were not tested in the same scanning sessions, only a qualitative comparison of the results is possible and any conclusions regarding particularly the individual activation patterns are tentative and subject to future investigations.

Bilateral activations were observed in the four subjects tested with this task. Similar to the memory-guided saccade task, the activations of each area had a strong bias toward memorized locations in the contralateral hemifield. Three of the four subjects had two distinct activations in the regions of the superior branch (PreCC/SFS) and inferior branch (PreCC/IFS) of precentral cortex (Figs. 7, A–C, and 8, A–C, and Supplemental Fig. 1 for an example of an fMRI time series). Only the PreCC/SFS region was activated in *subject S2* (Fig. 8A), consistent with the subject’s activation in the memory-

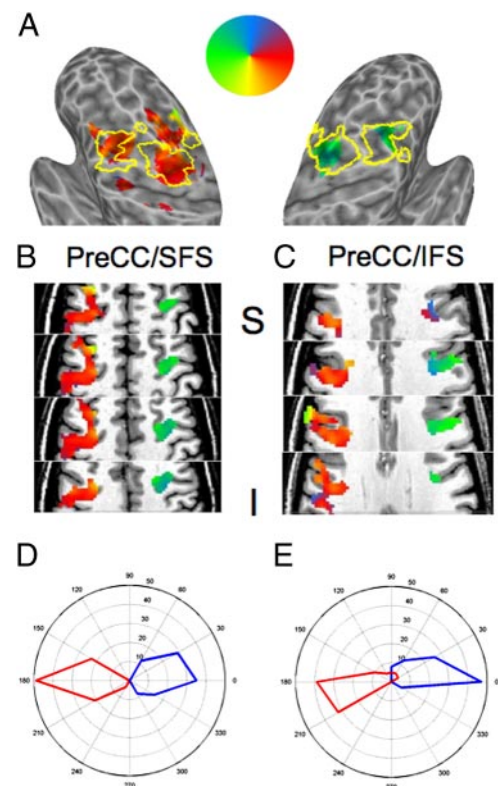


FIG. 7. Topographic maps obtained with the SWM task. Results from *subject S1* (same subject as in Figs. 2 and 6). The extent of the activations found with the saccade localizer are outlined in yellow. A: bilateral activations of 2 topographic maps were found in the superior and inferior branch of PreCC in similar locations compared with those found with the memory-guided saccade task, as shown overlaid on inflated right and left hemispheres. The spatial maps in both areas predominantly represented memorized locations in the contralateral hemifield. B and C: same activations as in A but overlaid on several sequential axial slices presented in enhanced views of superior and inferior frontal cortex. The color code is shown for voxels the responses of which were correlated with the fundamental frequency of the memorized location, $r > 0.20$, indicating the phase of the response. The visual field color legend in A labels the memorized location within the visual field to which each voxel is most responsive. D and E: volumetric representation of the visual field in polar coordinates for the regions in the PreCC/SFS (D) and PreCC/IFS (E) areas for this subject. The percentage of volume activated at each of the twelve locations was plotted for the areas activated in the left (blue) and right (red) hemisphere, respectively. Other conventions as in Fig. 2.

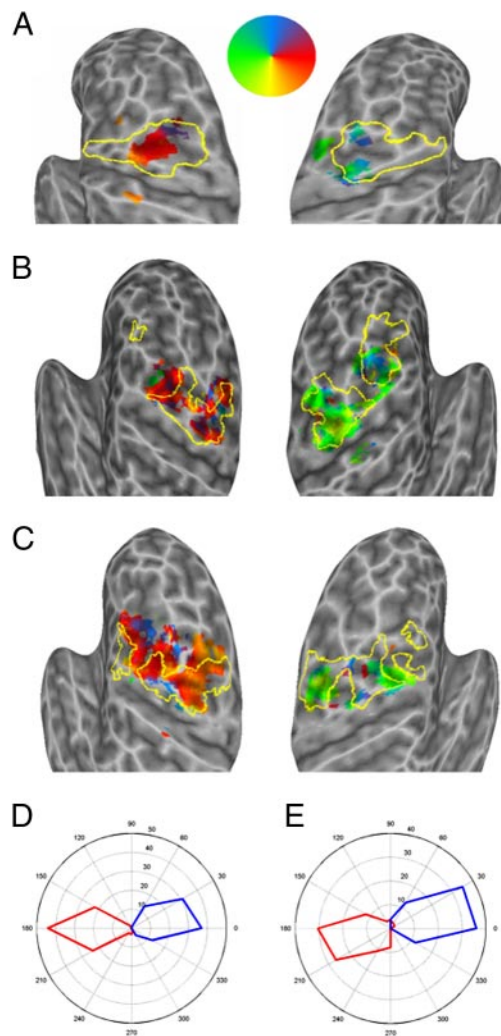


FIG. 8. SWM task: topographic maps of 3 additional subjects. Activations obtained in the SWM task in *subjects S2 (A), S3 (B), and S4 (C)* overlaid on inflated right and left hemispheres. See also Fig. 3 for activation maps obtained with the memory-guided saccade task. *D* and *E*: group analysis of volumetric representations of the visual field in polar coordinates for the regions in the PreCC/SFS (*C*; $n = 4$) and PreCC/IFS (*D*; $n = 3$) areas plotted for the left (blue) and right (red) hemisphere. For other conventions, see Figs. 2, 3 and 7.

guided saccade task (Fig. 3A). In all of the subjects, the activated regions overlapped heavily with those obtained in the memory-guided saccade task (Figs. 2 and 3) as well as with those obtained in the saccade localizer task (see outlines in Figs. 7 and 8). The mean Talairach coordinates for centers of mass of the activations obtained with the spatial working-memory task did not differ across the three tasks in the four subjects (see Table 1). Across subjects, the mean volume of each area activated by the spatial working memory task was $2,703 \pm 611 \text{ mm}^3$ for the right PreCC/SFS ($n = 4$), $4,791 \pm 1,510 \text{ mm}^3$ for the left PreCC/SFS ($n = 4$), $1,612 \pm 149 \text{ mm}^3$ for the right PreCC/IFS ($n = 3$), and $3,928 \pm 861 \text{ mm}^3$ for the left PreCC/IFS ($n = 3$). Similar to the results obtained with the memory-guided saccade task, no activations were found in the DMFC region that was identified with the saccade localizer.

The PreCC/SFS and PreCC/IFS areas showed a strong bias toward memorized locations in the contralateral field in these subjects. In the group of subjects, 99 and 94% of activated voxels coded for contralateral memorized locations in the left

and right PreCC/SFS, respectively, and 98 and 97% of activated voxels in the left and right PreCC/IFS, respectively (PreCC/SFS, PreCC/IFS: right vs. left visual field representation, $P < 0.001$). There appeared to be a progression of memorized locations with similar visual field locations represented adjacently to each other in the map, and multiple representations of certain memorized locations within the map. Individual differences in the topographic arrangements of the maps in the four subjects were observed. Some of the topographic features resembled those observed in the memory-guided saccade task. For example, memorized locations in the upper visual field tended to be more lateral, and those of the lower visual field more medial in S1's left PreCC/SFS in both tasks (Fig. 2B and 7B). Likewise, in *subject S2*, memorized locations in the upper visual field were represented anterior and medial to those of the lower visual field, which were located more lateral and posterior in the left PreCC/SFS in both tasks (Figs. 3 and 8A). However, the topographic maps obtained with the two tasks were certainly not identical (see DISCUSSION).

In the group of subjects, all memorized locations were represented in the two areas, as shown in the group polar plots in Fig. 8D for the right and left PreCC/SFS ($n = 4$) and in *E* for the right and left PreCC/IFS ($n = 3$). In the PreCC/SFS area (Fig. 8D), 18.5 and 22% of activated voxels represented the right and left horizontal meridian, respectively, whereas the vertical meridian was represented by 1% (upper) and 2% (lower) of activated voxels. The difference between the horizontal and vertical meridian representations was significant ($P < 0.01$). The four quadrants of the visual field were represented with 22.5% (upper right = 1 and 2 o'clock positions), 12% (upper left = 10 and 11 o'clock positions), 9% (lower right = 4 and 5 o'clock positions), and 13.5% (lower left = 7 and 8 o'clock positions) of activated voxels; the differences of which were not significant. In the PreCC/IFS (Fig. 8E), 18 and 15% of activated voxels represented the right and left horizontal meridian, whereas the upper and lower vertical meridian was represented by 4% of activated voxels each (horizontal vs. vertical meridian representation, $P < 0.01$). The four quadrants of the visual field were represented with 26% (upper right), 8% (upper left), 6% (lower right), and 19% (lower left) of activated voxels.

Behavioral results

Behavioral data were acquired by monitoring eye movements during the memory-guided saccade task and by requiring subjects to match test dots to memorized locations by button presses in the spatial working-memory task. Although the eye-tracking equipment used was not optimal for tracking saccades in the periphery of the visual field, we were nonetheless able to measure eye movements in the memory-guided saccade task during fixation and the saccades made to the remembered target locations. For the analysis, eye-movement regions (EMRs) were positioned around each of the average target locations (see METHODS). The percentage of saccades correctly made into an EMR over an entire experimental session was then calculated for each location and each subject. $92 \pm 3\%$ (mean \pm SE) of saccades were made to the correct locations while subjects performed the memory-guided saccade task. It is important to note that the 8% of saccadic errors were not made to random directions. On error trials, the

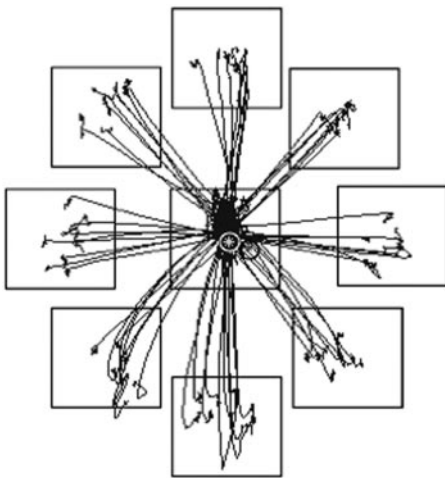


FIG. 9. Eye movement recordings during the memory-guided saccade task. A typical eye movement trajectory obtained from *S6* during a single run of the 8 locations version of the memory-guided saccade task. Black lines represent eye traces. Eight eye movement regions (EMR; represented by each box) were positioned around each of the average target locations. Each EMR was $5 \times 5^\circ$ in size to account for spatial jitter and was placed 10° from fixation. The percentage of saccades correctly made into an EMR over an entire experimental session was then calculated for each location and each subject. The white circle indicates the subject's eye location at the beginning of the run. The black circle indicates the subject's eye location at the conclusion of the run.

saccades were typically made to areas near the EMR. Thus all saccades were executed in approximately the correct direction. Taken together, the eye-tracking data verified that the subjects were performing the task correctly.

In the spatial working-memory task, subjects performed on average at an accuracy of $86 \pm 1\%$. The performance at individual locations ranged from 83 to 89%. No significant differences in performance across the 12 locations in the visual field were obtained (repeated-measures ANOVA, *n.s.*).

DISCUSSION

Using delayed response tasks and fMRI at improved spatial resolution, we found two topographic maps in frontal cortex of each hemisphere, one in the superior branch of PreCC, in the region of the human FEF (Beauchamp et al. 2001; Bermann et al. 1999; Brown et al. 2004; Corbetta et al. 1998; Lobel et al. 2001; Luna et al. 1998; Nobre et al. 2000; Paus 1996; Petit et al. 1997), and a second one in the inferior branch of PreCC. Both areas were also activated by visually guided saccades. The topographic representations had three characteristic features. First, there was a predominant representation of saccade directions and memorized locations of the contralateral hemifield in each area. Second, similar saccade directions and memorized locations were commonly represented in neighboring locations of the map. And third, particular saccade directions or memorized locations were represented in several parts of the map. Together, these organizational characteristics are compatible with a columnar organization of saccade direction and memorized locations in human frontal cortex. Such an organization is similar to that found in monkey FEF for saccade direction (Bruce et al. 1985; Robinson and Fuchs 1969; Schall 1991) and in monkey DLPFC for memory fields (Funahashi et al. 1989, 1990; Goldman-Rakic 1996). The representation of visual space in these frontal maps appears to

be different from the organization of visual and parietal maps, which typically show continuous point-by-point representations. Notably, no topographic organization was found in dorsomedial frontal cortex, the region of the human SEF (Beauchamp et al. 2001; Bermann et al. 1999; Brown et al. 2004; Corbetta et al. 1998; Lobel et al. 2001; Luna et al. 1998; Nobre et al. 2000; Paus 1996; Petit et al. 1997).

Experimental design

It is important to note that activated voxels in the frontal maps reflected the integrated activity at each of the 12 or 8 locations in the delayed response tasks. Each trial consisted of at least three components, the presentation of a visual stimulus cueing a target location, a delay period during which the location was maintained in working memory, and a saccadic eye movement toward the remembered location or a manual response to match a test stimulus to the remembered location. Due to the sluggishness of the hemodynamic response, these three components were not further dissociated with the present design. Because our task used a fixed sequence of target locations arranged clockwise around fixation, it is possible that subjects directed attention to the predicted target location during the 750 ms before the target appeared at the beginning of each trial. Expectation signals related to the allocation of attention at a precued target location in the absence of any visual stimulation have been found previously in the FEF (e.g., Hopfinger et al. 2000; Kastner et al. 1999). Such expectation signals during the brief period at the beginning of a given trial may have contributed to the integrated signal measured over the course of each 5-s trial.

Relation to previous fMRI studies

Our findings corroborate and extend a previous report showing the first evidence for spatial maps in human frontal cortex using a face working-memory task (Hagler and Sereno 2006). In the study by Hagler and Sereno, topographic maps preferring contralateral stimulation were demonstrated in the superior precentral sulcus and dorsolateral prefrontal cortex. The location of the former map appears to be similar to our activation in the PreCC/SFS area, demonstrating that this area may not only be activated by a simple spatial working-memory task, as used in the present study, but also by a more complex object working-memory paradigm. In contrast, the activation in the DLPFC found by Hagler and Sereno appears to be anterior to our PreCC/IFS area. Future studies probing spatial and object working-memory paradigms within the same scan sessions and subjects, thereby allowing for a direct contrast of the activations obtained with the two types of memory tasks, will be necessary to gain further insight into the local organization of spatial and object working-memory representations in frontal cortex.

Our findings extend the previous study by Hagler and Sereno in several ways. First and most importantly, we used a fairly different task. The memory-guided saccade task is a simple spatial working-memory task, allowing for a more direct comparison of our findings to monkey physiology studies, which have used this task extensively (see following text). Second, greater details in the topographic maps of individual subjects were revealed by using a three to seven times higher resolution

as compared with the Hagler and Sereno study. Third, we related the activations obtained with the memory-guided saccade task in the same subjects to those obtained with visually guided saccades, thereby providing a direct link to the human oculomotor system. And fourth, by testing the same subset of subjects in an additional spatial working-memory task that required a manual rather than a saccadic response, we provided evidence that topographic organization in the frontal maps appears to be driven by the delay activity irrespective of the response mode.

Individual variability of topographic activation patterns

A striking characteristic of the present findings was the individual variability in the topographic patterns obtained in our group of 10 subjects. For several reasons, we think that this individual variability is an important result of our study. First, the variability was unique to frontal cortex as we did not observe such variability in parietal cortex, which was also scanned in the same subjects and in the same sessions using the memory-guided saccade task. In agreement with previous findings (Schluppeck et al. 2005; Silver et al. 2005), several topographically organized areas were found along the intraparietal sulcus in each subject. Each map contained a point-by-point representation of the contralateral visual field separated by reversals in the visual field orientation (Konen et al. 2007). Importantly, these maps were highly consistent across all subjects. Thus although the spatial maps in parietal cortex obtained in the same subjects and scanning sessions using the same memory-guided saccade task were highly consistent across subjects, more variable spatial maps were found in frontal cortex. Second, similar to the present study, Hagler and Sereno (2006) noted considerable individual variability in the topographic organization of the spatial maps that they found in frontal cortex using a different working-memory task. Thus there is convergence from two independent studies using different cognitive tasks (memory-guided saccades and face working memory), suggesting that the topographic maps in frontal cortex are different from the less variable type of organization typically found in visual or parietal cortex. And third, we present evidence that the topographic patterns obtained in individual subjects as well as the volumetric polar plots of the representation of the visual field are reproducible within subjects. Given the general role of frontal cortex in cognitive control and adaptive behavior, one possibility is that the topographic maps in frontal cortex are more flexible than those in lower-order visual cortex or higher-order parietal cortex because they are shaped by the individual experience of subjects (see Duncan 2001 for details and references regarding such an account). However, the functional significance of this finding exceeds the scope of the present study and will deserve further study.

Relation to monkey physiology studies: memory-guided saccade task

The memory-guided saccade task has been extensively used to study neural response properties in the monkey oculomotor system. Neurons responding to the visual stimulation during the delay period, in which the target location is maintained in working memory, or in association with the execution of the

saccade have been found in the FEF, SEF, and DLPFC (e.g., Bizzi 1967; Robinson and Fuchs 1969; Niki 1974; Wurtz and Mohler 1976; Fuster et al. 1982; Bruce and Goldberg 1985; Bruce et al. 1985; Schlag and Schlag-Rey 1987; Funahashi et al. 1989, 1990, 1991; Schall 1991; Goldman-Rakic 1996; Umeno and Goldberg 2001). The “movement” and “memory” fields of these neurons are tuned to specific saccade directions or memorized locations in the visual field. Although these basic response properties appear to be similar in these different frontal areas, the proportions of neurons with memory- or saccade-related activity differ across these neural structures (Funahashi et al. 1991; Schall 1991). In our study, subpopulations of neurons responding to different aspects of the memory-guided saccade task were not distinguished. The topographic organization appeared to be subserved by the integrated population response of neurons coding for visual probe stimuli, memorized locations, and saccade directions. The resulting map in the region of the human FEF must be considered a partial map as we probed only one particular eccentricity of $\sim 10^\circ$. In the macaque, saccade amplitudes varying from $<1^\circ$ to $>30^\circ$ are represented in the FEF with small saccades located ventrolaterally and large saccades located dorsomedially (Robinson and Fuchs 1969; Bruce et al. 1985). Not surprisingly, the topographic map in the region of the human FEF that was obtained for one particular eccentricity activated only $\sim 40\%$ of those regions that were also activated by visually guided saccades. Future studies will be needed to derive a more complete map of the human FEF for different eccentricities and saccade amplitudes.

In the macaque, a set of all possible contralaterally directed saccades is represented by each hemisphere's FEF (e.g., Bruce et al. 1985; Ferrier 1875; Mott and Schaefer 1890; Robinson and Fuchs 1969). Our finding of a strong contralateral bias in the representation of saccade directions and memorized locations obtained with the memory-guided saccade task is in good agreement with this classical finding. In the group of subjects, but not necessarily in individual subjects, all directions were represented across the visual field, as shown by the volumetric polar plots (Fig. 4, *A* and *B*). In the macaque, it has been shown that saccade direction varies continuously across the FEF with the same direction being represented in several different locations within the FEF (Bruce et al. 1985; Funahashi et al. 1991; Schall 1991). A similar organization of neurons with memory fields has been found in the monkey's DLPFC (Funahashi et al. 1989; Goldman-Rakic 1996). From these findings, it has been suggested that saccade direction and memorized locations are organized in a columnar fashion similar to the distribution of orientation columns in striate cortex (Bruce et al. 1985; Goldman-Rakic 1996; Dias and Segraves 1999). Our findings, that similar saccade directions and memorized locations are represented in neighboring locations of the map and that saccade directions are represented in several parts of the map, are compatible with these observations. However, our spatial resolution, although improved compared with conventional fMRI techniques, was not sufficient to reveal a detailed map of cortical columns within these structures. Future studies at voxel resolutions of well under 1 mm will be necessary to reveal a more detailed account of the global organization of saccade directions and memory fields within precentral cortex. The somewhat coarse topography of the maps that we found in human frontal cortex may also be due to the broad tuning of

neurons' movement and memory fields within the frontal oculomotor system, which range from 30 to 50° in the macaque (Bruce and Goldberg 1985; Funahashi et al. 1989).

Activations related to spatial working memory

In the monkey, spatial working-memory tasks activate neurons in an area located anterior to the monkey FEF in DLPFC, defined by Brodmann as area 46 (Funahashi et al. 1989; Goldman-Rakic 1996; Sawaguchi 1996). In human fMRI, studies suggest that the region analogous to the monkey DLPFC region is shifted to a region in the superior frontal sulcus (Courtney et al. 1998; but see Postle et al. 2000). This superior frontal area, which appears to be specialized for spatial working memory, was located just anterior to the FEF and thus unresponsive to saccadic eye movements. Instead, we propose that the area identified in inferior PreCC/IFS may be a more likely candidate to be analogous to the monkey DLPFC area for the following reasons. First, this region contains a map of the contralateral visual space just like the monkey DLPFC area (Funahashi et al. 1989). Second, we found evidence for a columnar organization of this area as has been suggested in monkey physiology studies (Funahashi et al. 1989; Goldman-Rakic 1996; Sawaguchi 1996). And third, as in the monkey (Funahashi et al. 1991), this area is also responsive to saccadic eye movements. It is interesting to note that, if analogous to the monkey DLPFC area, this area is located more posteriorly in the human as compared with the monkey, in BA 44 instead of BA 46. A similar posterior shift also appears to occur with the location of the FEF, which is located in BA 8 in the monkey, but more posterior, in BA 6, in the human.

In the monkey, the area involved in spatial working-memory tasks (Funahashi et al. 1989; Goldman-Rakic 1996) has also been implicated in a variety of other cognitive operations related to object working memory, attention, categorical representation, and associative learning (e.g., Rao et al. 1997; Asaad et al. 1998; Rainer et al. 1998; Freedman et al. 2001). From these findings, it was concluded that neural coding in this area is adaptive and flexible according to the task demands at hand (Duncan 2001). In human fMRI studies, activations in the region of the inferior frontal sulcus have been demonstrated in a variety of tasks including the maintenance or updating of spatial and object information (e.g., Smith et al. 1996; Owen 1997; D'Esposito et al. 1998; Cohen et al. 1997; Courtney et al. 1997; Haxby et al. 2000; Leung et al. 2002; Roth et al. 2006), spatial attention (Vandenberghe et al. 1997; Corbetta et al. 1998; Hopfinger et al. 2000), language processing (e.g., Buckner et al. 1995; Thompson-Schill et al. 1997; Gold and Buckner 2002), and others. Therefore it is possible that, as in the monkey, this area adjusts flexibly to current task demands. Studies contrasting different cognitive tasks in the same subjects and scan sessions will be necessary to more substantially investigate the important issue of adaptive coding in this area of frontal cortex.

Role of the FEF in spatial working memory and attention

Interestingly, a topographic organization within the human FEF, as well as in the PreCC/IFS area, was revealed not only in the memory-guided saccade task but also in the spatial working-memory task that required a manual response and did

not involve the planning and execution of saccadic eye movements. Our findings suggest an important role of the FEF in spatial working memory, which is consistent with FEF lesion studies in both monkeys and humans (Pierrot-Deseilligny et al. 1991; Dias et al. 1995; Sommer and Tehovnik 1997; Schiller and Chou 1998; Dias and Segraves 1999). With both chronic and reversible lesion preparations, monkeys were highly impaired in their accuracy when attempting to execute saccades to locations of extinguished targets during delayed, but not during visually guided saccade tasks (Dias et al. 1995; Sommer and Tehovnik 1997; Dias and Segraves 1999). Thus the FEF may be part of a cortical system that controls the maintenance of spatial locations in working memory. Such a role is also consistent with the finding that ~60% of neurons in the FEF show elevated delay activity in spatial working-memory tasks (Umeno and Goldberg 2001).

It has been proposed that spatially directed attention presents a key mechanism in rehearsing encoded location information during delay periods of spatial working-memory tasks (e.g., Awh et al. 1999). Therefore it is possible that the activations obtained in human frontal cortex in the spatial working-memory task were related to the allocation of spatial attention at the peripheral target locations. Such an interpretation is compatible with a growing literature that demonstrates an important role of the FEF in spatial attention. In neuroimaging studies, the FEF has been consistently activated during covert attention tasks and constitutes an important part of the "general attention network" (see Kastner and Ungerleider 2000 for a review). In single-cell physiology studies, FEF neurons are modulated during covert attention tasks (Kodaka et al. 1997; Thompson et al. 2005), and behavioral performance in such tasks is impaired after reversible inactivation of the FEF (Wardak et al. 2006). Microstimulation of the FEF facilitates target detection and enhances responses in retinotopically matched sites in area V4, suggesting that visual processing in extrastriate cortex is directly controlled by the FEF (Moore and Fallah 2001; Moore and Armstrong 2003). The important role that the FEF plays in both spatial attention and spatial working memory underlines the intimate relationship of these cognitive operations that may share common neural mechanisms and circuits.

Topographic organization in SEF?

The existence of topographic organization of saccade direction in the monkey SEF has been highly debated. In the original description of the SEF (Schlag and Schlag-Rey 1987), the absence of any systematic organization of saccade direction or amplitude was noted. In later studies, evidence for an orderly representation of eye position in craniotopic coordinates was found (Tehovnik and Lee 1993). Russo and Bruce (2000) reported that the polar direction of the neurons' response fields remained constant in electrode penetrations perpendicular to the cortical surface, and that saccade direction progressively shifted across the SEF, suggesting a columnar organization similar to the one found in the FEF. We were able to identify the presumed human SEF in dorsomedial frontal cortex with our saccade localizer. However, notably no topographic organization was found in this region during the delayed response tasks. This result is not necessarily in contrast to the findings by Russo and Bruce because they tested a part of the SEF with neurons responding optimally to eccentricities

well beyond 10°, which was the eccentricity used in our study. Thus one possibility is that the SEF contains a topographic organization of saccade directions at large, but not at smaller, eccentricities. Future studies covering a larger set of saccade amplitudes will be necessary to reveal further details in the topographic organization of the human frontal oculomotor system.

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