Neural Mechanisms Underlying Reaching for Remembered Targets Cued Kinesthetically or Visually in Left or Right Hemisphere

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Abstract: Reaching for a target involves integrative coordinate transformation processes between the representation of the target location, the sensorimotor information of limb of reach, and body space. Although right hemisphere dominance for visuospatial information processing is well established, corresponding right hemisphere dominance for kinesthetic spatial information processing remains to be demonstrated. We explored neural mechanisms of encoding target locations using ¹⁵O-butanol positron emission tomography (PET) in normal volunteers in a factorial experiment, where modality (visual/kinesthetic) and hemisphere of target presentation (left/right of midsagittal plane) were varied systematically. After target presentation, subjects reached to the encoded target location. PET data analysis using SPM99 showed increased neural activity ($P < 0.05$, corrected) associated with left hemisphere target presentation in right hemisphere areas (sensorimotor, anterior cingulate, insular, and temporo-occipital cortex) only. By contrast, right hemisphere target presentation activated bilateral temporo-occipital cortex, which extended into the right temporo-parietal cortex and left sensorimotor cortex. A significant interaction of hemisphere and modality of target presentation observed in right temporo-parietal cortex resulted from an increase in neural activity with kinesthetic target presentation in right hemisphere. The data support an important role for the right temporo-parietal area in visuospatial processing and suggest a specific role of the right hemisphere in kinesthetic spatial processing. *Hum. Brain Mapp.* 21:165–177, 2004. © 2004 Wiley-Liss, Inc.

Key words: hemispheric asymmetry; functional specialization; positron emission tomography; posterior parietal cortex; kinematics; functional imaging

INTRODUCTION

Reaching to grasp and pointing are sensorimotor performances investigated extensively in both macaques and humans [Jeannerod et al., 1995; Mountcastle, 1995]. Using functional imaging, the cortical networks involved have been described for tracking a moving target with the finger [Grafton et al., 1992], preparation for reaching [Decety et al., 1992], reaching [Binkofski et al., 1998; Grafton et al., 1996; Kertzman et al., 1997], pointing to targets with [Inoue et al., 1998] and without [Desmurget et al., 2001] visual feedback, visuomotor learning [Kawashima et al., 1995], imagination of movements [Binkofski et al., 2000; Decety et al., 1994;

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Figure 1.

Experimental setup. Subject positioned supine in the PET gantry with arms freely movable. OPTOTRAK 3020 system was used to acquire 3-D position data. The small red LED target was presented by a robot. Vision was regulated using electro-optic shutter-glasses (PLATO). The dotted line from shutter-glasses to mirror represents subject's requirement to focus on a fixation cross. Computers, EOG electrodes, IREDs, and cabling have been omitted to enhance clarity. All targets were presented within subject's reach.

Stephan et al., 1995], continuous goal-directed aiming [Winstein et al., 1997], bimanual coordination [Fink et al., 1999; Stephan et al., 1999], and perceptual coding of visual or somatic sensory stimuli with respect to body midline [Galati et al., 2001]. Taken together, these studies delineated a dorsal occipito-parieto-frontal network of areas involved in visuospatial analysis and visuomotor transformation in the human.

Clinical studies suggest that unilateral parietal damage may differentially affect action in space, thus implying hemispheric specialization for action and spatial processing. For example, apraxia is observed most often after lesions of the language-dominant hemisphere [Liepmann, 1920]. Conversely, the right hemisphere seems to be dominant for spatial attention and spatial information processing [Heilman and Van Den Abell, 1980], because right hemisphere lesions result preferentially in constructional apraxia, spatial disorientation, and hemi-neglect. Some aspects of these impairments go beyond mere visuospatial dysfunction, as they refer to the patient's ability to interact with the environment. The wealth of clinical information about visuospatial and visuomotor behavior contrasts with sparse data on the role of kinesthesia in directing a limb to a given target, particularly data on kinesthetic spatial information processing. Interestingly, kinesthetically guided movements can be carried out with precision equivalent to that of visually guided movements [Darling and Miller, 1993]. Likewise, lack of kinesthetic information caused by deafferentation grossly interferes with target-directed movements [Paillard and Brouchon, 1974; Rothwell et al., 1982; Sanes et al., 1985] and can be compensated for by vision. However, from lesion studies it is not yet apparent whether there is hemispheric specialization for kinesthetically guided movements. Furthermore, functional imaging studies have relatively ignored the topic of hemispace. This is surprising given the robust hemispatial differences in reaching, which are partly biomechanical and partly cognitive [Tipper et al., 2001].

We address the hypothesis that right temporo-parietal cortex (in analogy to its specific role for visuospatial processing) is specialized also for kinesthetic spatial informa-

tion processing by studying neural mechanisms underlying reaching to remembered targets. This issue is explored by studying the neural mechanisms underlying reaching to remembered targets in an experiment wherein the modality of target presentation (visual or kinesthetic) and the hemispace of target presentation (left or right of the midsagittal plane) are systematically varied.

SUBJECTS AND METHODS

Subjects

Nine healthy, right-handed volunteers (7 men, 2 women; age 22–28 years) with no history of neurological or psychiatric illness were recruited. The local ethics committee of the Heinrich Heine University, Düsseldorf, Germany, approved experimental protocols and procedures and permission to administer radioactivity was obtained from the responsible federal authorities. Written informed consent was obtained before participation. Handedness was assessed by a short questionnaire based on the Edinburgh inventory [Oldfield, 1971].

Experimental Design

The experimental design was factorial; the two factors were *modality* (visual or kinesthetic) and *hemispace* (left or right of subject's midsagittal plane) of target presentation. In a dimly lit room, subjects were positioned supine with their head in the positron emission tomography (PET) scanner and their arms supported but free to move in the horizontal and vertical direction (Fig. 1). In this position the fingers, wrists, and elbows were freely moveable; however, shoulder joint movements were limited to approximately 50 degrees shoulder flexion, 25 degrees shoulder abduction, and 25 degrees shoulder adduction, with full internal and external rotation. In all trials, subjects were instructed to focus on a central fixation aid (a 1 × 1-cm black cross on white background; presented by a projector) reflected by a mirror positioned so that the subject could comfortably view stimuli in the supine position and reach to the targets.

Figure 2.

Experimental design. **A:** Targets were presented visually or kinesthetically (factor 1: mode of target presentation) on right or left of subject's midsagittal plane (factor 2: hemisphere of target presentation). Visual conditions: targets were placed in a position within the subject's right (VR) or left (VL) hemisphere while vision was occluded using a spectacle mounted electro-optic shuttering device. Shutterglasses were opened and target location disclosed while subject maintained focus on a central fixation aid. After visual target presentation, shutters were closed and the target removed. In kinesthetic conditions, subject's vision was occluded at all times. Subject's right (KR) or left (KL) arm was guided to the target location and back to the starting position. After target presentation, in all conditions a tone cued subjects to reach to the remembered target location. Subjects were asked to place their fingertip such that it would touch the target if present, and instructed to hold this position for about one sec before returning to the starting position. Filled circles, target position; black cross, fixation point. Visual information regulation: open circles, full vision; closed circles, vision occluded. **B:** Relative timing of target presentation, movement execution, and target change for all conditions.

Target locations were presented to the subjects in four different conditions (Fig. 2A). In Condition 1, target locations were presented visually in right hemisphere, i.e., right of the subject's midsagittal plane (visual right; VR). In Condition 2, target locations were presented visually in left hemisphere, i.e., left of the midsagittal plane (visual left; VL). In Condition 3, target locations were presented kinesthetically (with vision occluded) in right hemisphere, i.e., the experimenter guided the subject's right arm to the target location to the right of the subject's midsagittal plane (kinesthetic right; KR). In Condition 4, target locations were presented kinesthetically (with vision occluded) in left hemisphere, i.e., the subject's left arm was guided to the target location to the left of the subject's midsagittal plane (kinesthetic left, KL).

The target was a metal ball (3 cm diameter) embedded with a red LED (0.8 cm diameter). A robot (Kawasaki Robotics GmbH, Germany) was programmed to produce a total of 12 target locations in either hemisphere. Target locations in each hemisphere were arranged at the nodes of a two (cranio-caudal) by two (anterior-posterior) orthogonal lattice; each layer of the lattice included six targets (Fig. 1). The spacing between the nodes was 10 cm, so that the cranio-caudal and anterior-posterior dimension of the workspace in either hemisphere was 20 × 10 cm. The center of the array was 30 cm away from the subject's nose.

For conditions in which targets were presented visually (VR and VL), the robot placed the target in a position within the subject's right or left hemisphere, while the subject's vision was occluded using a spectacle mounted electro-optic shuttering device (PLATO Visual Occlusion Spectacles; Translucent Technologies, Toronto, Canada). After target positioning, the shutter glasses were opened for 2 sec and the target location was disclosed to the subjects while they maintained focus on the central fixation aid. Subjects could not see their arm or hand during the visual presentation phase, as the design of the shutter glasses did not allow full peripheral vision. After 2 sec of visual target presentation, the shutter glasses were closed again and the target was removed. Subjects were instructed to memorize the target location for subsequent reaching to it after a trigger cue.

For conditions in which the targets were presented kinesthetically (KR and KL), the subject's vision was occluded at all times. The experimenter passively guided the subject's right or left arm to the target location and back again to the starting position. To avoid a putative confound, no crossing of the midsagittal line was involved in these conditions. As in conditions VR and VL, subjects were instructed to memorize the target location for subsequent reaching to it after a trigger cue.

For all conditions, a trigger cue (a tone presented with 1.0-sec delay from the end of target presentation) signaled

the subjects to reach to the remembered target location (Fig. 2B). During the reaching phase, subjects' vision was occluded at all times (in all conditions). Subjects were instructed to place the fingertip of their right hand such that it would be touching the target if the target remained present, and to hold this end position for about 1 sec before returning to the starting position (midline of their abdomen). After each reach, there was a 4-sec intertrial interval while the robot positioned a new target. Each of the four conditions was presented in a blocked design during the regional cerebral blood flow (rCBF) measurements. For each condition, rCBF measurements were replicated three times per subject, for a total of 12 observations (scans) per subject and 108 observations for the group of subjects (12 repeats, 9 subjects). The order of conditions was counterbalanced within and across subjects. Target positions were varied pseudorandomly from trial to trial within right (VR or KR) or left (VL or KL) hemisphere. All targets were within reach of the subject.

The speed of execution was not emphasized. Subjects were instructed to reach to the remembered target at any speed they chose, but with the stipulations that they reach using their right index finger, maintain central fixation throughout each movement, and begin and end in the same starting position located on their abdomen. Before the PET scans, subjects were trained until they could carry out the tasks while maintaining fixation. When vision was occluded, subjects could not see the fixation aid and were asked to hold their eyes in this straightforward position.

The fundamental component of the task (right hand reaching to the remembered target location) was identical for all four conditions (and thus cancels out in the analysis). Differences in conditions were thus limited to modality of target presentation (factor 1, modality; levels, visual or kinesthetic) or the hemisphere in which targets were presented (factor 2, hemisphere; levels, left or right). Analysis of factor 1 (visual > kinesthetic, i.e., VR + VL > KR + KL; kinesthetic > visual, i.e., KR + KL > VR + VL) should reveal differences associated with visual or kinesthetic target presentation. We hypothesized that analysis of differences between visual and kinesthetic conditions would depict primary and secondary visual processing areas and primary and secondary sensorimotor areas, respectively. Analysis of factor 2 (right > left, i.e., VR + KR > VL + KL; left > right, i.e., VL + KL > VR + KR) should reveal differences associated with right and left hemisphere target locations, irrespective of modality. Because subjects were reaching with their right arm to the remembered target position, irrespective of whether the target was presented in left or right hemisphere, we expected this comparison to reveal: (1) activation of the sensorimotor cortices associated with kinesthetic cueing with left and right arm, respectively; and more importantly, (2) lateralized visuospatial and kinesthetic-spatial information processing associated activations in the right hemisphere (for left hemisphere) and in the left and right hemisphere (for right hemisphere). The latter was hypothesized on the assumption that hemispheric specialization for spatial

representation demonstrated previously [Heilman and Van Den Abell, 1980] extends beyond the visual information-processing domain. Finally, analysis of the interaction term would reveal any significant interactions between neural mechanisms underlying visual and kinesthetic spatial information processing and left and right hemisphere.

Factorial designs (as employed here) have become more prevalent than single factor designs because they enable inferences about interactions. At its simplest, an interaction represents a change in a change. Interactions are associated with factorial designs where two (or more) factors are combined in the same experiment. In the present study, the effect of one factor (left or right hemisphere) on the effect of the other (modality of target presentation, i.e., visual or kinesthetic), was assessed by the interaction term. The interaction term thus reflected modulation of hemisphere-dependent neural activations by modality of target presentation. Factorial designs have an important role in the context of cognitive subtraction and additive factors logic because they can be used to test for interactions or context-sensitive activations (i.e., to demonstrate whether there is an effect of modality of target presentation on neural mechanisms underlying the representation of hemisphere).

Arm Kinematics

To analyze reaching performance across conditions, fingertip and target object positions in 3-D space were recorded during rCBF measurements using a six-camera optoelectronic technique (Optotrak 3020 system; Northern Digital, Waterloo, Canada; see also Fig. 1). To identify finger and target location, two infrared light-emitting diodes (IREDs) were used, one near the tip of the subject's right index finger and one on the target object. Kinematic data were recorded at 100-Hz sampling rate for the 120-sec PET scanning period.

Raw 2-D data from each camera was reconstructed using an Optotrak conversion program. Kinematic analysis of Optotrak data was carried out using custom established routines created in *Matlab v. 4.2c* (Mathworks, Natick, MA) [Dohle et al., 2000]. To remove high-frequency noise, position data was low-pass filtered with a second order Butterworth filter with zero phase-shift and a cutoff frequency of 10 Hz. The start and end of each movement were determined automatically as first/last sample, respectively, when fingertip velocity exceeded a 5% threshold of maximum velocity. Each timing point was cross-checked manually. Because of apparatus failure, data from one subject could not be used. For the remaining eight subjects, some trials were identified and excluded because target or fingertip IREDs were occluded or out of view of the cameras. Thus, 997 of 1,512 (66%) trials were available for analysis. Absolute endpoint errors on individual trials were computed as the 3-D distance between mean target location during target presentation phase and fingertip location at the end of the movement. Path length of fingertip was calculated by integrating the absolute value of fingertip velocity between the start and end of movement. Path length ratio was defined as the ratio between the path length of the fingertip at the end

of the movement divided by the 3-D distance between fingertip locations at the start and the end of each movement. Data from three replicated conditions were combined and described as the average per condition.

Mean values of each dependent variable were compared using separate two-way repeated measure analysis of variance (ANOVA). Factors were modality (visual/kinesthetic) $\times$ hemispace (left /right) of target presentation. To exclude the effect of motor learning, a separate 2 (modality) $\times$ 2 (hemispace) $\times$ 3 (block) ANOVA on endpoint error was carried out. The significance level for all statistical tests of behavioral data was set at $P < 0.05$ uncorrected.

Eye Movements

Maintenance of central fixation (or gaze direction during kinesthetic presentation) in all conditions was monitored by electro-oculography (EOG). Four bipolar silver-silver chloride electrodes (recording diameter, 1 cm) were applied bitemporally near the lateral canthus of the orbitae and overlying the superior and inferior orbital fissures of the left eye. The reference electrode was attached to the subject's ankle. Electrode placements were confirmed by observation of electrical activity during movement consistent with the function of the desired muscle. EOG signals were preamplified (Biocommunications Electronics Model 301, input impedance $10^{11} \Omega$ with a fixed gain of 100; common mode rejection rate (CMRR) 40 dB boost of second stage) and further amplified using a bioamplifier (Biocommunications Electronics Model 301; CMRR 100 dB). Amplified analog signals were then filtered (20–1,000 Hz) before being digitized at 2,500 Hz. EOG data were recorded continuously (oscilloscope mode) allowing for constant online qualitative assessment of eye position. For each PET scan, two traces (horizontal and vertical components) of 2-min duration were recorded.

PET Scanning

rCBF was measured by recording the regional distribution of cerebral radioactivity after intravenous injection of [^{15}O] butanol (a positron emitter with a half-life of 2.05 min). PET measurements were carried out using an ECAT EXACT HR+ PET scanner (CTI Siemens, Nashville, TN), with total axial field of view of 155 mm covering the whole brain. Dynamic changes in brain activity were acquired in 3-D mode with inter-detector collimating septa removed and a "Neuro-Insert" installed to limit acceptance of events originating from out-of-field-of-view activity. Optimum resolution was determined to be 4.4 mm at the center in transaxial orientation and 4.1 mm at the center in axial direction.

A catheter was inserted into the left brachial vein for administration of the ^{15}O -labeled butanol in a manner that did not interfere with task performance. The subject's head was stabilized with an individually molded head support. Using standard PET procedures described previously in more detail [Weiss et al., 2000] each subject received an intravenous bolus injection of 555 MBq of ^{15}O -labeled butanol, followed immediately by flushing with 10 ml saline.

Emission scanning began when an activity threshold of 5% above background level was exceeded. Emission data were thereafter collected sequentially over 40 sec. This process was repeated for each emission scan, with a 10-min interval between successive administrations to allow for adequate decay of background activity. The emission scan was corrected for attenuation with transmission images of the subject collected in the same position before PET measurements, using three ^{68}Ge line sources. The attenuation-corrected emission data were reconstructed as 63 transverse planes (separation 2.4 mm) and into 128×128 pixels (size 2.1 mm) by 3-D filtered back projection using a Hann filter with a cut-off frequency of 0.33 cycles per pixel.

Magnetic Resonance Imaging

In a separate session, high-resolution, anatomical magnetic resonance (MR) scans were obtained from each subject with a Vision 1.5-T scanner (Siemens, Erlangen, Germany). A 3-D magnetization-prepared, rapid gradient echo (MP-RAGE) sequence was used with the following parameters: TR = 11.4 msec; TE = 4.4 msec; flip angle = 15° ; inversion time (TI) = 300 msec; matrix = 200×256 ; FOV = 22 cm, 128 sagittal slices, slice thickness = 1.33 mm. These scans were carried out to exclude the possibility of morphologic/pathologic abnormalities and to assist in stereotactic normalization of PET images into standard anatomic space [Talairach and Tournoux, 1988].

Image Processing

All calculations and image manipulations were carried out on an ULTRA 10 workstation (Sun Microsystems, Palo Alto, CA) using *MATLAB v. 5.3* (Mathworks). Statistical parametric mapping software (*SPM99*; Wellcome Department of Cognitive Neurology, London, UK) was used for image realignment, image normalization, smoothing, and to create statistical maps of significant relative rCBF changes.

To correct for head movement, all PET scans were realigned to the first emission scan using *SPM99* software. A mean relative rCBF image was created for each subject. Each subject's magnetic resonance imaging (MRI) and PET mean image (serving as a template for individual PET images) were co-registered and then transformed into a standard stereotactic anatomic space using linear proportions and a non-linear sampling algorithm and the template provided by *SPM99*. PET images were then filtered using a low-pass Gaussian filter (resulting in an image resolution of 10 mm) to reduce variance due to individual anatomic variability and improve the signal-to-noise ratio. The resulting pixel size in stereotactic space was 2×2 mm with an interplane distance of 4 mm. Data were expressed in terms of standard stereotactic coordinates (x, y, z) as defined in Table I.

Statistical Analysis

Statistical analysis was carried out after stereotactic normalization and image smoothing. The main effects of

TABLE I. Coordinates of local maxima

Region	Side	Coordinates			Extent (mm ³) K _E	z score*
		x	y	z		
Visual target presentation (VL + VR) > (KL + KR)						
Occipital cortex	R	+10	−86	+24	29,505	8.5 ^a
	L	−12	−90	+22	29,505	8.3 ^a
Superior posterior parietal cortex	R	+30	−62	+52	180	7.0 ^a
	L	−24	−60	+54	98	6.3 ^a
Kinesthetic target presentation (KL + KR) > (VL + VR)						
Sensorimotor cortex	R	+37	−30	+59	15,807	8.5 ^a
	L	−24	−46	+62	130	6.8 ^c
Lateral premotor cortex	R	+36	−14	+62	27,523	8.4 ^a
	L	−28	−9	+61	27,523	7.5 ^c
Anterior cingulate cortex	R	+6	−13	+49	27,523	8.1 ^a
Anterior cerebellum	L	−22	−48	−16	130	6.2 ^a
	R	+12	−53	−12	51	4.9 ^c
Posterior cerebellum	L	−8	−86	−24	194	5.2 ^b
Prefrontal cortex	R	+18	+33	+41	431	4.6 ^c
Left hemisphere target presentation (VL + KL) > (VR + KR)						
Sensorimotor cortex	R	+38	−30	+60	4,203	8.3 ^a
Anterior cingulate cortex	R	+10	−13	+48	99	6.0 ^a
Anterior cerebellum	L	−20	−49	−14	80	5.5 ^b
Insular cortex	R	+38	−21	+16	33	5.1 ^b
Temporo-occipital cortex	R	+44	−71	+11	22	5.0 ^c
Right hemisphere target presentation (VR + KR) > (VL + KL)						
Temporo-occipital cortex	L	−44	−69	+9	325	6.1 ^b
	R	+63	−54	−4	12	4.9 ^c
Sensorimotor cortex	L	−40	−28	+58	26	5.1 ^b
Interaction effect: hemisphere and mode of target presentation (KL > KR) > (VL > VR)						
Sensorimotor cortex	L	−42	−24	+56	404	6.1 ^a
Temporo-parietal cortex	R	+66	−49	+26	4	4.9 ^c
Inferior temporal cortex	L	−63	−11	−21	2	4.6 ^c

Relative increases in brain activation. The location of foci of increases in rCBF was defined as the coordinates of the local maxima found within individual planes corresponding to the stereotactic atlas of Talairach and Tournoux (1988). Brain regions are estimated from Talairach and Tournoux, after adjustment (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) for differences between MNI and Talairach coordinates.

* All foci with a z-score of more than 4.6 ($P < 0.05$ corrected for multiple comparisons; extent threshold 0 voxels) are reported. The z-values (representing significance of activation for individual foci) were averaged across all nine subjects for the left (L) and right (R) hemispheres.

^a $P < 0.001$, corrected for multiple comparisons; ^b $P < 0.01$, corrected for multiple comparisons; ^c $P < 0.05$, corrected for multiple comparisons.

the factors, modality and hemisphere of target presentation, and their interaction were estimated on a pixel-by-pixel basis using *SPM99*. For each pixel in stereotactic space, analysis of covariance (ANCOVA) generated a condition-specific adjusted mean rCBF value (arbitrarily normalized to 50 ml/min) and an associated adjusted error variance. This allowed the planned comparisons of the mean blood flow distributions across all sets of conditions. For each pixel, across all subjects and scans, the mean relative rCBF values were calculated separately for each of the main effects. Comparisons of the means were made using the *t* statistic and thereafter transformed into normally distributed Z-statistics. The resulting set of Z-values constituted a statistical parametric map (*SPM_Z*-map). For contrasts of interest, *SPM* significance was assessed by comparing expected and observed distribution

of the *t*-statistic under the null hypothesis of no differential activation effect on rCBF. Only activations that were significant at $P < 0.05$, corrected for multiple comparisons, are reported.

Localization of Activations

We determined stereotactic coordinates of pixels with significant changes in rCBF within an area of significant relative rCBF change associated with the four different factors. Anatomic localization of these local maxima was assessed with reference to the standard stereotactic atlas [Talairach and Tournoux, 1988]. Brain regions were estimated after adjustment (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) for differences between MNI and Talairach coordinates. Additional validation of this localiza-

Main Effect: Hemisphere of Target

Figure 3.

Relative rCBF increases associated with hemisphere of target presentation. Left vs. right hemisphere presentation (VL + KL > VR + KR) (**top**) relative to right vs. left hemisphere presentation (VR + KR > VL + KL) (**bottom**). Areas of significant relative rCBF increases ($P < 0.05$, corrected for multiple comparisons; extent threshold 0 voxels) are shown as through-projections onto representations in standard stereotactic space [Talairach and Tournoux, 1988; Friston et al., 1995]. R, right; L, left; P, posterior; A, anterior.

tion method was obtained after SPM_z-maps were superimposed onto the group mean MR image calculated after each individual's MRI had been stereotactically transformed into the same standard space.

RESULTS

Neural Activations

Effects of modality of target presentation

Visual relative to kinesthetic target location presentation (VL + VR > KL + KR) led to bilateral activations in striate and extrastriate visual processing areas, extending into superior posterior parietal areas bilaterally (see visual target presentation in Table I). By contrast, kinesthetic relative to visual target location presentation (KL + KR > VL + VR) led to increased neural activity in bilateral sensorimotor cortex, lateral premotor cortex, and anterior cerebellum. Activity was observed also in right anterior cingulate cortex, right prefrontal cortex, and left posterior cerebellar (see kinesthetic target presentation in Table I).

Effects of hemisphere of target presentation

Left relative to right hemisphere target presentation (VL + KL > VR + KR) activated a right hemispheric network of

sensorimotor cortex, anterior cingulate cortex, insular cortex, and temporo-occipital cortex. In addition, a corresponding activation of the left anterior cerebellum was observed (see left hemisphere target presentation in Table I; Fig. 3, top panels). By contrast, right relative to left hemisphere target presentation (VR + KR > VL + KL) led to bi-hemispheric activations in temporo-occipital cortex, and left sensorimotor cortex (see right hemisphere target presentation in Table I; Fig. 3, bottom panels).

Interaction of hemisphere and modality of target presentation

Factorial designs where two (or more) factors are combined in the same experiment can be analyzed also for interaction of factors. In the present study, the effect of one factor (right or left hemisphere) on the effect of the other (modality of target presentation, i.e., visual or kinesthetic), can thus be assessed. Accordingly, analysis of the interaction term may reveal modulation of hemisphere-dependent neural activations by modality of target presentation. A significant interaction of hemisphere and modality of target presentation was revealed within left sensorimotor cortex, left inferior temporal cortex, and right temporo-parietal cortex (see interaction effect in Table I; Fig. 4, top panels). The interaction effects in left sensorimotor and inferior temporal

Figure 4.

Interaction of hemisphere with mode of target presentation when pointing to remembered targets. Areas of significant relative rCBF increases ($P < 0.05$ corrected for multiple comparisons; extent threshold 0 voxels) are shown as through-projections onto representations of standard stereotactic space [Talairach and Tournoux, 1988] for sagittal and coronal views. Transverse SPM_z-maps were superimposed on group mean MR images, which had been spatially normalized into the same anatomic space [Talairach and Tournoux, 1988]. Exact local maxima coordinates within activation areas in right temporo-parietal cortex and the respective Z-statistic are given in Table I. For the region in right temporo-parietal cortex (indicated by green open circles), analysis of associated parameter estimates undergoing significant activation reveals specific involvement of this region when targets are presented kinesthetically on the right. Adjusted means rCBF (to a mean of 50 ml/dl/min) $\pm$ SEM for each condition are displayed for local maxima. VR, visual presentation/right hemisphere; VL, visual presentation/left hemisphere; KR, kinesthetic presentation/right hemisphere; KL, kinesthetic presentation/left hemisphere; R, right; L, left; P, posterior; A, anterior.

cortex result from augmentation of rCBF in the right kinesthetic cueing condition, reflecting kinesthetic cueing with the right arm. The statistically significant interaction effects observed in left sensorimotor and inferior temporal cortex result from an augmentation of rCBF in the right kinesthetic cueing condition reflecting kinesthetic cueing with the right arm. Accordingly, the nature of this interaction suggests a right hemisphere temporo-parietal involvement when targets are presented kinesthetically in right hemisphere (over and above its involvement in the other conditions). A test for

significance of the hemispheric asymmetry in temporo-parietal cortex revealed that the hemispheric asymmetry observed was indeed significant. The interaction term thus reflects modulation of hemisphere-dependent neural activations by modality of target presentation.

The reverse interaction showed activation in right sensorimotor cortex only. As in the above interaction, the interaction effect in right sensorimotor cortex was found to result from an augmentation of rCBF in the left kinesthetic cueing condition, reflecting right sensorimotor cortex activation as-

TABLE II. Behavioral performance

	VR	VL	KR	KL	Level of significance		
					Hemisphere	Modality	Interaction
Absolute endpoint error (cm)	7.2 (1.6)	7.0 (1.2)	5.9 (0.8)	6.5 (1.6)	$F_{1,28} = 0.20$ ($P < 0.66$)	$F_{1,28} = 4.14$ ($P < 0.05$)	$F_{1,28} = 0.71$ ($P < 0.41$)
Path length of fingertip (cm)	41.3 (4.1)	40.4 (4.1)	41.7 (2.2)	41.7 (2.1)	$F_{1,28} = 0.16$ ($P < 0.69$)	$F_{1,28} = 0.57$ ($P < 0.46$)	$F_{1,28} = 0.18$ ($P < 0.68$)
Path length ratio	1.07 (0.04)	1.08 (0.01)	1.07 (0.05)	1.09 (0.06)	$F_{1,28} = 2.14$ ($P < 0.16$)	$F_{1,28} = 0.37$ ($P < 0.55$)	$F_{1,28} = 0.24$ ($P < 0.63$)

The level of significance was set at $P < 0.05$

Mean ($\pm$ SD) absolute endpoint error, path length of fingertip, and path length ratio for each of the four conditions for eight subjects. Also presented are the results of the two-way repeated measures ANOVA. No significant differences were found in the dependent variables. VR, visual presentation/right hemisphere; VL, visual presentation/left hemisphere; KR, kinesthetic presentation/right hemisphere; KL, kinesthetic presentation/left hemisphere.

sociated with left kinesthetic cueing. No further significant interaction was observed.

Behavioral Performance

Accuracy of reaching

In general, accuracy of reaching to the remembered target location was good, as indicated by low absolute endpoint errors (Table II). Absolute endpoint errors were larger when presented in the visual modality ($F_{1,28} = 4.14$; $P < 0.05$), but did not differ for movements in the two hemispheres ($F_{1,28} = 0.20$; $P < 0.66$). The interaction effect of modality and hemisphere on endpoint errors was not significant ($F_{1,28} = 0.71$; $P < 0.41$), suggesting that the endpoint error depends on the mode of target presentation. Post-hoc comparison of means showed that 3-D endpoint errors were greater when targets were presented visually (7.1 cm) than when presented kinesthetically (6.2 cm).

Fingertip trajectories

A different pattern was found for the mean fingertip path length, which remained consistent when reaching in both hemispheres and for both modalities (Table II). There was no significant difference among the main effects of modality ($F_{1,28} = 0.57$; $P < 0.46$), hemisphere ($F_{1,28} = 0.16$; $P < 0.69$), or their interaction ($F_{1,28} = 0.18$; $P < 0.68$). There was no systematic difference in mean path length ratio between visual or kinesthetic presentation modalities ($F_{1,28} = 0.37$; $P < 0.55$; see Table II). Although there was a tendency toward greater mean path length ratios when subject reached in the left hemisphere when compared to the right, this difference was not significant ($F_{1,28} = 2.14$; $P < 0.16$). The two-way interaction between modality and hemisphere of presentation also failed to reach significance ($F_{1,28} = 0.24$; $P < 0.63$).

Lack of motor learning

The mean endpoint error for all conditions was found to be slightly higher during the first epoch (6.9 ± 0.31 cm) when compared to the second (6.5 ± 0.29 cm) and third (6.5

± 0.31 cm) epochs. Three-way ANOVA, however, with epoch number as a within-subject factor showed no significant effect of epoch ($F_{1,73} = 0.55$; $P < 0.58$), hemisphere ($F_{1,73} = 2.07$; $P < 0.16$), or their interaction on 3-D endpoint error. This suggests that there was no significant improvement in reaching performance from the first to the third epoch. Post-hoc comparison of means showed that 3-D endpoint error was greater when targets were presented visually compared to that when targets were presented kinesthetically, which was replicated in the aforementioned two-way ANOVAs.

Eye movements

Evaluation of EOG revealed that subjects were able to maintain central fixation during the scanning period. They were also able to maintain their central gaze direction when the shutter glasses occluded the fixation aid.

DISCUSSION

In this study, subjects carried out reaching movements guided entirely by working memory of the target location, which had been provided to the subjects either kinesthetically or visually before the reach. This allowed the study of effects of modality-specific encoding of a spatial target location and its transformation into arm-centered coordinates. A premotor-parietal-cerebellar circuit for kinesthetic encoding and an occipito-temporo-parietal circuit for visual encoding were observed. In addition, we investigated the effect of hemisphere of target presentation and found a right-hemispheric dominance for both visual and kinesthetic processing. Most importantly, we observed an interaction of the neural mechanisms underlying modality of target presentation (visual vs. kinesthetic) and hemisphere (left vs. right). The nature of this interaction suggests a specific role of right temporo-parietal cortex in kinesthetic spatial information processing (over and above its involvement in visual spatial information processing). The interaction effect observed cannot result from the fact that only the right arm was used for reaching to the remembered target location (irrespective of

which arm was used for kinesthetic cueing), because the motor output component of the task was identical in all four conditions. Likewise, the interaction effect in right temporo-parietal cortex cannot stem from neural activity underlying use of the arm for cueing (as was observed in sensorimotor cortex for left or right arm, respectively). This effect in right temporo-parietal cortex resulted from an increase in rCBF when the target locations were presented kinesthetically in the right hemispace (with the right arm being used for cueing), as illustrated in Figure 4.

Visual and Kinesthetic Encoding of Target Location

Previous studies have identified a fronto-parietal system for computing visuospatial coordinates [Caminiti et al., 1996; Vallar et al., 1999], egocentric or allocentric coding of space [Galati et al., 2000], and spatial sensorimotor transformations [Andersen et al., 1985; Colby, 1998]. Vallar et al. [1999] found a similar parietal-lateral premotor frontal network involving primarily right-hemisphere processing for visually locating the "mid-sagittal plane of the body." The present study identifies an analogous neural network for kinesthetically defined spatial targets. Our data thus complement and extend the above findings: activation of an analogous network during kinesthetic cueing suggests a much more general role for right temporo-parietal cortex in computing the egocentric reference frame that goes beyond computation of mere visuospatial information. The rCBF parameter estimate plot delineates that this area is involved in kinesthetic spatial information processing *per se*.

Specific Role of the Right Hemisphere for Spatial Processing

A right-hemispheric dominance for visuospatial processing has been suggested based on observations in patients with visuospatial neglect [Heilman and Van Den Abell, 1980; Kinsbourne, 1987; Mesulam, 1981]. The neural model of visuospatial attention proposed by Mesulam [1999] suggests that the left hemisphere contributes predominantly to the right side of events, coordinates the distribution of attention mainly within the right hemispace, and shifts attention mostly in a contralateral rightward direction. By contrast, the right hemisphere is assumed to contribute to events on both sides, to coordinate the distribution of attention within both hemispaces, and to shift attention in both the contralateral and ipsilateral directions, with only a slight contralateral bias [Mesulam, 1999]. Although the model is based mainly on evidence from studies of visuospatial neglect, one prediction that follows from it is that the right hemisphere should participate in encoding sensory events throughout extrapersonal space, irrespective of the modality of spatial information. By contrast, the left hemisphere should show a more limited response confined to contralateral (right-sided) events, again irrespective of the modality of spatial information. These predictions are supported by our data, which show significant right hemisphere activa-

tion for both visually and kinesthetically presented spatial information. For hemispace of target presentation, reaching to targets presented in the left visual hemispace or on the left side of the subject's midsagittal plane activated sensorimotor and visuospatial processing areas of the right hemisphere (including temporo-parietal cortex) and the left cerebellum only. By contrast, reaching to targets presented in the right visual hemispace or to the right side of the midsagittal plane led to bi-hemispheric activation. These observations are consistent with the notion of right hemisphere dominance for spatial information processing irrespective of the modality of information processing.

Support for greater involvement of the right hemisphere in non-visual spatial tasks comes from a study where right hemisphere activation was observed in a blindfolded manual exploration task, even when exploration occurred on the ipsilateral right side [Gitelman et al., 1996]. Taken together, the results of the latter study and the present data suggest strongly that the overall functional anatomy of extrapersonal spatial attention is independent of modality. Furthermore, damage to, or repetitive transcranial magnetic stimulation of, the right hemisphere diminishes the speed and accuracy of saccades to actual and remembered targets in both directions, whereas left hemisphere damage has an effect that is confined to saccades made in the contralesional direction [Oyachi and Ohtsuka, 1995; Pierrot-Deseilligny et al., 1991].

Some studies have suggested that the right hemisphere activation in spatial tasks may result from producing a mental representation of both sides of space, regardless of the location of the information being retrieved [Maguire et al., 1998; Moscovitch et al., 1995]. Our tasks involve holding a mental representation of space in working memory. The amount of working memory involved in all tasks was equal, however, although sides of hemispace and modality of presentation may have led to differential emphasis of specific working memory components.

Cerebellar Role in Sensory Acquisition

A notable finding in this study is the presence of bilateral cerebellar activation during kinesthetic presentation compared to that during visual presentation. Our findings are supported by a recent report, which provided evidence for a parietal-cerebellar circuit during reaching to non-visual targets [Desmurget et al., 2001]. We suggest that these activations reflect cerebellar involvement in acquiring sensory information. This conjecture is consistent with a cerebellar role in the assessment of kinesthetic cues required for establishing internal representations [Bloedel and Bracha, 1995] or its putative function as a sensory analyzer [Bower, 1997] and movement controller.

Memory-Guided Reaching

We investigated the neural mechanisms that permit one to reach to a position in space identified previously by kinesthetic or visual cues. The pointing errors in our study were of the same order of magnitude as those

reported previously [Baud-Bovy and Viviani, 1998; Soechting and Flanders, 1989], indicating that our subjects could carry out the pointing movement with relative ease and accuracy. Although there was a slight decline in the 3-D endpoint errors from the first to the last block of trials, there was no significant learning effect of epoch, hemisphere, or their interaction. This suggests that the activations observed were not influenced by a significant learning effect.

The largest absolute endpoint errors were observed in the visual presentation conditions. The lowest errors were observed when targets were presented kinesthetically in right hemisphere. There was no significant difference in modality or hemisphere. Because we normally locate objects with the use of vision, one might expect that performance would be best when objects are located visually. In terms of the accuracy of movement distance, however, the present study and previous work [Darling and Miller, 1993; Helms Tillery et al., 1991; Soechting and Flanders, 1989] show that subjects perform best in purely kinesthetic reaching tasks. To explain this finding, it has been suggested that reaching to a kinesthetically defined target has a clear advantage: both the target and the arm position are defined in the same frame of reference (the arm angles). In the case where no cross-modality transformation is required, one might then expect highest accuracy.

It has been shown previously that kinesthetic information from the left arm can be used to drive the right arm as effectively as information from the right arm itself [Baud-Bovy and Viviani, 1998]. Such observations are in keeping with the "target position hypothesis" that early intrinsic coding is followed by a stage in which target position is translated into an extrinsic 3-D coordinate system [Larish and Stelmach, 1982; MacNeilage, 1970] that operates irrespective of the locating hand. We have direct support for such a system not only because our endpoint errors were similar but also because neural activations associated with visual or kinesthetic target presentation were in overlapping areas.

Results from kinematic studies have also suggested an advantage (shorter movement duration and greater accuracy) for movements made to targets ipsilateral to the reaching limb, when compared to movements to contralateral targets (i.e., target on the other side of the body midline). This advantage has been demonstrated for both visually [Carey et al., 1996] and proprioceptively [Carey and Otto-de Haart, 2001] guided movements. Such a behavioral advantage might be based on information and motor processing being carried out within the same hemisphere as opposed to transcallosal information processing necessitated if the target had been presented in the contralateral (visual or proprioceptive) field. Increase in accuracy and shorter movement duration could thus result from more efficient within-hemisphere visuomotor transmission of target information or visual feedback from the reaching limb, or could be related to better organized

motor output for movements that do not cross the body midline [Carey et al., 1996].

We did not observe significant changes in each kinematic parameter of reaching associated with the different conditions. The mean fingertip path length was similar when reaching in both hemispaces and for both modalities. Likewise, there were no significant differences among the main effects of modality and hemisphere, nor was there a significant interaction. In addition, there was no systematic difference in mean path length ratio between visual or kinesthetic presentation modalities. Absolute endpoint errors were larger when presented in the visual modality but did not differ for movements in the two hemispaces. The present behavioral data is thus fully consistent with previous kinematic studies on reaching to targets.

It should be kept in mind that kinematic recordings in a PET environment are limited by the experimental set-up: subjects were lying supine with their head firmly fixed. In addition, the number of trials is limited in a PET study and behavioral differences may thus remain undetected due to the variance in task performance.

CONCLUSIONS

The observed right hemisphere asymmetry for kinesthetic processing fits well with the general concept of a significant right hemisphere role for spatial functions irrespective of modality. Future work with patients suffering from left and right parietal damage may help to clarify further the extent and nature of right temporo-parietal cortex involvement in kinesthetic information processing.

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