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A Parametric fMRI Study of Overt and Covert Shifts of Visuospatial Attention

Michael S. Beauchamp,* Laurent Petit,† Timothy M. Ellmore,* John Ingeholm,* and James V. Haxby*

**Laboratory of Brain and Cognition, National Institute of Mental Health, Bethesda, Maryland 20892; and †Groupe d'Imagerie Neurofonctionnelle, UMR 6095 CNRS-CEA-Université de Caen-Universite Paris 5, GIP Cyceron, Caen, France*

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It has recently been demonstrated that a cortical network of visuospatial and oculomotor control areas is active for covert shifts of spatial attention (shifts of attention without eye movements) as well as for overt shifts of spatial attention (shifts of attention with saccadic eye movements). Studies examining activity in this visuospatial network during attentional shifts at a single rate have given conflicting reports about how the activity differs for overt and covert shifts. To better understand how the network subserves attentional shifts, we performed a parametric study in which subjects made either overt attentional shifts or covert attentional shifts at three different rates (0.2, 1.0, and 2.0 Hz). At every shift rate, both overt and covert shifts of visuospatial attention induced activations in the precentral sulcus, intraparietal sulcus, and lateral occipital cortex that were of greater amplitude for overt than during covert shifting. As the rate of attentional shifts increased, responses in the visuospatial network increased in both overt and covert conditions but this parametric increase was greater during overt shifts. These results confirm that overt and covert attentional shifts are subserved by the same network of areas. Overt shifts of attention elicit more neural activity than do covert shifts, reflecting additional activity associated with saccade execution. An additional finding concerns the anatomical organization of the visuospatial network. Two distinct activation foci were observed within the precentral sulcus for both overt and covert attentional shifts, corresponding to specific anatomical landmarks. We therefore reappraise the correspondence of these two precentral areas with the frontal eye fields. © 2001 Academic Press

INTRODUCTION

Humans bring items of interest in the visual scene into the center of gaze using directed eye movements known as saccades. It has long been known that humans can also examine items away from the center of gaze by directing their focus of spatial attention towards an object (James, 1890). Rizzolatti and colleagues linked these phenomena by suggesting that saccades and covert shifts of attention are subserved by similar neural mechanisms (Rizzolatti *et al.*, 1987).

While the focus of attention can shift without any eye movement, shifts in eye position require shifts in attention. Hoffman and Subramamian (Hoffman *et al.*, 1995) showed that subjects cannot move their eyes to one location and attend to a different one. While covert shifts of attention consist of a shift in spatial attention alone, we may think of saccades as consisting of a shift in spatial attention in conjunction with a shift in eye position. To emphasize this commonality, we refer to saccades as "overt shifts of attention."

We performed a functional imaging experiment to determine the common network of brain areas active when subjects performed shifts of attention (overt or covert) and to determine the difference in activity in this network when subjects made eye movements (overt vs covert).

Previous neuroimaging studies have found that patterns of activations for covert shift of visuospatial attention resemble those in eye movement tasks both across subjects (Nobre *et al.*, 1997; Büchel *et al.*, 1998) and within individual subjects (Corbetta *et al.*, 1998; Gitelman *et al.*, 1999; Nobre *et al.*, 2000). This pattern of activation consists of activity in frontal cortex (especially the precentral sulcus) parietal cortex (especially the intraparietal sulcus) and lateral occipital cortex. There is less agreement about the differences in brain activity during overt and covert shifting. One previous study found greater activity for covert compared with overt shifts (Corbetta *et al.*, 1998), while another study found greater activity for overt than covert shifts (Nobre *et al.*, 2000). However, these studies compared overt and covert shifts made at a single rate using different visual stimuli, different tasks, or different amplitudes of overt and covert shifts relative to fixation. To better understand the relationship between overt and covert shifting, we examined overt and covert shifts using identical tasks and stimuli located at similar distance from fixation. In addition, overt and

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covert shifts were performed at three different rates. The use of a parametric design allows for a more accurate characterization of the difference between overt and covert shifts. By measuring activation at different shift rates, we estimated the slope of the response vs shift rate relationship for both overt and covert shifts, as well as the absolute response difference between overt and covert shifts at each rate.

We also wished to better characterize the anatomical location of the visuospatial network underlying overt and covert shifts of attention. Recently developed cortical surface modeling software makes it possible to accurately picture activation in relation to sulcal and gyral landmarks. We constructed cortical surface models for 18 hemispheres and mapped the location of the visuospatial network in each hemisphere.

MATERIALS AND METHODS

Subjects

9 human subjects (5 M, 4 F, average age 28.1 years) underwent a complete physical examination and provided informed consent (World Medical Association, 1997). Subjects were compensated for participation in the study and anatomical MR scans were screened by the NIH Clinical Center Department of Radiology in accordance with the NIMH human subjects committee.

Visual Stimulus

The visual stimulus (Fig. 1A) consisted of a central fixation cross and a small round target (0.15° diameter). In alternating 18-s control and test blocks, the target either remained stationary at the center of gaze (overlaid on the fixation cross) or periodically disappeared and immediately reappeared at a new, unpredictable location (average eccentricity 8°). In five subjects, the targets moved at one of three different rates (0.2, 1.0, 2.0 Hz) during test blocks. In four subjects, the targets also moved at an additional rate (2.5 Hz) during test blocks. Each test block was preceded and followed by a control block, so that every 234-s fMRI scan series contained six test blocks and seven control blocks. During each scan series, each rate was presented in two test blocks and the block order was randomized.

During both test blocks (moving target) and control blocks (stationary target) subjects performed the same visual task: detecting small luminance decrements of the target. At random intervals (mean of 8 s) the target dimmed for 200 ms. Subjects counted the dimming events and reported the total number at the end of each scan series. This task allowed maintenance of a constant level of arousal throughout each scan and ensured attention to the visual stimulus.

Subjects could perform the target-dimming task in one of two ways: either by making an overt shift of attention to each peripherally presented target as it appeared (shift of attention + eye movement to the target location) or by making a covert shift of attention to each target (shift of attention to peripheral target + central fixation). Subjects alternated between conditions on each successive scan series and were cued to the condition both prior to and during each scan series by the color of the fixation cross (green, overt; red, covert). The order of scan series (overt or covert first) was counterbalanced across subjects. Because the target moved away from fixation only during test periods, the control block for each condition was identical.

Eye Movement Acquisition and Visual Stimulus Presentation

Eye-movement data was collected using an infrared pupillary eye-tracking system (ISCAN, Inc., Burlington, MA) modified to allow operation in the MR scanner, similar in principle to the method described in (Gitelman *et al.*, 2000). A fiber-optic cable illuminated the subject's eye from a light source located outside the scan room. A dichroic mirror reflected visible light, allowing subjects to view a visual stimulus projected onto a screen located at the subjects' feet, while transmitting infrared wavelengths to a video camera located behind the subjects' head, outside the magnet bore. A zoom lens was used to obtain an enlarged image of the subject's left eye. The image was then passed to a dedicated eye-movement analysis computer in the scanner control room. Unlike other methods (Kimmig *et al.*, 1999) an image of the eye was displayed on a monitor in the control room to ensure continuing accurate acquisition of eye movements. Horizontal and vertical eye position were collected and calibrated using a sequence of test eye movements at the beginning and end of each session. Postprocessing was performed to remove eye blinks and other artifacts using Matlab (Mathworks, Natick, MA).

MRI Procedures

A high-resolution SPGR scan was collected in addition to 8 to 12 functional scan series. Each functional scan series contained whole brain volumes of 120 echoplanar images, collected using a 1.5 T scanner (General Electric, Milwaukee, WI) with a repetition time (TR) of 2000 ms, an echo time (TE) of 40 ms, and in-plane resolution of 3.75 × 3.75 mm. Sixteen axial slices with a thickness of 6 to 8 mm (depending on the geometry of each subject's brain) were collected to provide coverage of the entire cortex. The first two volumes in each series, collected before equilibrium magnetization was reached, were discarded. The last volume in each time series was collected using a TE of 50 ms and was not used for functional analysis, for an effective functional scan series length of 234 s.

Within each two-second TR, slices were acquired in temporal sequence, with a 125-ms offset between interleaved slices. To allow for accurate comparison across brain regions, a Fourier interpolation algorithm was used to correct this acquisition offset (Van de Moortele *et al.*, 1998). The resulting time-corrected images were registered to the single functional image collected closest in time to the high-resolution anatomical using a gradient-descent algorithm (Cox *et al.*, 1999).

Data Analysis

Multiple regression was used to find brain areas showing changes in the MR signal related to overt or covert shifts at any shift rate. A square-wave regressor (1 for shifting, 0 for stationary) was created for each shift rate. Each regressor was convolved with a gamma variate waveform $t^{b^*}e^{-t/c}$, with $b = 8.6$, $c = 0.547$ (Cohen, 1997) to account for the vascular filtering of the neuronal response. Active voxels were defined as those that showed a significant effect of any of the attention-shift regressors using a threshold of $z > 4.416$ ($P < 10^{-5}$ per voxel) to correct for multiple comparisons. This analysis detects brain regions active during overt shifts alone, covert shifts alone, or both overt and covert shifts, at any shift rate. Active voxels were interpolated to 1 mm^3 using a cubic interpolation algorithm and overlaid on each subject's anatomical scan before conversion to the standardized space of Talairach and Tournoux (1988) using AFNI Version 2.2 (Cox, 1996, 1998; Cox *et al.*, 1997).

Surface Modeling

Three-dimensional models of the cortical surfaces were constructed using FreeSurfer software (Cortechs, Inc., http://www.cortechs.net). From one to five high-resolution SPGR scans for each subject were collected and averaged using a correspondence of closest-gradients algorithm (Ostuni *et al.*, 1997). An automated segmentation routine then extracted the gray-white boundary and constructed a surface model (Dale *et al.*, 1999). The model was then inflated to allow inspection of active areas buried deep in cortical sulci (Fischl *et al.*, 1999). To allow more accurate mapping of functional data to the surface, in two subjects functional images were unwarped using a variable TE field map correction technique (Reber *et al.*, 1998). The overall model significance was thresholded and blurred with a spatial gaussian filter of root mean square width 3 mm before painting to the cortical surface. Only voxels intersecting surface nodes were mapped to the cortical surface.

Volumes of Interest

Examination of the cortical surface models revealed activity in a distributed network of brain areas during attentional shifts. In order to compare the response of these different regions to overt and covert shifts at different rates, 12 anatomically defined volumes-of-interest (VOIs) corresponding to the different regions of the visuospatial network were manually traced on each subject's high-resolution anatomy. The volumes were traced without reference to the functional data based on previously described anatomical landmarks for different areas in the visuospatial network. Two VOIs delineated bilateral precentral regions cortex encompassing the precentral gyrus and the precentral sulcus (PreCS), including 5 mm on the anterior bank of the sulcus from the junction with the superior frontal sulcus to the lateral convexity. The VOI for inferior precentral cortex extended along the PreCS from 20 mm above the bicommisural plane (AC–PC) to 10 mm above the intersection of the PreCS with the inferior frontal sulcus. The VOI for superior precentral cortex extended superiorly along the remainder of the sulcus. The VOI delineating the dorsomedial part of the superior frontal gyrus consisted of 15 mm of cortex on each side of the interhemispheric fissure anterior to the vertical plane passing through the posterior commissure (VPC) and extending forward to the anterior convexity. Its inferior limit corresponded to the cingulate sulcus in the posterior part and to the plane 45 mm above AC–PC in the anterior part. This inferior limit was chosen to delineate the medial part of Brodmann area 6 that contains both the supplementary motor area and the supplementary eye fields (SEF) (Picard *et al.*, 1996; Petit *et al.*, 1998). The VOI delineating intraparietal sulcus (IPS) included the cortex on both banks of the sulcus, namely both superior and inferior parietal lobules, from the junction with the postcentral sulcus to the posterior convexity. Its inferior limit corresponded to the plane 30 mm above the AC–PC plane and thus included the deepest part of the IPS. The VOI delineating bilateral regions at the lateral junction of the temporal and occipital cortex was centered on the junction of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus (LOS). Its anterior limit corresponded to the coronal plane 40 mm posterior to the plane passing through the anterior commisure (VAC) and extending backward to the coronal plane 85 mm posterior to the VAC. Its superior limit corresponded to the plane 12 mm above the AC–PC plane, and its inferior limit corresponded to the plane 4 mm below the AC–PC plane. This region was defined to include the area that is homologous to monkey MT/MST, also called V5 (Zeki *et al.*, 1991; Watson *et al.*, 1993; Tootell *et al.*, 1995). The VOI delineating the precuneus consisted of 15 mm of parietal cortex on each side of the interhemispheric fissure, posterior to the marginal ramus of the cingulate sulcus and extending backward to the posterior convexity. Its inferior limit corresponded to the plane 30 mm above the AC–PC plane. The two last VOIs delineated the medial part of the occipital cortex including both striate and extrastriate visual areas on both sides of AC–PC.

TABLE 1

Active Areas during Shifts of Attention, Averaged across Nine Subjects

		Coordinates				Volume fraction		Overt response amplitude		Covert response amplitude	
Volumes of interest		x	y	z	Volume (mm^3)	Overt	Covert	Slope	Intercept	Slope	Intercept
Precentral sulcus (Superior)	L	−29	−9	53	4230	0.93	0.30	0.25	0.39	0.10	0.23
	R	30	−8	54	3015	0.90	0.38	0.20	0.37	0.06	0.28
Precentral sulcus (Inferior)	L	−41	−2	35	1259	0.94	0.14	0.21	0.31	0.09	0.18
	R	40	−2	37	889	0.82	0.21	0.18	0.14	0.06	0.13
Medial frontal		−3	−6	62	2438	0.84	0.14	0.13	0.29	−0.02	0.14
Intraparietal sulcus	L	−26	−57	50	9253	0.90	0.34	0.22	0.36	0.07	0.26
	R	27	−59	50	7490	0.82	0.36	0.15	0.34	0.04	0.27
Lateral occipital sulcus	L	−40	−69	5	3645	0.84	0.23	0.26	0.28	0.14	0.09
	R	43	−67	4	3525	0.84	0.22	0.20	0.22	0.08	0.09
Precuneus		−1	−65	48	9742	0.88	0.20	0.20	0.62	−0.08	0.26
Medial occipital above AC–PC		2	−80	15	30521	1.00	0.05	0.38	0.60	0.00	−0.01
Medial occipital below AC–PC		0	−75	−8	23451	0.96	0.09	0.27	0.63	0.00	−0.03

Note. The first column is the location of anatomically defined volumes of interest (VOIs). The second column lists the hemisphere (L, left; R, right) for VOIs on the lateral surface of the hemisphere (activity in both hemispheres is grouped for medial VOIs). The third, fourth, and fifth columns are (x, y, z) normalized Talairach coordinates of the center of mass of the activity in each VOI, in mm from the anterior commisure. The "Volume" column lists the volume of cortex in each VOI that showed an experimental effect (shifts of attention vs fixation). The "Volume Fraction" columns list the fraction of active cortex that was active during overt or covert shifts considered independently. The "Response Amplitude" columns list the response characteristics to overt and covert shifts at different rates in each VOI in all active voxels. The slope column lists the slope of the shift rate vs MR response curve in units of percentage MR signal change per Hz, while the intercept column represents the intercept of this curve in units of percentage MR signal change.

Each anatomical VOI was then combined with the functional data. For each subject, average MR responses were calculated by averaging across all active voxels in each VOI. The center-of-mass of the activity in each VOI in each subject was also calculated (Table 1). The locations of active regions are reported in Talairach coordinates as the distance in mm from the anterior commissure in the form (x,y,z) where the x-axis is left-to-right, the y-axis is posterior-to-anterior, and the z-axis is inferior-to-superior.

RESULTS

Behavioral Results

A sample horizontal eye position trace obtained during fMRI acquisition is shown in Fig. 1B. During overt shift blocks, subjects moved their eyes to the position of each new target with an average saccadic reaction time (SRT) of 167 ms. The reaction time to the first target in each block was significantly slower (SRT = 312 ms) as subjects shifted set from central fixation to overt shifting, as was the final saccade to the fixation crosshairs at the end of each block (SRT = 340 ms) as subjects resumed central fixation. During covert scans, subjects maintained central fixation with an average of 0.4 fixation breaks (eye movements of greater than 1°) in each scan series. There was no significant performance difference in the target-dimming task between overt and covert scans.

fMRI Results

Anatomical description of active areas. A model of the cortical surface was created for each subject (Dale *et al.*, 1999; Fischl *et al.*, 1999). Cortical voxels exceeding the significance threshold for the main effect of interest (shifts of attention vs no shifts) were mapped to the surface model, and the model was inflated to reveal activation foci buried in sulcal depths. As shown for a single subject in Fig. 2A, a broadly distributed network of cortical areas was active when subjects made shifts of attention. On the lateral surface, activity was observed in superior and inferior precentral sulcus (PreCS), intraparietal sulcus (IPS), and lateral occipital sulcus (LOS). On the medial surface, activity was observed in medial frontal cortex, in precuneus, and above and below the calcarine fissure in occipital cortex.

A similar pattern of activity was seen in 18 hemispheres from 9 subjects (Fig. 2B). All hemispheres showed frontal lobe activity concentrated in the PreCS. In 16 of 18 hemispheres, activity was observed in two distinct locations along the PreCS, superiorly at the intersection of the PreCS with the superior frontal sulcus, and inferiorly at the intersection of the PreCS and the inferior frontal sulcus. In hemispheres in which these two intersections were nearby, this activation occurred as a single, extended focus (BL left hemisphere, BI right hemisphere). The PreCS activation included the precentral gyrus but did not extend

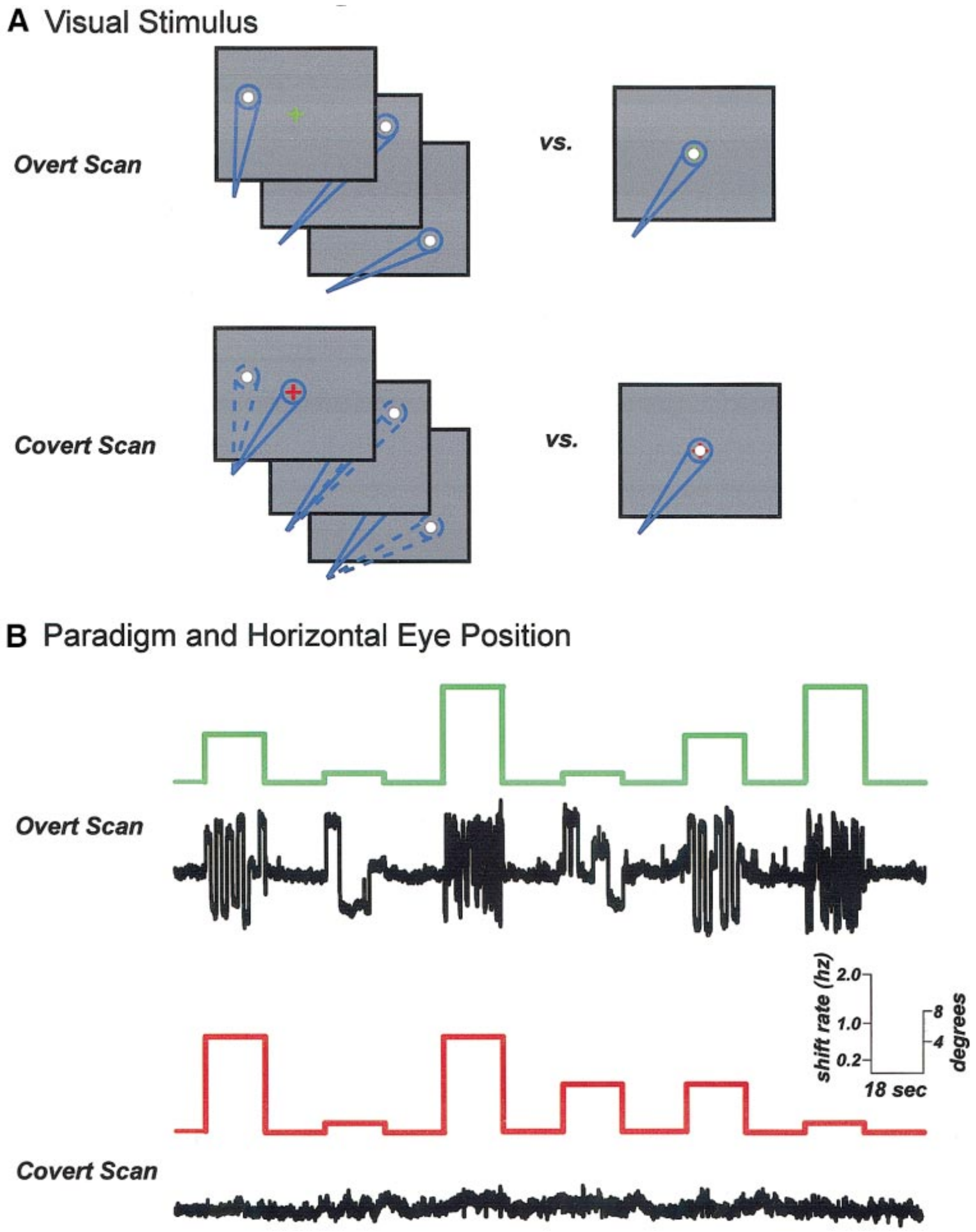
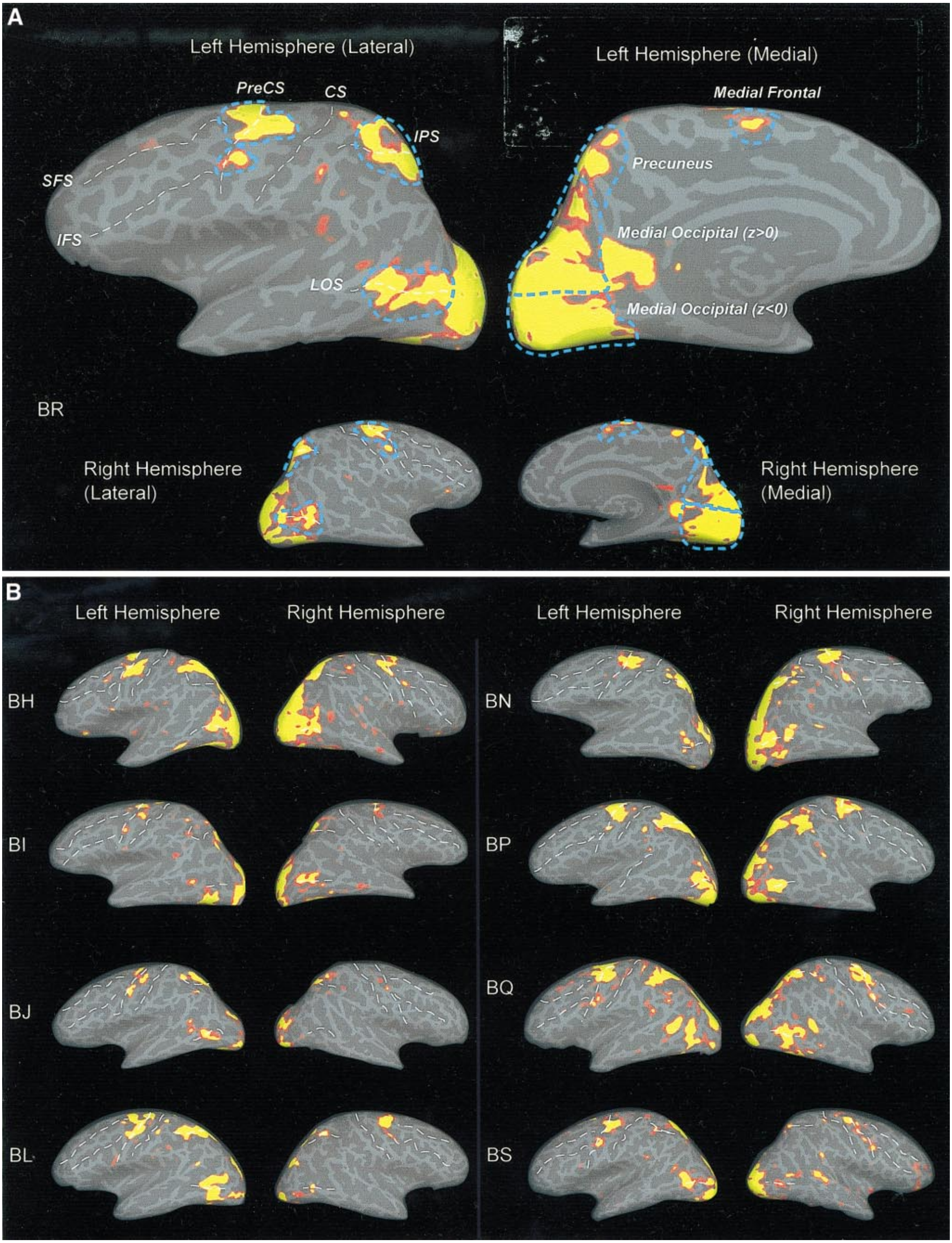


FIG. 1. (A) Subjects performed overt attentional shifts (shifts of attention with eye movements) or covert attentional shifts (shifts of attention without eye movements) during alternating fMRI scan series. Each 234-second scan series consisted of alternating 18-second test and control blocks. During overt scan test blocks (left top) the display contained a green crosshair and subjects made eye movements to the location of a target (eye position indicated schematically by solid blue line). During covert scan test blocks (left bottom) the display contained a red crosshair, and subjects fixated the crosshair while covertly shifting attention to the target location (attentional position indicated schematically by dashed blue line). During overt and covert scan control blocks (right top and bottom) subjects fixated a stationary target appearing at the center of gaze. (B) During each test block, subjects performed attentional shifts at one of three rates (0.2, 1.0, or 2.0 Hz). Each scan series contained two test blocks at each rate, in random order. Green and red lines illustrate alternating test and control blocks during sample overt and covert scan series (deviation from baseline indicates attentional shift rate in each test block). Black lines indicate horizontal eye position in a single scan series (deviation from baseline corresponds to distance from center of gaze). Data shown are from case BJ.

FIG. 2. (A) Brain areas showing a significant response to shifts of attention vs no shifts are displayed (in color) on the inflated cortical surface (in gray) of a single subject (case BR). 12 anatomically defined volumes of interest were traced without reference to the functional data in each subject. Labels indicated the location of each volume of interest; dashed lines outline active voxels falling within each volume of interest. (B) Activity in response to attention shifts in eight single subjects. Subjects are identified by two-letter code. Each panel depicts a lateral view of an inflated hemisphere (left and right labeled at top of column). Dark gray areas represent cortex located in sulcal depths; lighter gray represents cortex on exposed gyri. Colored regions represent brain areas more active during shifts of attention than no shifts. Dashed white lines illustrate major sulci, labeled for case BR. IFS, inferior frontal sulcus. SFS, superior frontal sulcus. PreCS, precentral sulcus. CS, central sulcus. IPS, intraparietal sulcus. LOS, lateral occipital sulcus.


A
Left Hemisphere (Lateral)
PreCS
CS
IPS
SFS
IFS
LOS
Left Hemisphere (Medial)
Medial Frontal
Precuneus
Medial Occipital (z>0)
Medial Occipital (z<0)
BR
Right Hemisphere (Lateral)
Right Hemisphere (Medial)
B
Left Hemisphere
Right Hemisphere
Left Hemisphere
Right Hemisphere
BH
BI
BJ
BL
BN
BP
BQ
BS

anteriorly into the superior or inferior frontal sulci or posteriorly into the central sulcus.

Medial frontal activity was located superior to the cingulate sulcus near the paracentral sulcus (Ono *et al.*, 1990) in seven of nine subjects. In the parietal lobe, activity was concentrated in and around the IPS. The center of mass of the activity lay in the depth of the posterior part of the IPS, extending dorsally into the superior parietal lobule. Activity did not extend anteriorly into the postcentral sulcus. In lateral occipital cortex (LOC), activity was strongest in the anterior part of the LOS but varied considerably. In some subjects, lateral occipital activity extended anteriorly into superior temporal sulcus (e.g., BS right hemisphere, BJ left hemisphere), while in others activity was restricted to the LOS (e.g., BP and BL, right and left hemispheres). In medial occipital cortex, activity extended from the calcarine fissure dorsally to the inferior bank of the parieto-occipital sulcus and ventrally to the ventral occipital cortex.

Activity was observed bilaterally for all subjects in the PreCS, IPS, and LOS. There was no significant difference in volume of active cortex in the LOS between hemispheres. In the PreCS, there was 40% more active cortex in left hemisphere than right hemisphere ($P = 0.02$) and in the IPS there was a trend ($P = 0.1$) in the same direction, with 29% more active cortex in left hemisphere. However, there was considerable variation between subjects in the magnitude of the laterality difference. Three of nine subjects had little volume difference between hemispheres in the PreCS and IPS.

Response to overt and covert shifts of attention. To characterize the active regions, twelve anatomically defined volumes of interest (VOI) were manually traced in each subject. For each subject, voxels within each VOI that showed a significant response to the main effect of interest (attentional shifting vs no shifting) were grouped. This allowed the calculation of the volume and Talairach coordinates of activity in each VOI in each subject. Table 1 lists these values, averaged across subjects.

To examine the response to different rates of overt and covert shifting, an average MR time series across subjects was created for each VOI at each shift rate (Fig. 3A). When subjects made shifts of attention, the MR signal increased. In every VOI, the response was greater for overt shifts (shifts of attention + eye movements) than covert shifts (shifts of attention alone) with an analysis of variance across subjects revealing an effect of shift type on response amplitude ($P < 10^{-4}$ in all VOIs). The response to overt shifts of attention across rates was significant in all VOIs. The response to covert shifts was significant in all VOIs except inferior medial occipital cortex ($P = 0.09$) and superior medial occipital cortex ($P = 0.4$).

While all VOIs were more responsive to overt than covert shifts, the difference between overt and covert responses varied. To quantify the parametric relationship between shift rate and response, the slope and intercept of the MR response vs rate curve was calculated for overt and covert shifts (Table 1 lists the values, averaged across subjects). The amplitude of the signal increase in each VOI for each rate was subjected to a random-effects analysis of variance. During overt shifting, all volumes showed an increase in response amplitude with increasing shift rate. For instance, in superior medial occipital cortex the response amplitude to overt shifts increased from 0.6% at 0.2 Hz to 1.0% at 1.0 Hz to 1.3% at 2.0 Hz ($F(1,25) = 47$; $P = 5 \times 10^{-7}$). In contrast, during covert shifting, only areas in the PreCS, IPS, and LOS showed a significant relationship between shift rate and response amplitude. For instance, in left superior PreCS the response amplitude to covert shifts was 0.4% at 0.2 Hz, 0.6% at 1.0 Hz, and 0.9% at 2.0 Hz ($F(1,25) = 7.58$, $P = 0.01$).

An average response at each rate was calculated for those areas showing an increase in MR response with increasing shift rate (PreCS, IPS, and LOS). As shown in Fig. 3B, the response increased for both overt and covert shifts between 0.2 and 2.0 Hz. However, the slope of the shift rate/response amplitude relationship was twice as steep for overt shifts than for covert shifts (0.20 vs 0.08% MR/shift Hz) and the intercept was 40% greater for overt than covert shifts (0.34% MR vs 0.25% MR).

Pilot studies revealed that 2 Hz was near the maximum rate at which subjects could accurately make visually guided saccades in our paradigm (at 2 Hz, an attentional shift was made to a new, unpredictable location every 500 ms). Four subjects also attempted to perform attentional shifts in the scanner at an even faster rate, 2.5 Hz. Responses in the attentional network appeared to saturate at 2.5 Hz. The amplitude of response in the PreCS, IPS, and LOS was significantly lower than the response at 2.0 Hz for both overt ($P = 0.01$) and covert ($P = 0.03$) shifts.

To compare the spatial extent of overt and covert responses, voxels showing a response to any type of shift were analyzed as to whether they showed a significant response to overt or covert shifts alone (Table 1, "Volume Fraction" columns). In all VOIs, most voxels showing an experimental effect responded to overt shifts of attention, ranging from 100% of the voxels in medial occipital cortex above the bicommisural plane to 82% of the voxels in right IPS. A different pattern was observed in the covert response. While in all VOIs fewer voxels responded to covert than overt shifts (effect of shift type in an analysis of variance across subjects, $P < 10^{-5}$ in all VOIs) one group of areas in the IPS, superior PreCS and LOS showed a relatively high fraction of voxels, averaging 31%, responsive to covert shifts. A second group of areas in medial frontal, medial parietal and inferior PreCS showed a more restricted response to covert shifts, averaging 17%. A third group of areas, located in medial and ventral occipital cortex, showed a small covert response, averaging 7% (significant interaction between region and volume fraction as determined by an analysis of variance, $P = 4 \times 10^{-6}$).

We wished to determine whether there was any anatomical segregation between the voxels active in overt and covert shifts, or at different shift rates. For each subject, voxels showing a significant response to overt and covert shifts at each rate were examined (results for the PreCS, IPS, medial frontal and precuneus are shown for a single subject in Fig. 4). At each rate, there was more activity during overt shifting than covert shifting, and at increasing rates the number of voxels exceeding the significance threshold increased. At the lowest shift rate, few voxels exceeded the single-voxel significance threshold, but the average time series from all voxels in the VOI indicated a small but significant response. At higher rates, higher response amplitude resulted in more voxels exceeding the significance threshold. However, these voxels remained tightly grouped within each region of the attentional network. For instance, even at the highest shift rate, activity in the PreCS did not extend into superior frontal or inferior frontal sulci. While the number of active voxels increased at increasing shift rates and for overt vs covert shifting, there was no systematic difference in the location of active voxels within each VOI between rates or between overt and covert shifting. Throughout the brain (both within and outside the VOIs) we found no voxels that were active only during covert shifts of attention.

DISCUSSION

The premotor theory of attention hypothesizes that covert and overt attentional shifts share neural mechanisms (Rizzolatti *et al.*, 1998). Our results, along with other recent neuroimaging studies (Corbetta *et al.*, 1998; Culham *et al.*, 1998; Gitelman *et al.*, 1999; Nobre *et al.*, 2000) bolster this theory by showing that oculomotor control areas, including the PreCS, IPS, and LOS are active during covert and overt shifts of attention.

The present study also provides three new findings regarding the human cortical areas that participate in overt and covert attentional shifts. First, by examining the parametric relationship between MR response amplitude and overt and covert shifts at different rates, we show that increasing shift rates lead to greater MR response. Second, we show that shifts of attention with eye movements cause a greater MR response than do shifts of attention without eye movements. Third, our results show distinct inferior and superior activation foci within the PreCS.

Greater Activity in the Attentional Network for Overt vs Covert Shifts of Attention

Though overt and covert shifts of spatial attention both involve activity in oculomotor control areas, covert shifts are not accompanied by overt eye movements. Our results show that this behavioral difference has a neural correlate. At every shift rate, less activity was observed in the visuospatial network during covert shifts than during overt shifts. This reduced activity suggests the following scenario. A moderate amount of activity in oculomotor control areas produces covert shifts of attention to a target location. This activity level is sufficient to orient the focus of spatial attention to the target, but is below the threshold necessary to generate an eye movement. If the target is particularly salient, bottom-up activity from visual areas or top-down modulation from frontal areas leads to more activity in the oculomotor network, producing an overt eye movement to the target that facilitates high-resolution inspection (Burman *et al.*, 1994).

Two previous fMRI studies compared the relative amplitude of overt and covert shifts at a single rate, with conflicting results. Corbetta *et al.* (1998) found greater activity in five subjects for covert shifts than overt shifts, the opposite of our finding. However, the task used by Corbetta may have influenced the relative amplitude of overt and covert activations. The subjects in the Corbetta study most often made overt shifts to a position 2 degrees to the left of the current fixation position. During covert scans, subjects made shifts to a position that averaged 5.2° from the current fixation position and varied between 1 and 10°. In nonhuman primates, different regions in the frontal eye fields code for saccades of different amplitude (Robinson *et al.*, 1969; Bruce *et al.*, 1985). Therefore, large amplitude shifts to a position that varied relative to fixation (as in the covert scans of Corbetta *et al.*) might be expected to activate more cortex than small amplitude shifts to a constant position relative to fixation (as in the overt scans of Corbetta *et al.*). An fMRI study of four subjects by Nobre *et al.* found greater activity for overt than covert shifts in precentral regions, but not in other areas in the visuospatial network. While the covert attention task in the Nobre *et al.* study was a complex task requiring speeded detection of a target in a cued location on the horizontal meridian at 7.5° eccentricity, performed at a rate of 0.5 hz, the saccade task required simple eye movements to a predictable location on the horizontal meridian at 12° eccentricity at a rate of 1 Hz. These differences in experimental task, eccentricity, and shift rate confound an amplitude comparison of overt and covert shifts.

Parametric Increases in Activity with Increasing Shift Rate

At each shift rate, overt shifts produced more activity in the visuospatial network than covert shifts. At

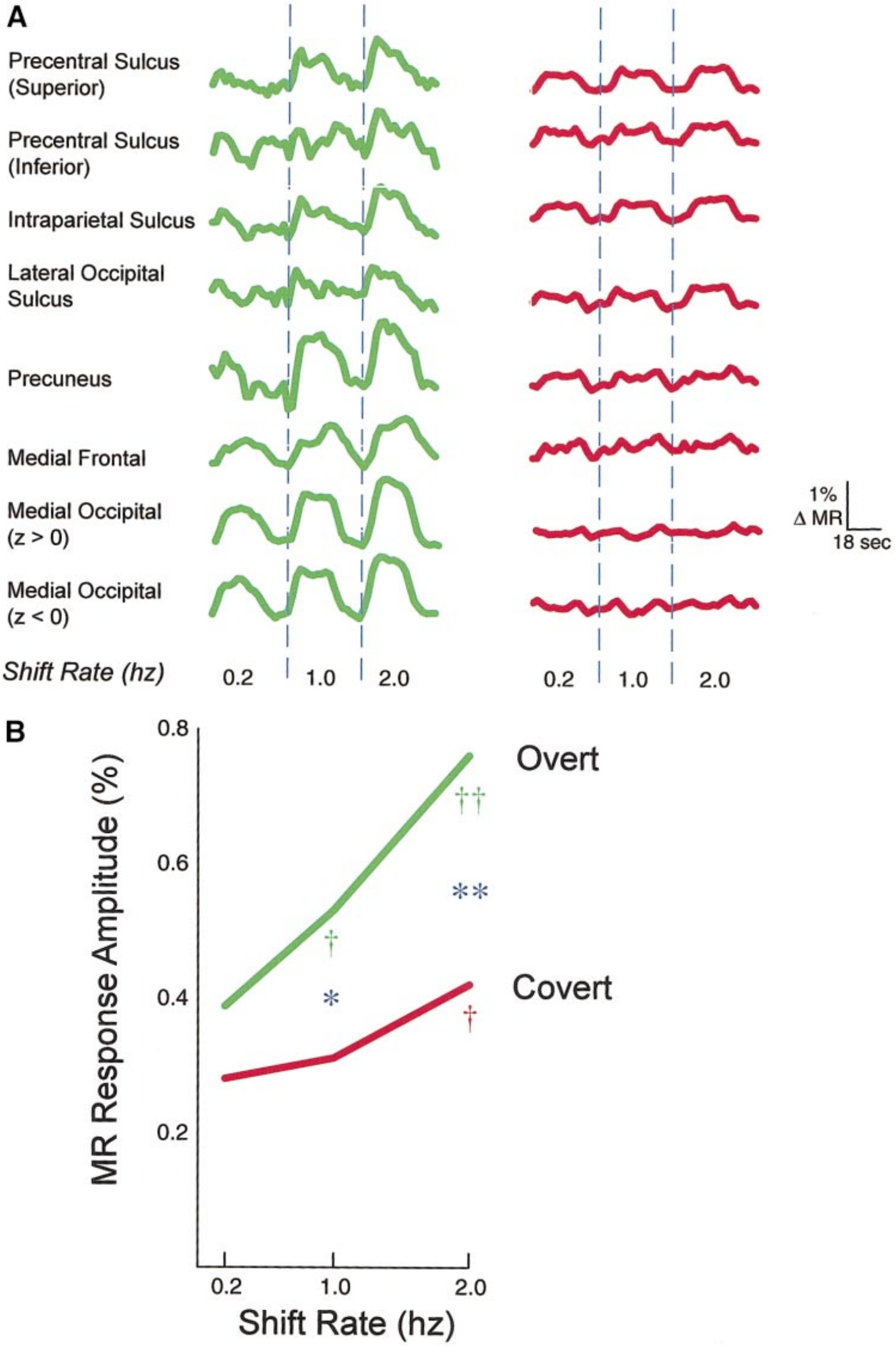


FIG. 3. (A) The average MR response in each anatomically defined volume of interest (VOI). The left column lists the anatomical location of each VOI. The middle column (green traces) shows average response in each VOI during overt shifts of attention at 0.2, 1.0, and 2.0 Hz. The right column (red traces) shows the average MR response to covert shifts at each rate. The response shown is the grand mean across subjects: within each subject, an average time series was created for each VOI from all voxels showing an experimental effect of attention shifts vs fixation; then the response in each VOI was averaged across nine subjects. (B) The relationship between shift rate and MR response amplitude for overt (green trace) and covert (red trace) shifts of attention. MR response amplitude calculated at each shift rate, averaged across subjects, for voxels showing an experimental effect in precentral sulcus, intraparietal sulcus and lateral occipital sulcus. An analysis of variance indicated a significant effect of overt vs covert shifting ($P = 5 \times 10^{-7}$) and shift rate ($P = 1 \times 10^{-5}$). Symbols show significance of comparisons (single symbol, $P < 0.05$, double symbol, $P < 0.01$). Daggers indicate significant difference within shift type (compared to 0.2 Hz shift rate) and asterisks indicate significant difference between shift types (at each rate).

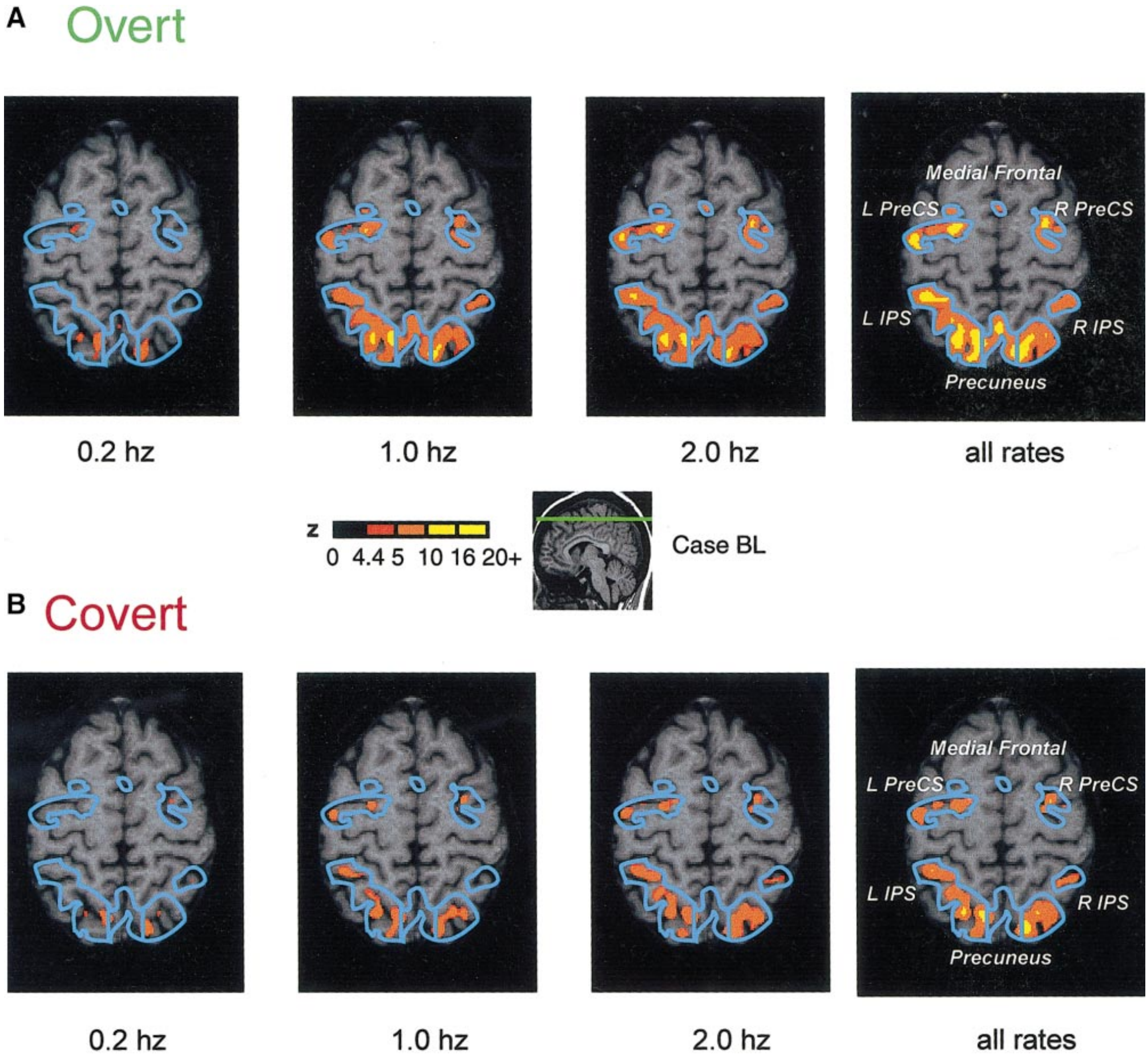


FIG. 4. Comparison of responses to overt and covert shifts of attention at different rates in a single subject (case BL). Each axial slice ($z = 52$ mm; green line on sagittal image) shows brain areas showing a significant ($z > 4.416$; $P < 1e\text{-}5$) response to shifts of attention vs no shifts. (A) Areas showing a significant response to overt shifts of attention at 0.2, 1.0, 2.0 Hz and all rates. (B) Areas showing a significant response to covert shifts of attention at 0.2, 1.0, 2.0 Hz and all rates. Color scale indicates significance of activation (same for all images). Blue line shows area of activation for overt or covert shifts at any rate (same on all images). PreCS, precentral sulcus; IPS, intraparietal sulcus.

increasing rates, increased activity was observed for both overt and covert shifts. While increasing shift rates produced more activity for both shift types, the activity increase was steeper for overt shifts (0.20 vs 0.08% MR/shift Hz). If overt shifts required only the presence of an additional constant neural gating signal (go vs no-go) we would expect more activity for overt shifts than covert shifts with a constant difference across rates. Instead, we observed a steeper slope for overt than covert shifts, suggesting that executing each individual saccade requires additional activity in the visuospatial network (not simply the presence of a constant gating signal) leading to an increasing difference between overt and covert shifts at increasing shift rates.

Because subjects performed the same target-dimming task throughout each scan, arousal and general visual attention were closely matched between control and test conditions. In the comparison of covert and overt test conditions, the visual stimulus was identical and subjects made shifts to unpredictable locations at similar eccentricities. An unavoidable effect of overt shifts of attention is that subjects foveate the peripheral targets, resulting in relatively more visual stimulation during overt compared with covert shifts. However, covert shifts of attention without visual stimulation produce activity similar to that of covert shifts with stimulation (Kastner *et al.*, 1999). Even in complete darkness, saccadic eye movements produce activation in PreCS, IPS and LOS (Petit *et al.*, 1993; Paus *et al.*, 1995; Law *et al.*, 1998), demonstrating that the activation observed in the attentional network is not due to visual stimulation alone.

Two Distinct Eye Movement Areas in the PreCS

The present study found evidence for two distinct activations along the PreCS for both overt and covert shifts of visuospatial attention in 16 of 18 hemispheres. One focus was located in the superior part of the PreCS at the junction with the superior frontal sulcus, while the other was found along the inferior part of the PreCS at the junction with the inferior frontal sulcus.

Early studies demonstrated the existence of a large region of frontal cortex (near the arcuate sulcus in monkeys and anterior to the central sulcus in humans) that when electrically stimulated, produced saccades to the contralateral visual field, leading to the notion of homologous frontal eye fields (FEF) in human and non-human primates (Ferrier, 1875; Penfield *et al.*, 1950). PET studies with greater resolution than electrical stimulation imaged a single, large FEF activation encompassing both the PreCS and the precentral gyrus (for review, see Paus, 1996; Luna *et al.*, 1998; Berman *et al.*, 1999; Petit *et al.*, 1999b). The higher spatial resolution provided by fMRI showed that in individual subjects FEF activation is concentrated in the PreCS (Petit *et al.*, 1997, 1999a; Luna *et al.*, 1998) and suggested that this activation might contain distinct foci within the PreCS (Corbetta *et al.*, 1998; Culham *et al.*, 1998; Luna *et al.*, 1998; Berman *et al.*, 1999).

We suggest that the inferior and superior precentral foci observed in this and previous studies form two distinct brain areas for visuomotor control. This proposal is supported by evidence from developmental studies: during development, the inferior and superior PreCS arise from distinct precursors in cortical morphogenesis (Turner, 1948). In adults, the PreCS is composed of superior and inferior divisions, often separated by a transverse connection between the precentral and middle frontal gyri (Ono *et al.*, 1990).

For clues to the function of the superior and inferior PreCS areas, we turn to evidence from non-human primates. The monkey FEF lies in the anterior banks of the arcuate sulcus (Bruce *et al.*, 1985; Goldberg *et al.*, 1989) and contains both saccade-related and smooth-pursuit related neurons (Gottlieb *et al.*, 1994). In humans, only the superior PreCS is responsive to execution of both saccadic and pursuit eye movements (Petit *et al.*, 1999a; Berman *et al.*, 1999), supporting claims that the superior PreCS contains the human homolog of monkey FEF (Paus, 1996). The homology of inferior PreCS is less certain. Posterior to the arcuate sulcus, monkey premotor cortex contains areas important for eye movements, such as PMVe (Fujii *et al.*, 2000) and areas where stimulation produces eye, head and neck movements (Preuss *et al.*, 1996). The human inferior PreCS also encompasses areas where stimulation produces eye, head, and neck movements (Penfield *et al.*, 1950; Godoy *et al.*, 1990) leading us to propose that the inferior PreCS activation may be important for the control of eye and head movements.

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