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Human medial intraparietal cortex subserves visuomotor coordinate transformation

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In the macaque, the posterior parietal cortex (PPC) integrates multimodal sensory information for planning and coordinating complex movements. In particular, the areas around the intraparietal sulcus (IPS) serve as an interface between the sensory and motor systems to allow for coordinated movements in space. Because recent imaging studies suggest a comparable functional and anatomical organization of human and monkey IPS, we hypothesized that in humans, as in macaques, the medial intraparietal cortex (area MIP) subserves visuomotor transformations. To test this hypothesis, changes of neural activity were measured using functional magnetic resonance imaging (fMRI) while healthy subjects performed a joystick paradigm similar to the ones previously employed in macaques for studying area MIP. As hypothesized, visuomotor coordinate transformation subserving goal-directed hand movements activated superior parietal cortex with the local maximum of increased neural activity lying in the medial wall of IPS. Compared to the respective visuomotor control conditions, goal-directed hand movements under predominantly proprioceptive control activated a more anterior part of medial IPS, whereas posterior medial IPS was more responsive to visually guided hand movements. Contrasting the two coordinate transformation conditions, changing the modality of movement guidance (visual/proprioceptive) did not significantly alter the BOLD signal within IPS but demonstrated differential recruitment of modality specific areas such as V5/MT and sensorimotor cortex/area 5, respectively. The data suggest that the human medial intraparietal cortex subserves visuomotor transformation processes to control goal-directed hand movements independently from the modality-specific processing of visual or proprioceptive information.

Keywords: MIP; Eye–hand coordination; fMRI; Human–monkey equivalence; Parietal cortex; Visual guidance; Efference copy; Optic ataxia

Introduction

A major behavioral characteristic of primates, and in particular of humans, is the skillful coordination of hand and arm movements in space for object-related action. For a successful eye–hand–object coordination in space, the respective spatial coordinates have to be transformed and integrated into a common spatial reference frame with the underlying processes relying on the integration of visual, motor, somatosensory, and spatial information. Neuropsychological data demonstrate that lesions of the posterior parietal cortex (PPC) can lead to transient or permanent visuomotor deficits (e.g., optic ataxia) affecting hand–eye coordination and action in space (Battaglia-Mayer and Caminiti, 2002). Although many behavioral and functional imaging studies (including both patients and healthy subjects) have shown that the parietal cortex, and especially the cortex within and adjacent to the intraparietal sulcus (IPS), is crucially involved in computing object- and space-relevant information (see e.g., Corbetta et al., 2002; Fink et al., 1997; Vogeley and Fink, 2003), our knowledge of the neural mechanisms and the specific cortical areas subserving visuomotor coordinate transformation is still incomplete.

For the macaque, the posterior-parietal cortex and especially the areas around the intraparietal sulcus (IPS) have been well characterized during the last decade, all in terms of electrophysiological response properties, their anatomical arrangement, and their connections with other cortical areas. The current view is that IPS contains highly specialized modules that are integrated into complex parietofrontal and parietooccipital networks subserving goal-directed and object-centered movements. One of these modules, the medial intraparietal area (MIP) situated in the posterior aspect of medial IPS plays a major role in planning and execution of goal-directed reaches (Colby, 1998; Colby et al., 1988) involving the implementation of target coordinates into planned or ongoing reaching movements (Cohen and Andersen, 2002; Eskandar and Assad, 2002). Macaque area MIP is situated in the superior aspect of the medial wall of IPS. Neurons in MIP

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specifically discharge dependent on the direction of hand movements before and after movement onset (Eskandar and Assad, 1999). In contrast, the lateral intraparietal area (LIP) on the lateral wall of IPS is known to subserve visuomotor transformation processes and movement planning for eye movements (Andersen et al., 1998; Snyder et al., 1997). In both MIP and LIP, sensory data are computed in a common, predominantly eye-centered frame of reference providing spatial information for different motor effectors (Andersen et al., 1998; Batista et al., 1999; Cohen and Andersen, 2000).

Although many studies have addressed the issue of coordinate transformation and reaching movements in monkeys, there have been only a few studies that investigated the role of human IPS for object-related motor behavior. Recent imaging studies suggest a homologue functional organization of human and macaque IPS (Astafiev et al., 2003; Bremmer et al., 2001a,b; Grefkes et al., 2002). However, other studies reported activation associated with reaching movements not in IPS but rather on the mesial cortex within the interhemispheric fissure (Astafiev et al., 2003; Connolly et al., 2003), which would suggest that human medial IPS is not involved in visuomotor transformations for visually guided hand movements.

To address this issue, we designed an functional magnetic resonance imaging (fMRI) paradigm based upon macaque MIP experiments by Eskandar and Assad (1999, 2002). In these experiments, monkeys performed a visuomotor coordinate transformation task using a joystick executing precise movements toward a visual target. We expected that, as in macaques, such a task should delineate areas concerned with visuomotor coordinate transformation and online control of movements, and therefore possibly activate human medial intraparietal cortex.

Materials and methods

Subjects

Eleven healthy, right-handed volunteers (five male, six female; aged 19–31) with no history of neurological or psychiatric disease gave informed consent. All subjects reported strong right hand preference as measured by the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the local ethics committee.

Behavioral background

We adopted and modified a paradigm originally employed by Eskandar and Assad (1999, 2002) for electrophysiological recordings of MIP neurons in macaques. In that study, fixating monkeys were trained to use a joystick to guide a spot to a target (both presented on a computer monitor). Various conditions were tested. In one condition, the moving spot was visible during the whole task, in another condition the spot was transiently hidden to separate visually driven neurons from neurons directed by extraretinal (i.e., proprioceptive) input. The latter activity is considered to be typical for neurons involved in planning and executing movements (Eskandar and Assad, 1999). The results of that experiment showed that the tasks involving coordinate transformation activated neurons in MIP irrespective of whether there was visual movement feedback. Rather, MIP neurons specifically discharged dependent upon the direction of hand movements before and after movement onset.

Task and study design

Accordingly, we designed a two-factorial blocked design fMRI experiment with the factors "task" (comprising the levels "visuomotor transformation" and "visuomotor control") and "visual movement feedback" (comprising the levels "present" and "absent") (see Fig. 1). The joystick used within the MR scanner was a metal-free, glass fiber optic-based device (Cold-switch Technologies Inc., Burnaby, BC/Canada) with two degrees of freedom. In the scanner, the joystick was placed on the right side near the subject's hip while the right arm lay comfortably on a plastic pillow. This arrangement ensured that subjects could execute joystick movements without generating significant movements of the head or the whole body. The software "Presentation" (Version 0.50, Neurobehavioral Systems Inc., CA/USA, http://www.neurobehavioralsystems.com) was used for visual stimulus presentation and joystick control. Subjects viewed the display (diameter of 31 cm, horizontal visual angle of 52°, vertical visual angle of 20°; resolution = 1024 × 768 pixels, pixel size = 0.35 mm) via a mirror mounted on the head coil from a total distance of approximately 30 cm. There were four conditions, presented in a blocked design with blocks lasting 21 s (plus 3 s for instruction texts), and an interleaved baseline condition lasting 12 s. In every condition (except baseline), the stimulus display (Fig. 1) consisted of a white and a black circle (width = 3.7°, height = 3.7°, r = 28 pixels) that appeared at random coordinates and a centrally placed square (width = 2,1°, height = 2.1°, r = 28 pixels, a = 16 pixels) with a tilt of 45°. The circles had a minimum distance of 100 pixels (i.e., 6.7°) and a mean distance of 252 ± 13 pixels (i.e., 16.4 ± 0.9°) per block per subject, and did not occur in the central fixation field (defined as the 40 pixels [i.e., 2.7°] around the central fixation aid) to ensure that the fixation aid or the circles did not interfere with each other. The maximum distance of the two circles limited by the screen properties and the head coil was 707 pixels (39.5°). The central fixation aid was also used to provide directional information because two adjacent sides of the square were displayed in bold, rendering an arrow pointing either up, down, left, or right. In all four conditions, the positions of the circles and the direction of the central fixation arrow were randomized for each trial.

In conditions 1 and 2, a complex visuomotor coordinate transformation task involving goal-directed precision movements had to be performed by the subjects using the joystick ("transitive" movements). Conditions 3 and 4 served as visuomotor control conditions for conditions 1 and 2, and did not require complex, ongoing coordinate transformation processes for precisely aiming at visual targets but a rather simple transformation of the directional meaning of the centrally presented cue ("intransitive" movements). The movements associated with the use of the joystick consisted of rotation and translation of the right wrist and the forearm (pronation and supination in cubital joint), and to a small degree rotation in the shoulder joint while the finger rested on the shaft of the joystick. The joystick was not visible for the subjects during the experiment.

In condition 1 (C1, Fig. 1), subjects used the MR joystick with their right hand to guide a black square (width = 2.0°, height = 2.0°, a = 30 pixels) from a white circle (starting point) to a black circle (target) while maintaining central fixation. Subjects were instructed to ignore the centrally presented cue that was noninformative in these trials. A trial was ended as soon as the square reached the target points ±70 pixels (i.e., 4.7°, this

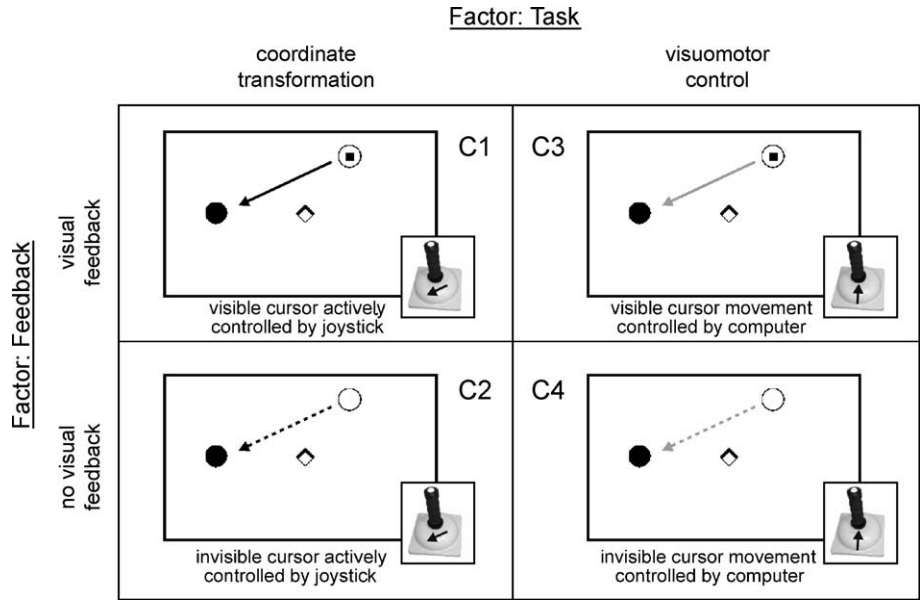

Fig. 1. Study design and conditions. The experiment consisted of four conditions, all involving the use of a joystick. In the experimental conditions of interest involving permanent visuomotor coordinate transformation (C1 and C2), subjects were asked to guide a square (visible in C1, not visible in C2) from a white to a black circle while fixating the fixation aid (arrow pointing either forward, backward, left, or right; here: forward) in the center. The trial was ended as soon as the square reached the target coordinates (pathway here schematically shown as long black arrow, dashed for "invisible square" in C2), and a new trial began with new random positions for the coordinates of the circles and new direction (forward, backward, left, or right) of the central fixation arrow. In the visuomotor control conditions (C3, C4), the positions of the circles had to be ignored, and subjects were instructed to move the joystick in the direction indicated by the central fixation arrow (here: forward). As soon as the correct movement was performed, a black square (C3) automatically moved (here schematically indicated as gray arrow) with constant velocity (adjusted to the mean velocity from C1 and C2) from the white to the black circle to compensate for the visual movement stimulation of C1. In C4, the square was not visible for the subjects. A trial was ended when the (visible/not visible) square hit the black circle. Hence, C3 was the control condition for C1, C4 for C2.

criterion was introduced according to the results of pre-experimental task evaluations; see below) or if the trial exceeded a duration of more than 3 s. Then, a white screen was shown for 1.5 s, and a new trial started with new, random circle positions and arrow directions.

Condition 2 (C2, Fig. 1) was similar to condition 1 but with the crucial difference that the spot guided by the subjects was hidden throughout the whole trial. Thus, subjects had no direct visual movement feedback and had to rely on proprioceptive information and visuomotor imagery. Again, the trial was ended as soon as the spot reached the target coordinates ± 80 pixels (i.e., 5.3°, this criterion was introduced according to the results of the pre-experimental task evaluations; see below) or if the duration of the trial was longer than 3 s.

In condition 3 (C3, Fig. 1), subjects were instructed to ignore the black (target) and white circles (starting point). Rather, subjects were asked to move the joystick in the direction of the now informative central cue. Therefore, a visual cue had to be transformed into a motor action but no transformation of spatial coordinates was necessary. As soon and as long as the correct joystick movement was performed, a black square (as described for condition 1) automatically moved from the white (starting point) to the black spot (target). This feature was introduced to provide equal visual stimulation between C3 and C1 because C3 served as visuomotor control condition for C1. However, no precision movements for reaching the target area, online control, or adjustments of the joystick movements were necessary in C3 (unlike in C1). The velocity (8 pixels [0.53°] per frame, i.e., 17 ms, on x-axis) matched the mean cursor velocities in conditions 1 and 2 as determined in the pre-experimental task evaluations (see below). As soon as the black square reached the target coordinates ± 70 pixels (4.7°), the trial was ended, and a white screen appeared for 1.5 s before the next trial started with new circle positions and arrow directions.

Condition 4 (C4, Fig. 1) was similar to condition 3, but this time the cursor moving to the target circle was invisible (like in condition 2). Accordingly, C4 served as control condition for C2, and again, as in C3, no precision movements for reaching the target area, online control, or adjustments of the joystick movements were needed (unlike in C2). The trial was ended when the cursor hit the target coordinates ± 80 pixels (5.3°) as in C2. Like in the other conditions, a white screen appeared before the next trial with random coordinates for the circles and a new arrow direction.

Subjects were instructed to fixate the central fixation aid during all conditions. Before each condition, a short text was presented for 3 s that instructed the subjects for the upcoming task.

Pre-experimental task evaluation and training

Before MR scanning, all experimental conditions were tested on six subjects (which did not participate in the MR experiment) for evaluation of the task design and to obtain feasible experimental parameters. After a training session of 8 min outside the scanner, reaction times, the ability to maintain fixation, and the performance using the joystick all reached a steady state. As outlined above, subjects only had to reach a certain area around the target coordinate for a successful completion of a given trial to match overall task difficulty. The size of this area (70×70 pixels in the trials with a visible

movement; 80 × 80 pixels in the trials when the cursor was hidden) was chosen as the best trade-off between task difficulty and a reasonable number and duration of trials within one block of trials. The bigger size of the target field in C2 (80 × 80 pixels) led to an approximately equal mean number of trials per block (i.e., 7) as performed in C1. This criterion ensured a comparable motor output across C1 and C2, although reaching the target under pure proprioceptive feedback in C2 is likely to have stressed aspects of motor attention and ongoing monitoring demands. Likewise, the velocity of the automatically moving cursor in conditions 3 and 4 was calculated for the MR experiment based upon the mean velocity of the joystick movements in conditions 1 and 2 to ensure a comparable stimulation and number of trials across the conditions of interest (C1 and C2) and the control conditions (C3 and C4).

All subjects participating in the fMRI study were trained twice, once outside the scanner, once in the scanner before starting the experiment, to ensure steady-state task performance during the fMRI experiment.

Functional magnetic resonance imaging (fMRI) and scanning paradigm

A Siemens Sonata 1.5-T whole body scanner with echo planar imaging (EPI) capability was used for the acquisition of functional MR images. Standard sequence parameters were used: Gradient-echo EPI, TE = 66 ms, TR = 3020 ms, flip angle = 90°, 30 axial slices of 4 mm thickness, 0.4 interslice gap, matrix = 64 × 64, field of view (FOV) = 200 mm, in-plane resolution = 3.125 × 3.125 mm. The 30 slices covered the brain from the vertex to upper parts of the cerebellum and were parallel to the anterior and the posterior commissure (AC–PC line) as determined by a midsagittal scout image. For all subjects, additional high-resolution anatomical images were acquired using the 3D MP-RAGE (magnetization-prepared, rapid acquisition gradient echo) sequence with the following parameters: TE = 3.93 ms, TR = 2200 ms, flip angle = 15°, inversion time (TI) = 1200 ms, 128 sagittal slices of 1.5 mm thickness, matrix = 200 × 256, FOV = 256 mm, in-plane resolution = 1.4 × 1.0 mm.

Each fMRI time series consisted of 145 images preceded by three dummy images allowing the MR scanner to reach a steady state. Each of the four time series per subject comprised 12 cycles of a 21-s (7 × TR) activation period (four conditions, three repetitions), each preceded by a 3-s (1 × TR) instruction text, and each followed by a 12-s baseline period (4 × TR). At the end of each of run, subjects were shown an "end" text (1 × TR). The order of conditions was counterbalanced between time series and between subjects.

Eye movement recording and analysis

The eye movements of each subject were monitored and recorded using an infrared video-based eye tracking device (ASL 504, fitted with a long-distance optics module; Applied Science Laboratories, Bedford, MA, USA). Due to technical problems, only data from 9 of the 11 subjects could be used for further analysis. However, the online monitor control of the eye movements of the two missing subjects showed an almost perfect fixation performance during the activation blocks. We analyzed the duration of fixation in a square (visual angle = 2°) around the central fixation aid. An analysis of variance (ANOVA) was used for testing for differential eye movements between the four conditions.

Image processing

All calculations and image manipulations were performed on UNIX workstations (SUN Microsystems Computers, CA/USA) using MATLAB 5 (The Mathworks Inc., Natick, MA/USA) and SPM99 (Statistical Parametric Mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). SPM was used for image realignment, image normalization (using the MNI template), smoothing, and to create statistical maps of significant regional BOLD (blood oxygen level dependent) response changes.

Transformed functional data were smoothed with a Gaussian kernel using 6 mm (full width half maximum, FWHM) for single-subject analyses and 10 mm for group analysis to meet the statistical requirements of the theory of Gaussian fields presupposed by the General Linear Model employed in SPM and to compensate for interindividual variability in macro- and micro-anatomical structures across subjects.

Statistical analysis

Following spatial normalization and smoothing, statistical analysis was performed. Global means were normalized by proportional scaling and box-car vectors for each condition (i.e., each block of trials) were convolved with the hemodynamic response function (Friston et al., 1995b). Movement parameters as assessed by the realignment algorithm were used as additional regressors in the single subject analysis (first level analysis) to control for movement effects, for example, resulting from the use of the MR joystick.

The experimental conditions were then compared between subjects (n = 11), thereby effecting a random effects model, allowing inference to the general population. Linear contrasts were applied on the parameter estimates for the experimental conditions resulting in a one-sample t statistic for each voxel. These t statistics were transformed to Z values and subsequently interpreted by referring to the probabilistic behavior of Gaussian random fields. Voxels were identified as significant only if their t values passed a height threshold of $t = 4.14$ ($P < 0.001$, uncorrected). Correction for multiple comparisons was then applied on the cluster level ($P < 0.05$).

Additionally, because our a priori hypothesis predicted activations associated with visuomotor coordinate transformation within IPS, we performed an additional ROI analysis (small volume correction (SVC); Worsley et al., 1996) on the left and right intraparietal sulcus to correct the local maxima also for multiple comparisons on the voxel level. The search volume (sphere of 40 mm diameter) was centered upon either intraparietal sulcus (stereotaxic coordinates: ±30/−50/50) based on the anatomical data given by the atlas of Ono et al. (1990).

Localization of activations

The stereotaxic coordinates of the pixels of local maxima were determined within areas of significant relative activity change associated with the different tasks. The anatomical localization was assessed by superimposition of significant activation clusters with the group's mean MR image composed of the subject's individual

MR data sets that have been normalized and transformed into standard MNI stereotaxic space (Friston et al., 1995a).

Results

Task performance

The mean number of trials per block per subject ($n = 11$) for the coordinate transformation conditions (C1, C2) was $n = 6.7$ (standard deviation [SD] = 0.8; mean trial duration (mDur) = 1313 ± 465 ms), and for the control conditions (C3, C4) $n = 6.9$ (SD = 0.7; mDur = 1208 ± 237 ms). There was no statistically significant difference in the numbers of trials ($P = 0.47$) or trial duration ($P = 0.37$) between the coordinate transformation conditions (C1, C2) and the visuomotor control conditions (C3, C4). Furthermore, no significant increase of task performance ($P = 0.79$) or reaction time ($P = 0.28$) as a function of time (learning effects) was observed during scanning because subjects had been trained before the scanning sessions. There was no statistical significant difference ($P = 0.84$) in the fixation performance/amount of eye movements between conditions (fixation performances within a ROI [visual angle = 2°] covering the central fixation aid in all four conditions: C1: 96 ± 4%, C2: 96 ± 3%, C3: 97 ± 3%, C4: 96 ± 4%). The data show that there were no significant differences in eye movements across the conditions and that subjects were able to maintain fixation.

Main effect of task: coordinate transformation vs. control

The critical contrast (C1 + C2 > C3 + C4) for isolating areas specifically involved in complex visuomotor coordinate transformations and online control of hand movements revealed a significant cluster of increased neural activity ($P < 0.05$, corrected for multiple comparisons on the cluster level; voxel level: $P_u < 0.001$) centered upon the intraparietal sulcus bilaterally with a stronger activation in the left hemisphere extending onto the free cortical surface (Fig. 2A). No other significant activation was observed. Additionally, because our a priori hypothesis predicted the involvement of the medial intraparietal cortex in visuomotor coordinate transformation, we also performed a correction on the voxel level applying a small volume correction (SVC; Worsley et al., 1996) upon the intraparietal sulcus (search volume: 40 mm sphere at the center of IPS [±30/−50/50]; see Materials and methods). The local maxima of the two significant clusters in the left and right hemisphere (stereotaxic coordinates left: −28/−50/+52 [$T = 9.48$]; right: +28/−56/+50 [$T = 7.55$]) survived SVC correction ($P_{SVC} < 0.05$, corrected). Superimposition of functional and anatomical images of the same group of subjects normalized to the same stereotaxic MNI reference space (Friston et al., 1995a) demonstrated that the local maxima of the observed activations (see Fig. 2B: red voxels at $P_{SVC} < 0.05$, corrected on the voxel level, $t > 6.7$) lay as hypothesized on the medial bank of the posterior part of IPS (Fig. 2C + D) and were embedded in extended areas of activation in the depth of either IPS (see Fig. 2B: yellow voxels at $P < 0.05$, corrected on the cluster level, $P_u < 0.001$), covering predominantly the medial wall of IPS.

The plots of the relative BOLD signal changes in the local main maxima of either side (Fig. 3) illustrate that both conditions drawing specifically upon complex visuomotor coordinate transformation processes and precision movements toward targets (C1, C2) elicited a significantly stronger activation in MIP than the visuomotor control conditions (C3, C4). There was no statistical difference between C1 and C2 on either IPS, indicating that the differential stress on visuomotor transformation processes in C2 (and a putative greater reliance on efference copy information resulting from the absence of visual feedback) did not alter the BOLD signal observed. That the BOLD responses were generally more prominent for the left than for the right IPS, especially for the conditions relying on nonvisual (i.e., proprioceptive) feedback information (C2, C4), most likely reflects that subjects moved the joystick with their right (contralateral) hand.

To assess whether the activations observed are part of an attentional network or part of the neural system supporting eye movements (or fixation), a post hoc analysis was applied where the statistical threshold was reduced. However, at uncorrected values ($P < 0.001$), only scattered spots of small activations were observed in frontal insular cortex (−32/22/06; 36/22/04), right middle frontal gyrus (32/02/50), anterior cingulate cortex (8/18/38), right supramarginal (48/−38/46), left occipitoparietal (−32/−78/28), left occipitotemporal (−44/−64/−02), and left cerebellar areas (−24/−68/−28). Specifically, there was no activation in the frontal eye fields or in the supplementary frontal eye fields.

Interaction of main factors

No significant interaction between the two factors (task, feedback) was observed ($P < 0.05$, corrected).

Differential effects of visual movement control vs. proprioceptive movement control

Testing for differences between the two main tasks drawing upon complex visuomotor transformation processes to guide the square using the joystick (C1 and C2) revealed the areas that showed differential activations during coordinate transformation (and hand movements) depending upon whether there was a visual movement feedback or not.

C1 vs. C2

Visual movement feedback relative to predominantly proprioceptive movement control (C1 > C2) showed a significant differential activation in the ascending branch of the right inferior temporal sulcus (ITS) (44/−62/14; T = 13.52; $P < 0.05$, corrected; Fig. 4). At a lower statistical threshold ($P < 0.001$, uncorrected), also the cortex around left ITS was active (−42/−60/0; $T = 6.48$). These activations are likely to correspond to the V5/MT complex (Watson et al., 1993; Zeki et al., 1991) known to be involved in the analysis of moving stimuli. There was no differential activation of the intraparietal sulcus.

C2 vs. C1

Guiding the joystick under predominantly proprioceptive movement control (no visual feedback) relative to when the subjects had a visual feedback (C2 > C1) differentially activated the left sensorimotor areas (contralateral to the hand used) including the motor cortex (−22/−12/60, $T = 6.01$), SI (−26/−40/62; $T = 6.13$), and SII (−40/−26/16; $T = 6.36$) ($P < 0.05$, corrected; Fig. 5). The activation cluster in the central region also extended to the cortex posterior to the postcentral sulcus onto the superior parietal lobule (−26/−36/74; $T = 6.92$). This region might correspond to area 7A or lateral area 5 that in humans usually abuts area 2 at its caudal border near the interhemispheric fissure (Brodmann, 1909; Grefkes

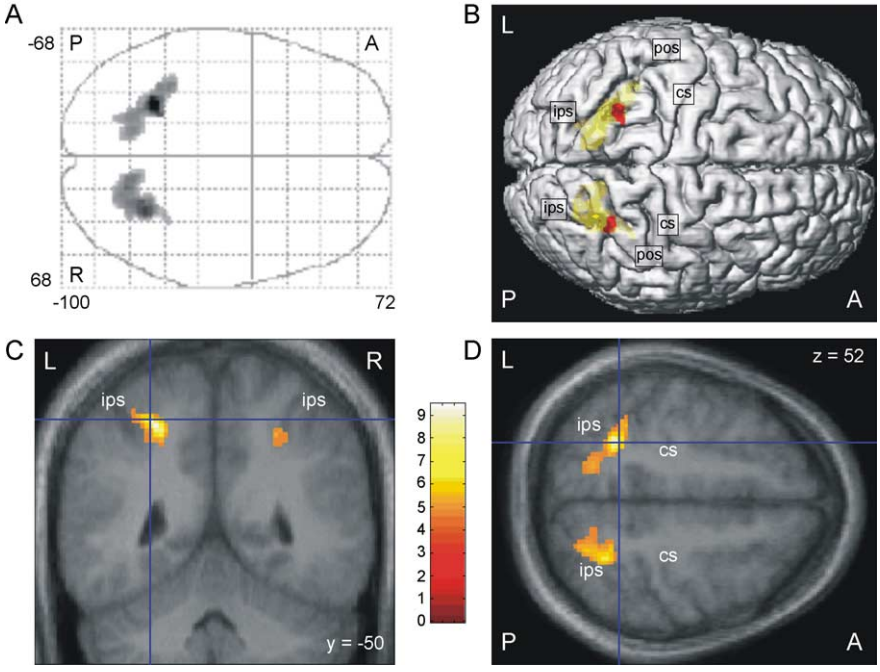

Fig. 2. Visuomotor coordinate transformation in human medial IPS. Cortical activations (main effect) associated with visuomotor coordinate transformation (C1 + C2) vs. visuomotor control (C3 + C4). A bilateral activation cluster in the left and right intraparietal cortex survives the statistical threshold ($P < 0.05$, corrected for multiple comparisons at cluster level; voxel-level: $P < 0.001$, uncorrected) as illustrated by the SPM glass brain (A). The projection (B) on a single subject surface rendering (subject 11) shows an activation of the medial intraparietal cortex. The local maxima at −28/−50/52 ($Z = 4.70$) and 28/−56/50 ($Z = 4.27$) survive correction for multiple comparisons ($P < 0.05$, $t > 6.7$; red voxels) on voxel level after applying a small volume correction (SVC, Worsley et al., 1996) The significant cluster ($P < 0.05$, corrected on a cluster level for the whole brain) is displayed in yellow. Note that the true position of the projected voxels is found in the medial wall of either intraparietal sulcus as demonstrated on the sections in C and D, and not on the surface. (C) Coronal section ($y = -50$) and (D) horizontal section ($z = 52$) through the group's normalized mean anatomical MR image. Activation foci in human medial IPS are more pronounced in the left than in the right hemisphere (because subjects used their right hand). L, left; R, right, A, anterior; P, posterior; cs, central sulcus; pos, postcentral sulcus; ips, intraparietal sulcus.

et al., 2001, Scheperjans et al., 2002). There was no activation of either IPS even at lower statistical threshold ($P < 0.001$, uncorrected), although task difficulty was higher in C2 than in C1 due to the missing visual movement feedback.

C1 vs. C3, C2 vs. C4

We finally compared each task of interest with its respective control condition separately (C1 > C3; C2 > C4). Now, the IPS activations under visual movement feedback (C1 > C3) were found more posterior and medial (−14/−62/56, $T = 7.17$; 16/−62/56, $T = 5.62$, Fig. 6A) compared to the condition where no visual feedback of the joystick movements was present (C2 > C4: −28/−58/66, $T = 5.16$; 30/−56/50, $T = 4.97$, Fig. 6B). In other words, movement control based on predominantly somatosensory (proprioceptive) information activated more anterior parts of medial IPS while visually controlled movements enhanced activity in

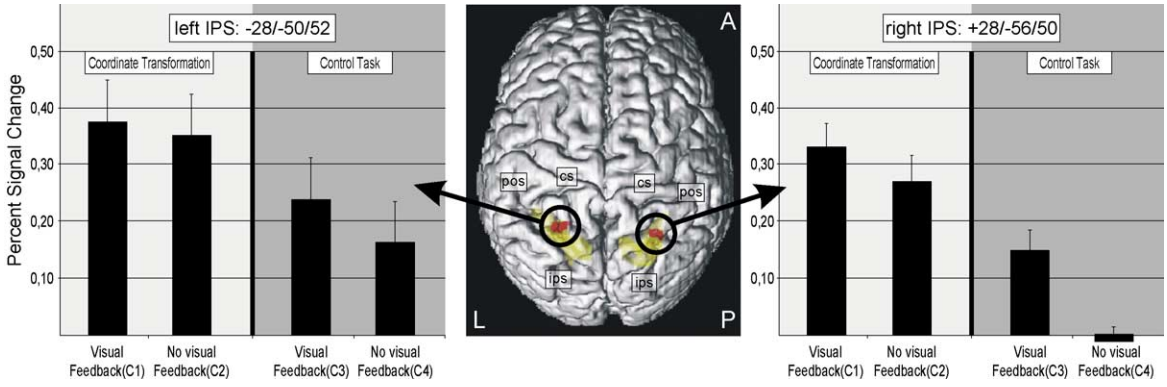

Fig. 3. Relative signal changes of the BOLD responses in the local maxima of either IPS. The plots of the BOLD signal for the main maxima as shown in Fig. 2 (C1 + C2 > C3 + C4) confirm that the human medial IPS is significantly more active during visuomotor coordinate transformation (C1, C2) than during the visuomotor control tasks (C3, C4). In the main maxima of either IPS, there is no statistical significant difference in neural activation between reaching the target coordinates under visual (C1) or without visual (C2) movement control ($P < 0.001$, uncorrected), although visuomotor attentional demands are higher in C2 than in C1. Activations are more prominent in left than in right IPS. Error bars indicate SEM.

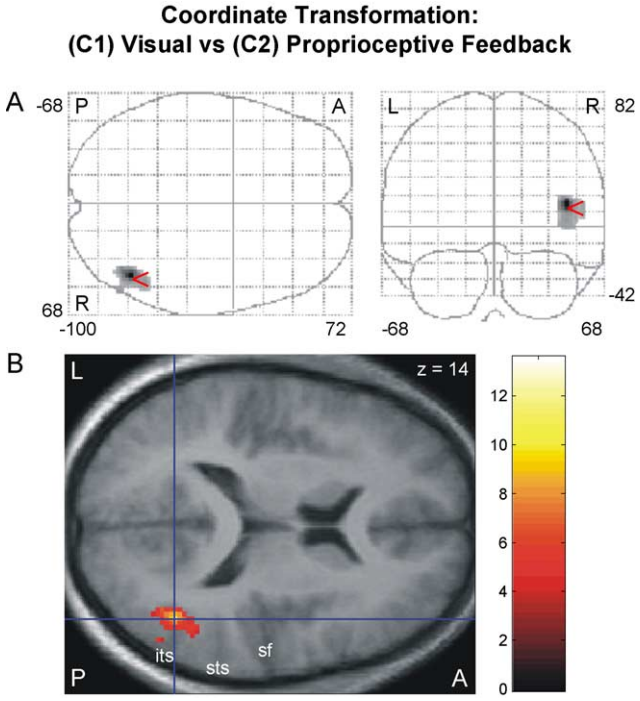

Fig. 4. Increased neural activity while guiding the joystick under visual feedback. When testing for additional activations during coordinate transformation and visual movement control relative to proprioceptive control (C1 > C2), the only activation surviving correction for multiple comparisons is the right occipitotemporal cortex (44/−62/14; $T = 13.52$; $P < 0.05$, corrected on the cluster level) as illustrated by the SPM glass brain (A). At uncorrected values, the corresponding activation on the left hemisphere becomes significant (−42/−60/0; $T = 6.48$; $P < 0.001$, uncorrected). (B) Superimposition on the group's mean anatomical MR demonstrates that the activation is found on the cortex lining the ascending branch of inferior temporal sulcus probably corresponding to the V5/MT+ region (Watson et al., 1993). its, inferior temporal sulcus; sts, superior temporal sulcus; sf, Sylvian fissure; L, left; R, right; A, anterior; P, posterior.

more posterior parts of medial IPS. This sort of topographical dissociation has also been observed for neurons in the medial bank of macaque IPS (Colby and Duhamel, 1991; Colby and Goldberg, 1999). Note, the BOLD responses in the two main maxima (Fig. 6A + B), however, demonstrate that there were no statistical differences between the two tasks of interest (C1, C2) or between the two control conditions (C3, C4), indicating that these topographical effects were too subtle to be detected in direct comparisons or in the interaction contrasts.

Discussion

The aim of the present study was to assess whether the human medial intraparietal cortex subserves visuomotor coordinate transformation. We accordingly designed an fMRI paradigm from experiments used for the characterization of macaque area MIP (Eskandar and Assad, 1999, 2002). The data show that an area in the medial aspect of the left and right human intraparietal sulcus is crucially involved in the transformation of visual coordinate information into a sensorimotor reference frame while performing target-oriented visually and proprioceptively guided hand–arm movements. As described for macaque medial IPS (Colby and Duhamel, 1991), we found hints for a topographical dissociation of neural activity related to visual and nonvisual (somatosensory) movement control. Differences in task demands resulting from presence or absence of a visual movement feedback during coordinate transformation did not significantly influence activity in the medial intraparietal cortex but rather differentially recruited additional and modality specific areas like V5/MT for visual information processing and sensorimotor areas for proprioceptive movement control, respectively.

Areas in the intraparietal sulcus of macaques

The intraparietal sulcus of macaques consists of several areas particularly concerned with the perception of peripersonal space, spatial object processing, movement planning, and execution (Cavada, 2001): Area AIP (anterior intraparietal area) in the lateral wall of anterior IPS is specifically concerned with polymodal processing of 3D object features, hand shaping, and visually guided grasp movements (Murata et al., 2000; Sakata et al., 1995). Neurons in area VIP (ventral intraparietal area), situated in the fundus of the IPS, specifically discharge upon (polymodal) stimuli conveying motion information (Bremmer et al., 1997, 2001b; Colby et al., 1993). Area LIP (lateral intraparietal area) in the lateral wall of posterior IPS is involved in saccadic eye movements and visuospatial attention (Andersen, 1995; Snyder et al., 2000).

Area MIP

Area MIP (medial intraparietal area)—which is the area of interest in the present study—is situated in the medial wall of posterior IPS and is crucially involved in planning and execution of reaching movements (Colby, 1998; Colby et al., 1988). Together with other areas of the macaque superior parietal lobule (e.g., area PO/V6A), it constitutes the parietal reach region (PRR; Cohen and Andersen, 2002). The electrophysiological response properties of MIP neurons change depending on their topographical position from somatosensory dominated neurons found dorsally, to bimodal neurons further down the IPS that are responsive to both somatosensory and visual stimuli, and visually dominated neurons deep in the posterior portion of the medial IPS (Colby and Duhamel, 1991). Neurons in MIP specifically discharge dependent on the direction of hand movements before and after movement onset (Eskandar and Assad, 1999). Target–stimulus-related responses of MIP neurons on forthcoming reaching movements have been interpreted as activity related to movement planning (Eskandar and Assad, 1999; Johnson et al., 1996; Snyder et al., 1997). Furthermore, MIP is supposed to transform sensory (e.g., visual, auditory) target information into a common eye-centered reference frame that can be "read out" by the motor system independent of the type of action planned (Cohen and Andersen, 2000, 2002). This coordinate transformation computed in MIP facilitates eye–hand coordination. By integrating hand-related directional activity with goal-directed information, MIP may also contribute to monitoring ongoing movements (Eskandar and Assad, 2002).

Cognitive components of the paradigm

The present study addresses several key functions of this area. However, activating area MIP in a visuomotor coordinate transformation task using whole-arm reaching movements (as used in many macaque studies) is not feasible in an MR scanner environ-

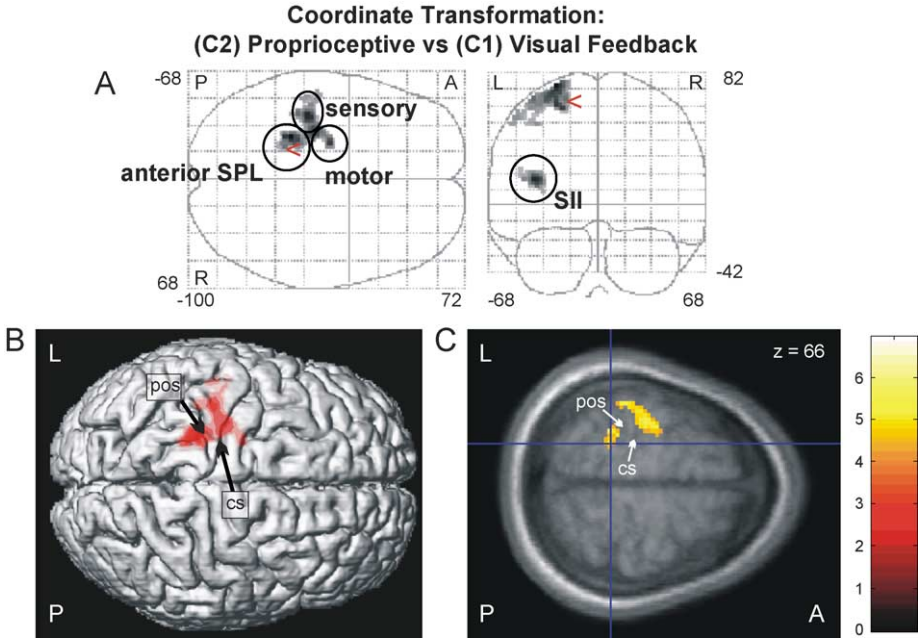

Fig. 5. Increased neural activity while guiding the joystick under proprioceptive control. When testing for additional neural activation due to pure proprioceptive movement control relative to visual movement feedback during visuomotor coordinate transformation (C2 > C1), various sensorimotor regions become active. These activations lie in the central region and parietal operculum (SII, −26/−36/74; $T = 6.92$) as shown on the SPM glass brain (A; $P < 0.05$, corrected). The main maxima of the cluster in the central region are localized in the precentral gyrus (motor cortex, −22/−12/60, $T = 6.01$), postcentral gyrus (somatosensory cortex, −26/−40/62; $T = 6.13$), and in the cortex posterior to the postcentral sulcus (anterior SPL, −26/−36/74; $T = 6.92$), as also shown on the 3D reconstruction of a single subject brain (B). The superimposition of the latter activation with the group's mean anatomical MR confirms the position posterior to the postcentral sulcus near the interhemispheric fissure (C). Because in the human brain area 2 is always located on the anterior wall of the postcentral sulcus (Grefkes et al., 2001), this activation may correspond to area 5 known to be involved in proprioceptive movement control and visuomotor coordinate transformation (Buneo et al., 2002; Graziano and Tayler, 2000). Note that there is no significant increase in IPS activity due to the increased attentional demands, even at uncorrected values ($P < 0.001$). cs, central sulcus; pos, postcentral sulcus; SPL, superior parietal lobule; L, left; R, right; A, anterior; P, posterior.

ment. We here, therefore, used a metal-free MR joystick as a tool for a visuomotor transformation task conveying hand/arm movements that was adopted from neurophysiological experiments designed to study macaque MIP neurons (Eskandar and Assad, 1999, 2002). As a result of a successful transformation of visual target coordinates (i.e., the black circle, Fig. 1) into a representation appropriate for the motor system (i.e., "reaching" the target coordinates with the black spot using the joystick), the correct movement trajectories could be executed by the subject without inducing significant motion artifacts.

One might argue that the control conditions also required transformation processes as subjects had to assign a (simple) motor action to a (simple) visual cue. Furthermore, these (albeit very simple) transformations had to be learned—a process that has been associated with activation in the IPS region (Clower et al., 1996). However, the crucial difference between C1/C2 (our conditions of interest) and C3/C4 (our control conditions) is that the former conditions contain a "reaching-the-target" component that requires a successful ongoing computation and transformation of spatial coordinates for precisely driving the hand to the target. Neural mechanisms providing online control, adjustment, and redirection of movements were therefore particularly needed in conditions C1 and C2. In other words, subjects had to assess the location of the circles (targets), and subsequently to compute how to reach the target coordinates relative to the start position of the joystick. Finally, the movement was performed under visual or solely proprioceptive control.

Although the control task also necessitates transformation of a visual cue into a motor program, it lacks a visuospatial coordinate transformation of the target to be reached. Furthermore, it does not require the precision of the final positioning of the movement as in conditions C1 and C2. Thus, because the computer program ensured the correct placing of the cursor, no online control and movement adjustments were needed in C3 and C4 for guiding the cursor to the target area. Accordingly, during the control tasks, subjects did neither compute spatial coordinates nor any reaching/approaching information but rather performed a stereotyped joystick movement (left, right, forward, backward) as being instructed by the central cue (i.e., not goal directed, "intransitive" movements).

Finally, our finding of increased neural activity in medial IPS in conditions C1 and C2 is also consistent with previous lesion and transcranial magnetic stimulation (TMS) studies that have associated IPS/SPL with the on-line control of movements (e.g., Desmurget et al., 1999; Pisella et al., 2000). These processes are also needed for computing objected-centered (transitive) reaching movements (Kalaska et al., 2003).

Attention and superior parietal cortex

Although we controlled for the sensory and motor loads across task and control conditions (for example, the number of trials per condition was approximately equal), it is, however, difficult to control for the putative differential attentional load because

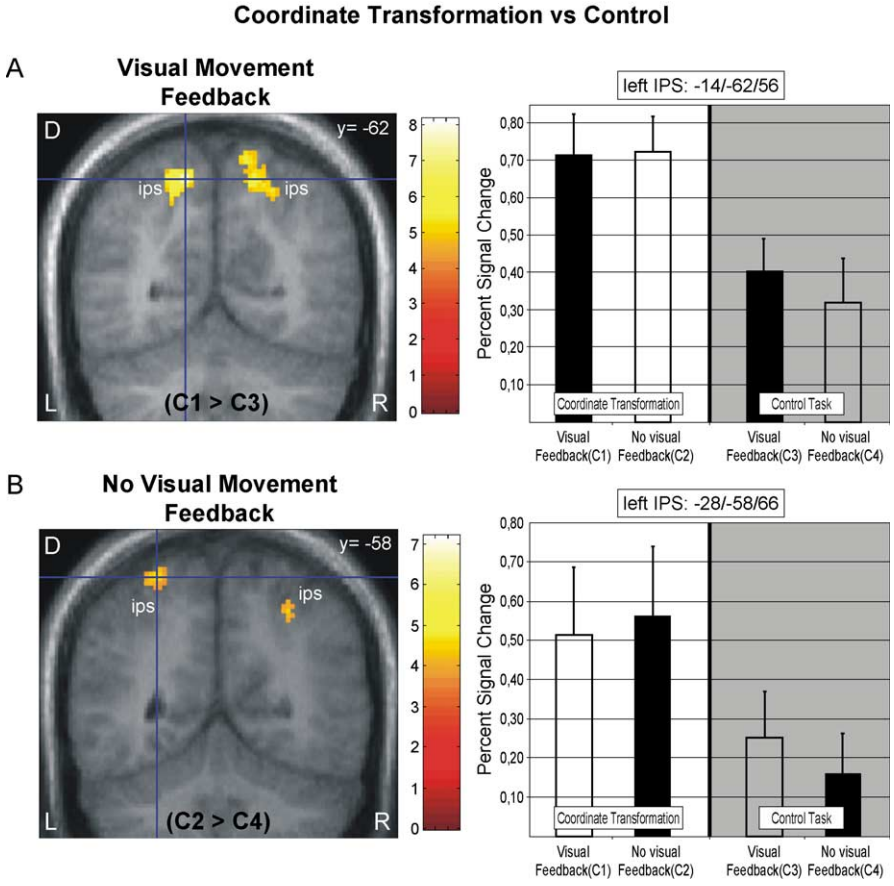

Fig. 6. Functional topography of IPS activations dependent upon the modality of feedback. Neural activity in medial intraparietal cortex associated with coordinate transformation and visual movement feedback relative to the low level control conditions ($P < 0.001$, uncorrected). When subjects experienced a permanent visual update of the effect of their joystick movements while reaching the target objects on the screen, activation in medial IPS (C1 > C3) was found more posterior and medial (A) compared to the condition (C2 > 4) when subjects had to rely only on proprioceptive information for guiding the joystick because visual feedback was absent (B). A similar dissociation for visual and somatosensory responsive neurons has also been described for macaque medial intraparietal cortex (Colby and Duhamel, 1991). As shown in both bar charts representing the main maximum of activation in left IPS, there are, however, no significant differences in neural activity between C1 and C2 or between C3 and C4. L, left; R, right; D, dorsal. Error bars: SEM.

transformation of coordinates and active reaches may require more attention than simple intransitive movements. Therefore, attention is a possible confound that has to be carefully considered when interpreting the activations.

Differences in attentional load or switching between tasks have been shown to involve the superior parietal cortex (Corbetta et al., 1993; Fink et al., 2000; Gurd et al., 2002). Shifts in visuospatial attention are known to activate IPS (Corbetta et al., 1998; Shulman et al., 2003). The medial intraparietal cortex has been demonstrated to become more active when switching between two visuomotor tasks (Rushworth et al., 2001). Accordingly, although no switching of task strategy was necessary within any of the four conditions, the increased BOLD responses in the medial intraparietal cortex (Fig. 3) could at least in principle result from an increased attentional load during C1 and C2 (compared to the control conditions). However, Culham et al. (2001) demonstrated that areas directly involved in attentional processing show steadily increasing activation with increasing attentional demands, whereas areas mediating task-related functions remain unaffected. Although we observed an increase of the BOLD response for C1 and C2 relative to the control conditions, we did not observe any further increase of neural activity in C2 (which further enhanced attentional demands due to the lack of any visual feedback) compared to C1. Rather, areas known to be involved in sensorimotor functions showed greater activity to cope with the increased transformation demands resulting from the absence of visual movement feedback (Fig. 5). The activation observed in rostral superior parietal cortex close to the interhemispheric fissure may correspond to area 5 (Brodmann, 1909; Scheperjans et al., 2002), which in macaques is essential for monitoring arm movements in space in relation to proprioceptive information and which also mediates coordinate transformation (Buneo et al., 2002; Graziano and Tayler, 2000). Area 5 also encodes efference copy information from motor areas (Rushworth et al., 1997), and a greater reliance on efference copy information may have been necessary, in particular in condition C2, for controlling the joystick after the removal of the visual feedback. Thus, the absence of a further significant increase in neural activity due to elevated attentional task demands provides support for our interpretation that the activity observed in medial IPS indeed reflects visuomotor coordinate transformation processes. Furthermore, motor attention rather activates the left inferior parietal cortex (Deiber et al., 1991; Rushworth et al., 2003).

Shifting visuospatial attention to peripheral stimuli while fixating is also known to activate a complex network of intraparietal, frontal (especially bilateral frontal eye fields, FEF), temporal (STS), and occipital areas (e.g., MT complex, lateral occipital cortex) (Corbetta et al., 1998). Although in the main tasks (C1, C2) attention had to be shifted to the peripherally displayed circles, none of the aforementioned areas was significantly activated except IPS (Fig. 2). A post hoc analysis confirmed this finding. Even at a lower statistical threshold ($P < 0.001$, uncorrected), the activation pattern did not match the network reported for shifting visuospatial attention from the center to periphery (Corbetta et al., 1998). Therefore, the absence of increased neural activation in all the other regions previously associated with shifting visuospatial attention (especially the missing activation of both FEFs) even at low statistical thresholds argues against a dominant influence of shifting attention from the center to the peripheral stimuli on the observed activations in medial intraparietal cortex.

Eye movements and superior parietal cortex

Planning of eye movements also requires coordinate transformation, and differences in eye movements across conditions may also activate human IPS, in particular area LIP (Andersen et al., 1998; Snyder et al., 1997). However, eye movement recordings in the scanner showed that subjects did not move their eyes differentially during the four conditions although planned but not executed saccades could also potentially account for bilateral activations in intraparietal sulcus. Yet, saccades and also the suppression of eye movements typically show strong bilateral activations of the frontal eye fields (Astafiev et al., 2003; Connolly et al., 2002; Corbetta et al., 1998; Cornelissen et al., 2002; Culham et al., 2001; Koyama et al., 2004; Paus, 1996; Shulman et al., 2003). In the present study, as mentioned above, such bilateral activations of the FEF were not detected even at uncorrected P values. Therefore, eye movement-related neural activity is unlikely to account for the observed activation pattern in medial intraparietal cortex during our visuomotor coordinate transformation tasks.

Coordinate transformation and superior parietal cortex

Previous studies support our results. For example, Chaminade and Decety (2002) found activations in the right intraparietal cortex (30/−50/50) close to the coordinates reported for the present study (28/−56/50) when subjects used a computer mouse to guide a blue circle to follow a red circle on a video screen. In another study, single pulse transcranial magnetic stimulation (TMS) in healthy subjects over left IPS caused disturbances in reaching movements in response to sudden changes of target locations (Desmurget et al., 1999). Simon et al. (2002) demonstrated that pointing to different locales on a video screen activated the superior parietal cortex and also an area in right medial intraparietal cortex (40/−40/60). Other studies, however, did not report involvement of medial IPS in pointing tasks. For example, Connolly et al. (2003) observed bilateral activation of the mesial parietal cortex (−1/−74/38) when subjects intended to point to a remembered location but not when they planned to perform a saccade. The authors suggested that this activation represented the human equivalent of the parietal reach region (PRR). Likewise, Astafiev et al. (2003) observed increased neural activity associated with preparation of pointing movements in the mesial parietal cortex extending into the precuneus and posterior cingulate cortex. The authors, however, were cautious to assign their activations to the putative human equivalent of the PRR because they studied finger-pointing movements (in humans) whereas monkey studies usually employ arm-reaching movements. This caveat is also valid for our paradigm with respect to true reaching movements.

Optic ataxia and visuomotor coordinate transformation

The significance of IPS for reaching movements can also be demonstrated in patients suffering from "optic ataxia" (Bálint, 1909). Such patients are impaired in performing visually guided arm reaches, grip formation, and prehension (Garcin et al., 1967; Jacobson et al., 1991; Jeannerod, 1986). Furthermore, these patients may have problems modifying reaching movements when the location of a visual target is altered during the movement (Pisella et al., 2000). Although some authors refer to this phenomenon as "visuomotor apraxia" (Classen et al., 1995), the praxis of a movement or movement sequence is not disturbed when optic–ataxic patients perform reaching movements with their eyes closed (Bálint, 1909; Battaglia-Mayer and Caminiti, 2002). Rather, optic ataxia seems to be a deficit in visuomotor coordinate transformation and online control of movements (Battaglia-Mayer and Caminiti, 2002), which is observed for either unilateral or bilateral lesions of the superior parietal lobule, especially when affecting the intraparietal sulcus (Perenin and Vighetto, 1988; Pisella et al., 2000). Because our data showed an involvement of medial IPS in visuomotor coordinate transformation processes and online control of hand movements, we suggest that optic ataxia may result from lesions causing damage to medial intraparietal cortex. Support for this hypothesis was recently demonstrated by Roy et al. (2004), who reported that a focal lesion restricted to the medial wall and fundus of IPS caused optic ataxia in a stroke patient. It should, however, be mentioned that functional recovery from reaching deficits after lesions to the superior parietal lobe is rapidly provided by locally networked areas reestablishing prelesional behavior even after bilateral lesions, so that lesions restricted to this region produce relatively small clinical deficits (Battaglini et al., 2002, 2003).

Functions of medial intraparietal cortex in humans

Taken together, the results of the present study provide evidence that the medial intraparietal cortex is involved in visuomotor coordinate transformation, and that this involvement is independent from the modality predominantly used to control hand movements. Lesion data from human patients underpin the significance of medial IPS for coordinate transformation and reaching movements. Therefore, it might seem reasonable to assign the activations observed in the present study to the human homologue of macaque area MIP.

However, there are some concerns for such a straightforward conclusion. As discussed above, there are studies demonstrating that medial IPS is also involved in attention processes (Corbetta et al., 1998) and control of saccades (Heide et al., 2001). In a recent fMRI study, Koyama et al. (2004) used an identical saccade task in humans and monkeys. While the monkeys activated the lateral intraparietal cortex (LIP), the corresponding activations in human IPS were found in the medial intraparietal cortex (−22/−62/60; +22/−62/60), posterior but close to the activations observed in the

present study for the putative MIP homologue (−28/−50/52; 28/−56/50). Although other authors localized human LIP on the lateral wall of IPS (e.g., Konen et al., 2004; Rushworth et al., 2001), the data of Koyama et al. cannot be neglected because they used identical tasks and identical methods (fMRI) to demonstrate homologue areas in humans and monkeys. Consequently, the functional anatomy of medial IPS—with area MIP and LIP both located on the medial bank of human IPS—would differ between human and macaques although the topography of the anterior portion of IPS comprising areas AIP and VIP is well conserved across both species (Binkofski et al., 1998; Bremmer et al., 2001a; Grefkes et al., 2002).

The topographical relationship of human MIP and LIP on medial IPS cannot be established from the present study (as our experiment was not designed to do so). In this context, however, one should keep in mind that even in the monkey the separation of the neural processes underlying arm and eye movements can be difficult. In macaques, the separation between arm and eye movement encoding in LIP and MIP is most apparent before the actual movement is made, and both areas are best dissociated in tasks where eye and hand movements are executed in opposite directions (Batista et al., 1999; Snyder et al., 1997, 2000). Furthermore, there is evidence that human oculomotor areas in IPS and FEF are also involved in pointing preparation and execution (Astafiev et al., 2003; Simon et al., 2002), which speaks against a strong functional distinction between macaque LIP and PRR (including MIP). Andersen and Buneo (2003) also emphasize the extremely similar coding strategies in PRR and LIP, suggesting that both areas are parts of a single network for the purpose of coordinating hand and eye movements.

Conclusions

Accordingly, for the present study, there are three possible conclusions with regards to MIP. First, the IPS activations demonstrated in the present study represent the homologue of macaque area MIP. Second, the activations associated with visuomotor coordinate transformation do not reflect the recruitment of human MIP but rather take place in human oculomotor areas comprising human LIP. However, no other activity associated with eye movements and attention (especially FEF) was observed (as discussed above), and the experiment was based on a paradigm known to activate macaque MIP neurons (Eskandar and Assad, 1999, 2002). The third possible conclusion is that human medial intraparietal cortex might function as a common site for coding spatial location of visual targets independent from the motor effector. Depending on the effector (eye, hand), different additional areas could be recruited for planning and performing the actual movement (e.g., FEF for saccades; sensorimotor cortex/area 5 for hand movements). Lesion in this area would then disturb such coordinate transformation and movement controlling processes, and hence result in optic ataxia (Roy et al., 2004). Further studies that test whether the human medial IPS subserves visuomotor coordinate transformation for both hand and eye movements (e.g., testing for common activations by a conjunction analysis in a coordinate transformation task involving saccades or manual responses) could also help to clarify the issue of the topographical relationship between human MIP and LIP. The present study, however, already indicates that a homologue area for monkey area MIP may also exist in human intraparietal cortex at a similar topographical position.

Acknowledgments

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