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Integration of Target and Effector Information in the Human Brain During Reach Planning

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Beurze, S. M., F. P. de Lange, I. Toni, and W. P. Medendorp. Integration of target and effector information in the human brain during reach planning. *J Neurophysiol* 97: 188–199, 2007. First published August 23, 2006; doi:10.1152/jn.00456.2006. To plan a reaching movement, the brain must integrate information about the location of the target with information about the limb selected for the reach. Here, we applied rapid event-related 3-T fMRI to investigate this process in human subjects ($n = 16$) preparing a reach following two successive visual instruction cues. One cue instructed which arm to use; the other cue instructed the location of the reach target. We hypothesized that regions involved in the integration of target and effector information should not only respond to each of the two instruction cues, but should respond more strongly to the second cue due to the added integrative processing to establish the reach plan. We found bilateral regions in the posterior parietal cortex, the premotor cortex, the medial frontal cortex, and the insular cortex to be involved in target–arm integration, as well as the left dorsolateral prefrontal cortex and an area in the right lateral occipital sulcus to respond in this manner. We further determined the functional properties of these regions in terms of spatial and effector specificity. This showed that the posterior parietal cortex and the dorsal premotor cortex specify both the spatial location of a target and the effector selected for the response. We therefore conclude that these regions are selectively engaged in the neural computations for reach planning, consistent with the results from physiological studies in nonhuman primates.

INTRODUCTION

In the process of planning and preparing a reaching movement, the brain must integrate information about the location of the selected target with information about the effector selected for action (Buneo et al. 2002; Mascaro et al. 2003; Shadmehr and Wise 2005). Take, for example, the simple task of picking up a cup of coffee. In this case, the brain must combine its internal representation of the location of the cup with its representation of the hand selected for use to formulate the reach plan that ultimately leads to the motor commands for control of the necessary muscles. It is generally accepted that this integrative action is accomplished through interactions between posterior parietal and premotor areas of the brain (Caminiti et al. 1998; Kalaska et al. 1997; Medendorp et al. 2005; Thoenissen et al. 2002; Wise et al. 1997). However, the precise role of the areas involved and exact nature of the computations along this parietofrontal network is a matter of ongoing debate (Andersen and Buneo 2002; Colby and Goldberg 1999; Medendorp et al. 2005; Thoenissen et al. 2002; Toni et al. 2001).

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One way to assess how the coding of the spatial goal of the movement and that of the effector to be used interact is by using a paradigm where the two types of information are presented sequentially, in either order, and separated in time by a delay. Using such a paradigm, Hoshi, Tanji, and coworkers investigated the characteristics of the integration process for reach planning in the monkey frontal cortex. In some trials, the monkey was first cued which hand to use (left or right) and then, after a delay, the target for movement (left or right from fixation) was presented. In other trials, the instruction order was reversed. In a series of papers, they described the specific involvement in this process of motor planning of the dorsolateral prefrontal cortex (dl-PFC) (Hoshi and Tanji 2004a), the dorsal (PMd) and ventral (PMv) premotor regions (Hoshi and Tanji 2000, 2002, 2006), the motor areas on the medial wall, including the presupplementary and supplementary motor areas (pre-SMA and SMA) (Hoshi and Tanji 2004b), and the cingulate motor areas (CMA) (Hoshi et al. 2005). In particular, their results show that the neural networks interconnecting the pre-SMA, PMd, and dorsal dl-PFC play a central role in integrating the two sets of information, implicating these regions in the computation of a motor plan based on sensory signals.

The process of integrating information to plan forthcoming actions is not solely restricted to frontal regions, but has also been observed in monkey posterior parietal cortex, which is not surprising given their massive recursive connections (Wise et al. 1997). Calton et al. (2002) studied a cluster of neurons situated on the medial bank of the intraparietal sulcus in the monkey PPC, also termed the parietal reach region (PRR). In their design, the effector cue signaled either a saccade or a right-hand reach. They reported that many PRR neurons can be activated by spatial information without an effector cue that specifies the motor plan, but also by the plan to use a specific effector in the absence of spatial target information. A subset of PRR neurons coded both instructions, suggesting that this region seems active in sensorimotor control by selecting both the targets for action and the effectors to perform these actions (Snyder et al. 1997).

The aim of the present study was to investigate the process of target–arm integration for reach planning in humans by using a similar two-stage instruction paradigm in rapid event-related functional magnetic resonance imaging (fMRI). As far as we know, human reaching studies in fMRI have only examined the blood oxygenation level–dependent (BOLD)

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activation while both effector and spatial information were known. As such, numerous studies have reported activity along the dorsal parietal–frontal network during the preparation and execution of simple finger-pointing movements (Astafiev et al. 2003; Connolly et al. 2000; DeSouza et al. 2000; Kertzman et al. 1997; Medendorp et al. 2005; Prado et al. 2005; Simon et al. 2004). Several studies showed that some of the areas in this network are specifically more responsive for reaching than for making saccades and vice versa, thus acting in an effector-specific way (Astafiev et al. 2003; Connolly et al. 2003; Medendorp et al. 2005). One of our objectives was to separate target- and effector-specific activity in the various regions that have been implicated in human reach planning. This allows us to further specify the contributions of these regions to the visuomotor transformation for a reaching movement, while directly relating these findings to the vast body of knowledge acquired in nonhuman primates.

In this study, subjects prepared either a left-hand or a right-hand reaching movement following two successive instruction cues, i.e., a target cue and an effector cue, given in random order. Each cue was followed by a random delay of <5 s. After a go-signal, the subjects executed the reach while maintaining central eye fixation. Thus subjects could only store the information about either the goal location or hand choice after the first cue, whereas they were able to integrate the information for the reach plan after presentation of the second cue. Based on monkey and previous fMRI literature (Calvert et al. 2001; Meredith and Stein 1983), we hypothesized that regions that respond to the first cue and subsequently increase their activity after the second cue are involved in integrating spatial and effector signals for planning human reaches.

METHODS

Subjects and ethics approval

Sixteen healthy, right-handed subjects with normal or corrected-to-normal vision participated in this study (ten male, six female, ages 22–37 yr). All subjects gave their written informed consent in accordance with the institutional guidelines of the local ethics committee (CMO Committee on Research Involving Human Subjects, region Arnhem–Nijmegen, The Netherlands). One or two days before scanning, each subject received a practice session on the task using a mock setup, to ensure that the task and paradigm were correctly understood. Also, a few monitored practice runs were performed inside the scanner before the actual experiment began. Four subjects (the authors) were aware of the purpose of the experiment. No systematic differences were found between their results and those of the naïve subjects.

Experimental setup

Subjects were positioned in the magnet with their torso and head tilted such that they viewed the targets in front of them without mirrors, to make the task as natural as possible. Their torso was tilted 30° relative to the bore's main axis by means of a wooden support board that was placed on the scanner bed. The holder that contained the phased-array receiver head coil was firmly attached to the torso support. Within the head coil, the head and neck were tilted and stabilized with foam wedges and sandbags, such that the head was in a relatively comfortable position for viewing the targets. Subjects were strapped at the level of the chest, just above the elbows, to prevent excessive movement. The elbows were positioned on cushions and a foam block was placed underneath the knees. Two

MR-compatible keypads (MRI Devices, Waukesha, WI) were placed on top of each subject's lap, each a few centimeters away from the body midline, and were pressed by the index finger of each hand. The keypads served to record the start and finish of the reaching movements. A stimulus device was attached to an arch of about 40 cm in height that was placed over the subjects hips, so that the device was about 80 cm away from the eyes. The stimulus device contained one central multicolor (red, orange, green) light-emitting diode (LED) and three peripheral orange LEDs on either side, arranged at an eccentricity of about 7° and at angular elevations of 18, 0, and –18°, respectively, from the central LED. During the actual experiment, only the four LEDs in the upper and lower visual fields (at the nonzero elevation angles) served as targets. This configuration enabled subjects to view the stimuli with a comfortable, slightly downward gaze direction relative to the head. Stimuli were presented using Presentation software (Neurobehavioral Systems, San Francisco, CA). This program also recorded the start and finish of the reaching movements. Reaching movements involved mostly the elbow joint, to minimize the amount of mass that was displaced with the movement. The hand displacement had a magnitude in the order of 20 cm. Because the experiment was performed in complete darkness, subjects could not see their hand during the reaching movement. During imaging, we did not record the eye movements. Recently, however, in a control study for a very similar reaching experiment in fMRI (Medendorp et al. 2005), it was confirmed that subjects are able to keep central eye fixation while performing a reaching task.

MRI scanning

Functional images were acquired on a Siemens 3-Tesla MRI system (Siemens TRIO, Erlangen, Germany). Using an eight-channel phased-array head coil, 28 axial slices were obtained by a gradient-echo planar imaging sequence (slice thickness 3 mm, gap = 17%, in-plane pixel size 3.5 × 3.5 mm, TR = 2060 ms, TE = 40 ms, FOV = 224 mm, flip angle = 90°). All 1435 functional images were acquired in one run, lasting 49 min. After this, high-resolution anatomical images were acquired using a T1-weighted MP-RAGE sequence (176 sagittal slices, voxel size = 1 × 1 × 1 mm, TR = 2300 ms, TE = 3.93 ms, FOV = 256 mm, flip angle = 8°).

Experimental paradigm

Subjects were tested in complete darkness using a rapid event-related paradigm. Figure 1 illustrates the paradigm, in which subjects had to plan and perform a reaching movement toward a remembered target by following a set of two instruction cues, presented in random order. One cue indicated the effector to be used (right or left hand); the

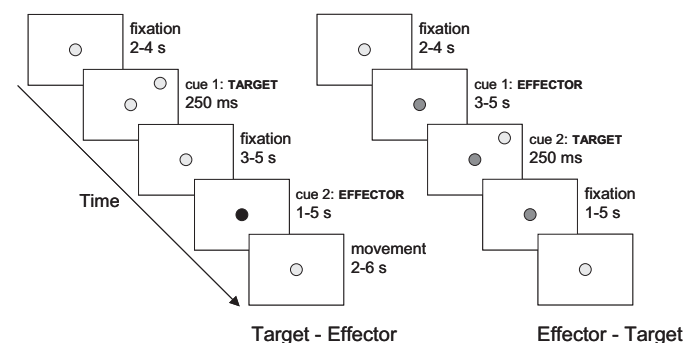


FIG. 1. Two-stage delayed instruction paradigm. Subjects fixated a central light-emitting diode (LED) and prepared a reach instructed by 2 successive visual cues: target location (brief flash of a peripheral LED either left or right) and effector choice (color change of the central LED, indicating the use of either the left or the right hand), presented in random order. A go-signal prompted execution of the reach, which had to be performed while maintaining central eye fixation.

other indicated the target location to reach for (right or left). This resulted in target–effector and effector–target trials, according to the instruction order of the cues.

A trial started with the appearance of an orange central fixation LED that subjects had to fixate for the total duration of the trial. After a variable delay of 2–4 s the first cue was given. In the case of a target–effector trial, the first cue indicated the target location by a brief flash (250 ms) of one of the orange peripheral target LEDs. Subsequently, after a variable delay of 3–5 s, the effector cue (left or right hand) was signaled by a color change of the central fixation LED into red or green, which remained on for a variable delay of 1–5 s. Then, the color of the central LED changed back to orange, serving as the go-signal for the subject to execute a swift and accurate reaching movement toward the remembered target, immediately followed by a return movement to the hand's starting position on the button box, while maintaining central eye fixation. After a variable delay of 2–6 s, the central LED turned off and on again, indicating the start of a new trial. Effector–target trials were similar to the target–effector trials, but with the effector instruction given first and the peripheral target indicated second. Target–effector and effector–target trials were randomly interleaved. The color instructions of the effector cue were counterbalanced over subjects.

Duration of a total trial was jittered between 8 and 20 s. To further optimize the paradigm, after every five trials there was a longer (13–17 s) period of sole central fixation to obtain more data for the fixation baseline and to allow the BOLD signal to return to baseline level. Subjects performed 160 trials, grouped in blocks of 20 trials. As indicated earlier, during each block of trials, subjects were instructed to maintain central fixation of the eyes at all times and thus also when they made the reaching movements. After each block of trials there was a rest period of 30 s, during which subjects could freely move or close their eyes. Near the end of the rest period, 5 s before a new block of trials started, all LEDs on the stimulus device briefly flashed three times, instructing the subject to prepare for the next series of trials and fixate at the center. The total experiment lasted for 49 min.

Behavioral analysis

We used the following criteria to distinguish error trials from correct trials. A trial was excluded from the analysis if: 1) no reaching movement was made, 2) the reaching movement was made with the wrong hand, or 3) the reaching movement was started before the go-signal was given. We further characterized the correct trials by the reaction time of the reaching movement: the time between the onset of the go-cue and the start of the movement, as detected by the button box. Statistical tests were performed with the type I error set at the 0.05 level ($P < 0.05$).

fMRI data analysis

fMRI data were analyzed using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). Subsequent analyses were performed using Matlab (The MathWorks, Natick, MA). The first three volumes of each subject's data set were discarded to allow for T1 equilibration. Functional images were corrected for slice scan time acquisition and motion. The data were temporally filtered by using a high-pass filter of 11 cycles per time course (filter cutoff: ± 268 s). The functional images were coregistered with the anatomical scan and transformed into Talairach coordinate space using the nine-parameter landmark method of Talairach and Tournoux (1988). The images were smoothed with an isotropic Gaussian kernel of 8-mm full-width-at-half-maximum.

Data were analyzed using a standard general linear model (GLM), under the assumption that the BOLD signal adds linearly and does not saturate (Miezin et al. 2000). For each of the 16 subjects, the following 16 predictor functions were defined. Four predictor functions were composed to characterize the response to the first instruc-

tion cue (cue1), resembling the four different types of information: leftward target, rightward target, left hand effector, and right hand effector. Accordingly, the information from the first cue could be combined with two different types of information provided by the second cue. For example, if the first cue signaled the left hand, then the second cue instructed either a leftward target or a rightward target, thus consisting of two predictor functions, left hand–leftward target and left hand–rightward target, respectively. This led to eight different predictors in response to the second instruction cue (cue2). Furthermore, the response to the go-signal was modeled by four different predictor functions: reaching with the left hand to a remembered target either in the left visual field or in the right visual field, or reaching with the right hand in the left or right visual field. To construct each of the predictor functions, we defined a box car function extending over each instance of the appropriate epoch occurring in each subject's run, and convolved it with the hemodynamic response function (modeled using a gamma function with a tau of 2.5 s and a delta of 1.5 s). Together, the cue1, cue2, and go-regressors allowed separation of three stages in the sensorimotor process for reaching: an information-processing stage (cue1), a retrieval-and-integration stage to prepare a reach plan (cue2), and a movement-execution stage (after the go-signal). In addition, we incorporated eight predictors of no interest. One regressor was designed to capture the error trials, as defined using the criteria described above. Furthermore, six regressors were designed to represent the head motion. These regressors were modeled using the six parameters provided by BrainVoyager's motion-correction algorithm. Finally, even with the head perfectly stabilized, the dislocation of a mass near, but outside of, the head coil can induce signal changes in the images (Diedrichsen et al. 2005). Therefore one regressor was used to model the changes in the mean signal intensity of the cerebrospinal fluid (CSF), as supposed to be caused by hand motion in the magnetic field and thereby representing the magnetic field fluctuations (Verhagen et al. 2006).

GLMs were calculated on individual subject data sets with a correction for serial correlations in the time courses. A random-effects group analysis was performed to test the effects across subjects. The false discovery rate (FDR) controlling procedure to correct for multiple comparisons was used, with a maximum threshold value of 0.05; thus $q(\text{FDR}) < 0.05$ (Genovese et al. 2002).

Image analysis and regions of interest

Using random-effects group analysis, contrasts relative to baseline were computed individually for each of the 16 regressors and for the two subgroups of interest: cue1 > fixation and cue2 > fixation. We hypothesized that regions involved in integrating spatial and effector signals should respond significantly to the first cue as well as increase their activity after the second cue, when all information is available for the development of a movement plan. To this end, we first computed the contrasts cue1 > fixation at $q(\text{FDR}) < 0.05$ and cue2 > cue1 at $q(\text{FDR}) < 0.05$. We then masked the activation map cue2 > cue1 by the map cue1 > fixation. This ensured that all voxels identified by the conjunction analysis were significantly activated in response to both cues, but more so for cue2 than for cue1. Centered on each point of peak activation in the resulting map, a region of interest (ROI) was defined as all the contiguous voxels within a cubic cluster of $9 \times 9 \times 9$ mm that exceeded a threshold of $q(\text{FDR}) < 0.05$. We further characterized these ROIs by computing not only their degree of spatial and effector selectivity, but also their specificity to the components of movement preparation and execution. To study these properties, the mean beta weight for each regressor reflecting one of the three epochs of interest (cue1, cue2, and reaching) was computed and used for post hoc comparative analysis using repeated-measures ANOVAs, setting the type I error at the 0.05 level ($P < 0.05$).

RESULTS

Task performance

Table 1 presents the accuracy, reaction time, and movement duration data recorded during the fMRI experiment for each type of reaching movement (left hand to leftward target, left hand to rightward target, right hand to leftward target, right hand to rightward target). On average, participants scored >95% correct responses for all conditions. A 2×2 repeated-measures ANOVA with target location (left/right) and effector hand (left/right) as factors revealed no significant main effect [target: $F_{(1,15)} = 0.4, P = 0.5$; effector: $F_{(1,15)} = 1.0, P = 0.32$] or interaction effect [$F_{(1,15)} = 0.08, P = 0.78$].

Reaction time analysis of the correct responses revealed a mean reaction time of 583 ± 117 ms (mean \pm SD), across all conditions, which is consistent with previous reports (Simon et al. 2002; Thoenissen et al. 2002). The differences among the four conditions were not statistically significant [target: $F_{(1,15)} = 0.001, P = 0.97$; effector: $F_{(1,15)} = 0.0002, P = 0.99$; interaction: $F_{(1,15)} = 0.1, P = 0.75$]. In addition, no significant difference in reaction time was found between target–effector and effector–target trials (paired t -test: $t_{15} = -1.5, P = 0.17$).

The mean movement duration of a to-and-fro movement was 1643 ± 359 ms across all conditions and subjects, indicating that subjects always had their hand returned to the starting position before cue1 of the next trial appeared. Again, the differences among the four conditions were not statistically significant [target: $F_{(1,15)} = 2.7, P = 0.12$; effector: $F_{(1,15)} = 0.02, P = 0.90$; interaction: $F_{(1,15)} = 0.5, P = 0.49$].

Together, the behavioral results, showing similar performance in all conditions, imply that the observed differences in corresponding fMRI activation patterns cannot be related to different levels of task performance.

fMRI activation data

RESPONSE TO CUE1. We first identified regions of the brain that were activated in response to the first cue (cue1 > fixation). Using a random-effects group GLM, a contrast that involved the four weighted regressors constituting the first cue (target left, target right, left hand, right hand) was constructed. Figure 2, A and B shows two anatomical views of these results, in neurological convention, thresholded at $q(\text{FDR}) < 0.05$, at a viewpoint centered on the parietal activation [intraparietal sulcus (IPS)]. This functional activation map was rendered onto an inflated representation of the left hemisphere of a single subject, providing a direct overview of the activated voxels relative to other anatomical landmarks (Fig. 2, C and D). As shown, a bilateral occipital–parietal–frontal network was activated in response to the first cue. Significant activity was found in the lateral and medial regions along the IPS,

TABLE 1. Percentage correct responses, mean reaction times, and mean movement duration times for each of four reaching movements

Condition	%	RT ms	MT ms
Left hand, left target	95.2 \pm 3.8	587 \pm 125	1609 \pm 351
Left hand, right target	95.5 \pm 3.4	579 \pm 113	1630 \pm 346
Right hand, left target	95.8 \pm 3.0	578 \pm 118	1675 \pm 373
Right hand, right target	96.6 \pm 3.3	589 \pm 143	1659 \pm 397

Values are \pm SD. RT, reaction times; MT, movement duration times.

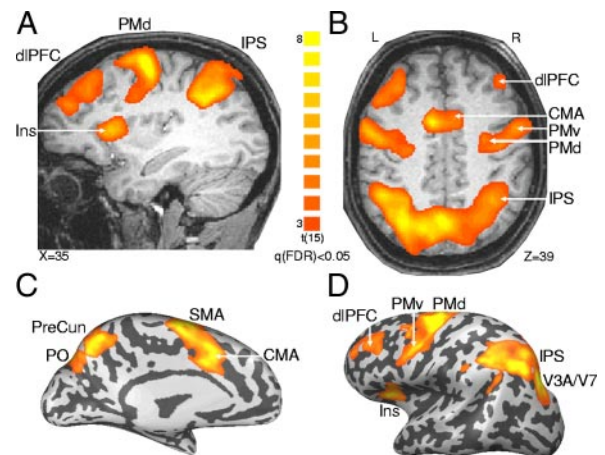


FIG. 2. Brain activation in response to the first cue (cue1 > fixation) averaged across 16 subjects, presented in 2 anatomical views in neurological convention (A, B) and on an inflated representation of the left hemisphere of a single subject (C, D). $P < 0.05$, false discovery rate (FDR) corrected. A parietofrontal network including the supplementary and cingulate motor areas (SMA, CMA), dorsal and ventral premotor cortex (PMd, PMv), dorsolateral prefrontal cortex (dl-PFC), and regions along the intraparietal sulcus (IPS) is involved in processing the information represented by the cue. Also, activity can be found in the insula (Ins), precuneus (PreCun), extrastriate area V3A/V7, and the right lateral occipital cortex (not shown).

extending more posterior into the transverse occipital sulcus, likely into area V3A or V7 (Medendorp et al. 2005; Tootell et al. 1998). Significant voxels were also observed within the parietal–occipital sulcus (PO) and the precuneus (PreCun). Within the frontal lobe, significant responses were found in the precentral gyrus and sulcus, which correspond to the dorsal and ventral premotor areas (PMd/PMv) (Medendorp et al. 2005; Picard and Strick 2001; Wise et al. 1997). On the medial wall, activation extended from the superior frontal sulcus, corresponding to the supplementary motor area (SMA) (Picard and Strick 2001), into the posterior rostral and caudal zones of the anterior cingulate sulcus [cingulate motor area (CMA)]. Furthermore, significant activations were observed in the dorsolateral prefrontal cortex (dl-PFC) (DeSouza et al. 2003; Hunter et al. 2004) and in the frontal insular cortex (Ins) (Grefkes et al. 2004; Kincade et al. 2005). Notably, no significant activation was found in any of the subcortical regions or the cerebellum (not shown). Table 2 lists the average Talairach coordinates (in millimeters) of the peak voxel within each region and its t -value across all subjects. The goodness-of-fit value (R^2) indicates how well the GLM model described the data in each region.

RESPONSE TO CUE2. Figure 3 provides an overview of the regions that responded significantly to the second cue (cue2 > fixation), in the same format and at the same statistical threshold as Fig. 2. Several observations can be made when comparing this figure with the previous one. First, virtually all of the regions that responded to the first cue were also activated in response to the second cue. Second, there is more widespread activation in response to the second cue. More specifically, the presentation of the second cue led to additional bilateral activation in the central and postcentral sulcus, corresponding to the primary motor (M1) and somatosensory (S1) cortices, respectively (Diedrichsen et al. 2005; Yousry et al. 1997). Cue2 also induced activity peaks in a region along the posterior cingulate sulcus. Furthermore, in the occipital cortex, two

TABLE 2. Brain regions activated for cue1

Anatomical Region	Functional Label	Side	x	y	z	t-Value	R ²
Anterior cingulate sulcus	CMA	L/R	-3	8	46	11.3	0.36
Dorsolateral prefrontal cortex	dl-PFC	L	-33	32	34	5.3	0.37
		R	39	38	37	3.9	0.23
Frontal insular cortex	Insula	L	-30	20	7	9.6	0.45
		R	33	17	10	5.6	0.37
Intraparietal sulcus	IPS	L	-15	-67	40	8.7	0.50
		R	15	-61	46	6.6	0.53
	—	L	-39	-43	34	8.2	0.45
		L	-27	-65	34	9.7	0.51
		R	33	-46	37	6.6	0.45
Lateral occipital cortex	Lat. Occ.	R	39	-58	7	4.4	0.52
Medial occipital sulcus	Precuneus	L/R	-3	-61	40	9.7	0.33
Occipital cortex	V3A/V7	L	-27	-73	22	9.0	0.55
		R	24	-70	22	6.1	0.55
Parieto-occipital sulcus	PO	L	24	-67	31	11.8	0.54
		R	18	-73	28	5.5	0.47
Precentral sulcus	PMd	L	-36	-10	52	12.3	0.44
		R	33	-10	52	9.4	0.44
	PMv	L	-51	-1	43	8.3	0.27
		R	45	-4	46	8.5	0.33
Superior frontal sulcus	SMA	L	-12	-7	64	13.1	0.39
		R	6	-1	52	10.8	0.45

Coordinates in millimeters: x (lateral/medial), y (anterior/posterior), and z (superior/inferior), according to Talairach and Tournoux (1988). The *t*-values represent the areas' statistics across all subjects; *R*² values give the goodness-of-fit of the GLM model.

regions exhibited significant activity in response to cue2. More precisely, one area was found close to the calcarine fissure (V1/V2) and the other situated in the lateral occipital cortex (Lat.Occ.) (Astafiev et al. 2004). Finally, subcortical activity was found in the thalamus and putamen (Kertzman et al. 1997), whereas cerebellar activity was primarily observed in the anterior cerebellum (not shown) (Hanakawa et al. 2003). Table 3 presents the Talairach coordinates, peak *t*-values, and *R*² values of all regions activated in response to cue2.

It is important to emphasize here that the sensory aspects of the first and second cue were identical. Either the first cue signaled the target and the second cue indicated the effector, or vice versa. Because this was balanced over trials, the activity of the regions that were activated only for cue2 must reflect a stage that transcends mere stimulus processing because they

did not become activated when the same stimulus information was presented by cue1. Thus this activity can be assumed to encode information that resembles a computation using both cue1 and cue2 information. In this respect, these regions may reflect the preparation of a motor plan, as formulated after the consecutive presentation of target and effector cues. Importantly, some of these regions are more typically observed during motor execution than during preparation, such as M1, S1, posterior CMA, thalamus, and putamen (but see Simon et al. 2002; Thoenissen et al. 2002). We can therefore not exclude that their activity is the result of descending corticospinal activation arising from anticipatory finger tensing while pressing the button box or of some other preparatory movement, which would not have been detected if no active finger pressing were involved. Also worth mentioning, because these regions do not respond significantly to the single presentation of the cues, they may not be attributed a direct role in integrating spatial and effector signals for human reaches.

INTEGRATING SPATIAL AND EFFECTOR SIGNALS. So far two types of regions have been described: 1) regions that were activated by both cue1 and cue2 and 2) additional regions that were responsive only to cue2. The first type of regions may just respond to the mere sensory aspects of the cues, or reflect a response related to a single aspect of the stimulus, whereas the second type probably reflects a stage of computation that follows the actual integration process. It could be argued that the regions that are crucially implicated in the combination of the two cues should respond to each of the two cues, but with a stronger response to the second cue than to the first, as a result of the additional integrative processing to establish a reach plan following cue2 (Calvert et al. 2001; Meredith and Stein 1983). Because the BOLD signal represents the averaged response from a large population of cells within the same area, the more lenient requirement of simply a response to cue1 and a response to cue2 could indicate stimulation of separate populations of effector-specific and target-specific cells within

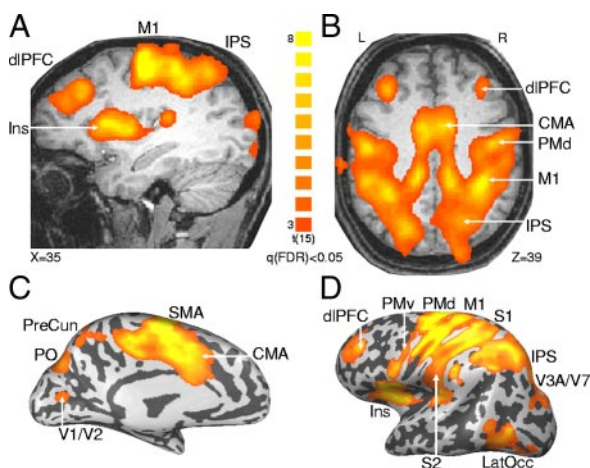


FIG. 3. Brain activation in response to the second cue (cue2 > fixation). Data in same format as that in Fig. 2. Various regions that responded to cue1 (Fig. 2) are also activated in response to cue2. In addition, activation can be observed in the primary motor (M1) and somatosensory (S1, S2) cortices, occipital cortex (Lat.Occ.), and in the thalamus, putamen, and cerebellum (not shown).

TABLE 3. *Brain regions activated for cue2*

Anatomical Region	Functional Label	Side	x	y	z	t-Value	R ²
Anterior cingulate sulcus	CMA	L	-9	5	39	7.3	0.53
		R	9	5	39	7.7	0.49
Central sulcus	M1	L	-30	-28	58	8.9	0.45
		R	24	-22	52	10.1	0.51
Dorsolateral prefrontal cortex	dl-PFC	L	-33	26	37	7.6	0.37
		R	33	32	34	6.3	0.32
Frontal insular cortex	Insula	L	-39	8	7	11.5	0.40
		R	24	7	10	9.2	0.58
Intraparietal sulcus	IPS	L	-24	-61	46	8.6	0.55
		R	21	-64	46	7.1	0.40
		L	-33	-43	43	8.7	0.53
		R	27	-46	46	8.6	0.54
Lateral occipital cortex	Lat. Occ.	L	-45	-64	4	8.1	0.51
		R	45	-67	4	7.0	0.35
Medial occipital sulcus	Precuneus	L	-12	-73	7	4.5	0.37
		R	9	-70	10	3.7	0.39
Parieto-occipital sulcus	PO	L	-21	-70	37	7.8	0.48
		R	12	-77	34	6.1	0.36
Occipital cortex	V3A/V7	L	-21	-79	19	5.5	0.59
		R	12	-79	28	7.8	0.44
Postcentral sulcus	S1	L	-30	-37	55	13.0	0.45
		R	33	-37	55	7.8	0.39
	—	L	-39	-31	16	9.3	0.39
		R	36	-31	16	9.4	0.43
	S2	L	-48	-34	25	6.9	0.46
		R	51	-34	28	8.1	0.40
Postcingulate sulcus	—	L	-12	-31	40	8.6	0.52
		R	6	31	43	11.5	0.45
Precentral sulcus	PMd	L	-36	-13	52	14.4	0.46
		R	30	-16	52	10.9	0.50
	PMv	L	-57	-1	28	7.4	0.33
		R	51	-1	34	7.3	0.37
Putamen	Putamen	L	-24	2	7	10.6	0.43
		R	21	2	10	11.1	0.48
Superior frontal sulcus	SMA	L	-6	-7	49	13.6	0.46
		R	6	-10	49	16.0	0.50
Thalamus	Thalamus	L	-15	-19	7	7.8	0.52
		R	12	-22	7	7.5	0.48

See Table 2 for explanatory details.

a single voxel sampled in fMRI. The present definition of integration, however, ensures the detection of a single neural population that receives both target and effector information and combines these cues to formulate a movement plan, with the computational effort of integration and movement plan preparation potentiating the activity after presentation of the second cue. The critical contrast for isolating such regions is

computed by cue2 > cue1, masked by cue1 > fixation (see METHODS).

As listed in Table 4 and illustrated in Fig. 4, several brain regions met these requirements, including a bilateral region in the posterior parietal cortex (IPS), the regions in the premotor cortex (PMd, PMv), and the motor regions on the medial bank of the frontal cortex (SMA, CMA) and the insular cortex (Ins).

TABLE 4. *Areas playing a role in target–arm integration*

Anatomical Region	Functional Label	Side	x	y	z	t-Value	R ²
Anterior cingulate sulcus	CMA	L	-9	6	34	6.0	0.50
		R	2	0	41	6.8	0.43
Dorsolateral prefrontal cortex	dl-PFC	L	-31	30	29	3.6	0.41
Frontal insular cortex	Insula	L	-39	5	7	8.9	0.43
		R	36	9	10	5.1	0.33
Intraparietal sulcus	IPS	L	-26	-52	52	6.6	0.48
		R	15	-54	49	6.9	0.55
Lateral occipital cortex	Lat. Occ.	R	54	-64	4	5.0	0.43
Precentral sulcus	PMd	L	-30	-19	53	13.1	0.52
		R	29	-19	55	11.4	0.49
	PMv	L	-57	2	26	3.9	0.34
		R	51	-1	34	5.2	0.36
Superior frontal sulcus	SMA	L	-6	-16	54	14.0	0.45
		R	6	-10	50	13.3	0.49

See Table 2 for explanatory details.

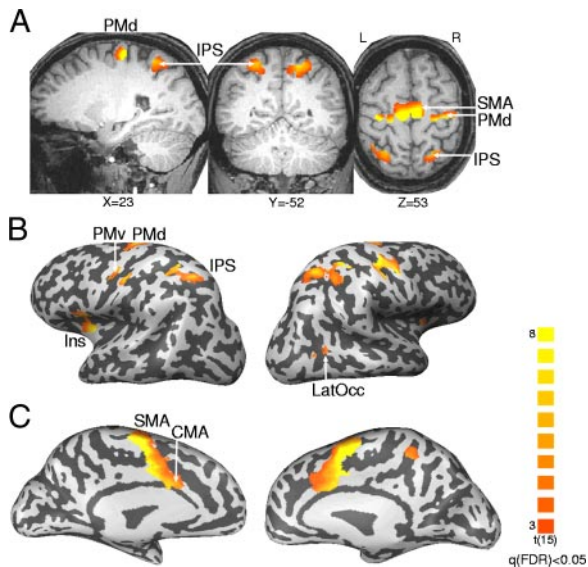


FIG. 4. Regions involved in target–arm integration. Mean data of 16 subjects presented in 3 anatomical views in neurological convention (A) and on an inflated representation of both hemispheres of a single subject (B, C). All regions responded significantly to cue1 as well as increased their activity after cue2, when all information was available for the development of a movement plan (contrast: cue2 > cue1, masked by cue1 > fixation). This analysis identified the bilateral SMA, CMA, PMd, PMv, IPS, and insula, together with the left dl-PFC and an area in the right lateral occipital sulcus (Lat.Occ.) in planning movements based on sensory signals. $P < 0.05$, FDR-corrected.

Furthermore, the left dorsolateral prefrontal cortex (dl-PFC) and an area in the right lateral occipital sulcus (Lat.Occ.) showed activation for this contrast. This suggests that these regions play an important role in integrating spatial and effector signals when planning a reaching movement in humans, consistent with much of the neurophysiological data from nonhuman primates (Calton et al. 2002; Hoshi and Tanji 2000, 2002, 2004a,b,c, 2005; Hoshi et al. 2005). In the remainder of this paper, we refer to these regions as target–arm integration regions.

How much are these integration regions also involved in executing the reach? As outlined in METHODS, our design separated three stages in the sensorimotor process for reaching: an information-processing stage (cue1), a retrieval-and-integration stage to prepare a reach plan (after cue2), and a movement-execution phase (after the go-signal). Figure 5 demonstrates the activation of the target–arm integration regions in each of these phases, by plotting the mean group beta weights estimated by the GLM analysis for these ROIs. Obviously, by definition, all integration regions were significantly more activated in response to cue2 than to cue1. In addition, virtually all of these regions demonstrated significantly higher activation during reach planning than for reach execution, consistent with a specialized role of transforming visual information into information required for motor planning. By contrast, primary motor cortex (M1), shown in the *bottom panel* of Fig. 5, shows virtually no response to cue 1, whereas this region demonstrates more activation during reach execution than during reach planning.

SPATIAL AND EFFECTOR SELECTIVITY. So far, our findings provide insight into the neural circuit engaged in integrating target and effector information to establish a reach plan. As shown in Fig. 6, all regions in this circuit appear to encode both the

position of the reach target (spatial information) and the arm to be used for the reach (effector information) because in all of these regions either spatial information or effector-specific information can evoke activity without the other—but how specific are these regions to each of these instructions in isolation?

In this study, the four regressors in the GLM (leftward target, rightward target, left hand effector, right hand effector) that model the total response to cue1 (see METHODS) effectively characterize the response to spatial target information and effector information in isolation. For each of the identified regions, we performed post hoc comparisons of the respective beta weights associated with these regressors using repeated-measures ANOVAs (see METHODS). In a lumped comparison of

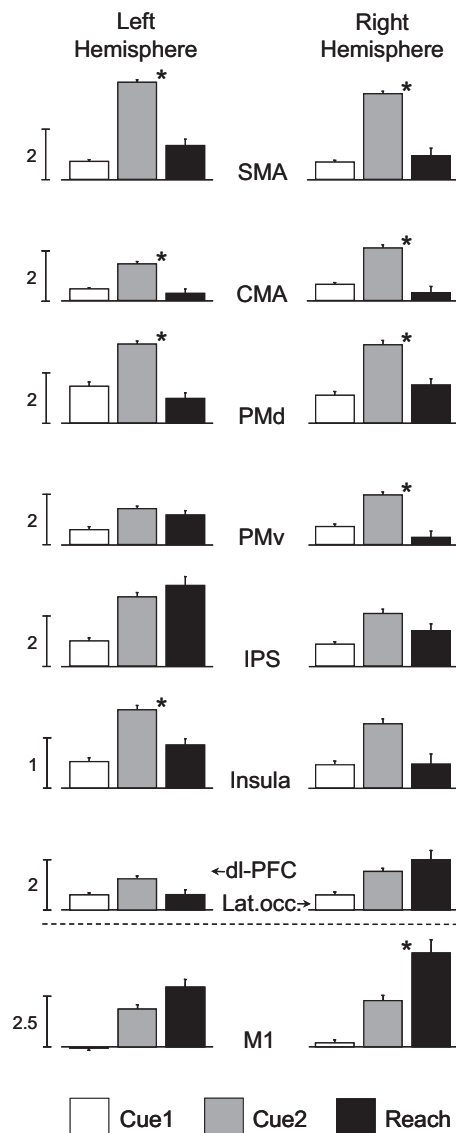


FIG. 5. Comparison of the level of activation (beta weights, in arbitrary units) in the integration regions during the 3 phases of the visuomotor transformation of a reach: information retrieval (cue1), integration (cue2), and reach execution (go-cue). Data of M1 are given for comparison. Average of 16 subjects. Error bars: SE. Given their definition, all target–arm integration regions responded significantly more strongly to cue2 than to cue 1 ($P < 0.05$). In addition, stars indicate regions that showed significantly ($P < 0.05$) more activity during the preparation interval (cue2) than during the reach (after the go-cue).

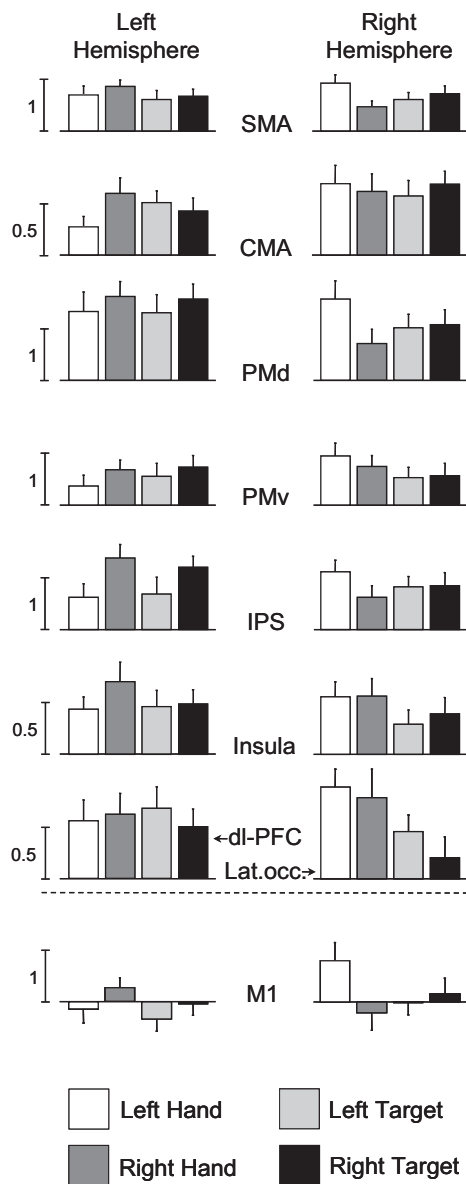


FIG. 6. Spatial and effector selectivity in response to cue1. Averaged beta weights (in arbitrary units) of 16 subjects for all regions involved in target–arm integration, for each of the 4 types of cue 1: left hand, right hand, leftward target, and rightward target. Contralateral hand preferences are shown for SMA, CMA, PMd, IPS, and the insula. Data of M1 are shown for comparison, showing virtually no response to cue1. Error bars: SE.

the data following cue1 presentation (leftward + rightward target vs. left hand + right hand effector), we observed no significant difference in the average response to a target or effector cue in most regions, except for the bilateral insula [$F_{(1,15)} = 5.2$, $P = 0.037$] and the right lateral occipital area [$F_{(1,15)} = 17.3$, $P = 0.001$], that showed a preference for effector over target information. In separate analyses, we tested for laterality effects, either for target location (left/right) or for effector hand (left/right). As such, only bilateral CMA showed a spatially selective response, i.e., a significantly different activation for leftward and rightward targets [$F_{(1,15)} = 5.5$, $P = 0.033$]. A larger set of regions showed effector-specific modulations, including the SMA, CMA, PMd, IPS, and the insula. These regions demonstrated significantly larger responses to

cueing the contralateral effector hand than the ipsilateral hand [for all regions, $F_{(1,15)} > 5.0$, $P < 0.05$]. These regions thus specify which hand is intended to act in a later response, even in the absence of a selected goal for this action. For comparison, M1 seemed virtually not activated in response to the first cue; if anything, it showed a small response to the contralateral effector cue.

We also quantitatively analyzed the degree of spatial and effector specificity during the second delay period, i.e., during the preparation of the movement. Because a repeated-measures ANOVA generally revealed no significant main effect of the order in which target and effector cues were presented [$F_{(1,15)} < 4.4$, $P > 0.05$ for all regions but the right Lat.Occ: $F_{(1,15)} = 7.7$, $P = 0.014$] we made no distinction between target–effector and effector–target trials. Figure 7 illustrates the activation (using the mean beta weights of the respective regressors in the GLM) of each of the integration regions in the four different planning conditions, defined by a combination of either the left or right hand and either a leftward or rightward target. As shown, spatial-selective responses were found in bilateral PMd and IPS, with each region showing a preference for targets located in the contralateral hemifield. This observation was confirmed by a significant interaction effect in a two-way ANOVA, with target location (left/right) and hemisphere (left/right) as factors [PMd: $F_{(1,15)} = 6.1$, $P = 0.026$; IPS: $F_{(1,15)} = 4.8$, $P = 0.045$]. Furthermore, effector specificity was found in the same regions as during the first instruction stage, including SMA, CMA, PMd, PMv, and IPS [all regions, $F_{(1,15)} > 5.0$, $P < 0.05$]. Complete lateralization to the contralateral effector was observed in M1 [$F_{(1,15)} = 74.4$, $P < 0.001$], as shown in the *bottom panel* of Fig. 7.

Figure 8 demonstrates the interaction effect in a clearer fashion, by plotting the differences in activation (\pm SE) in relation to effector hand (Fig. 8A) or target location (Fig. 8B), averaged across both hemispheres. As shown, during the movement-preparation phase, only the activation of IPS and PMd is significantly modulated by both effector hand and target location, consistent with a role in specifying the effectors and targets for action (Calton et al. 2002; Medendorp et al. 2005).

To complete our analysis, we investigated the degree of spatial selectivity and effector specificity during the reaching period. In none of the regions did we observe spatial-selective activation during the reach [$F_{(1,15)} < 1.8$, $P > 0.05$ for all regions]. Hand specificity remained present in SMA, PMd, and IPS [$F_{(1,15)} > 7.0$, $P < 0.05$], whereas such selectivity had disappeared in bilateral CMA and PMv during this phase [$F_{(1,15)} < 0.6$, $P > 0.05$]. Very strong hand selectivity remained in M1 [$F_{(1,15)} = 50.4$, $P < 0.001$].

DISCUSSION

To prepare a goal-directed reaching movement the brain must integrate information about the selected arm with information about the selected target. Here, we used a rapid event-related fMRI design to identify the neural correlates of this integration process in humans. We used a sequential instruction paradigm, adopted from monkey neurophysiological research and modified to comply with fMRI standards. Because this paradigm used time delays between the occurrence of the three instruction cues (cue1, cue2, go), we could dissociate in

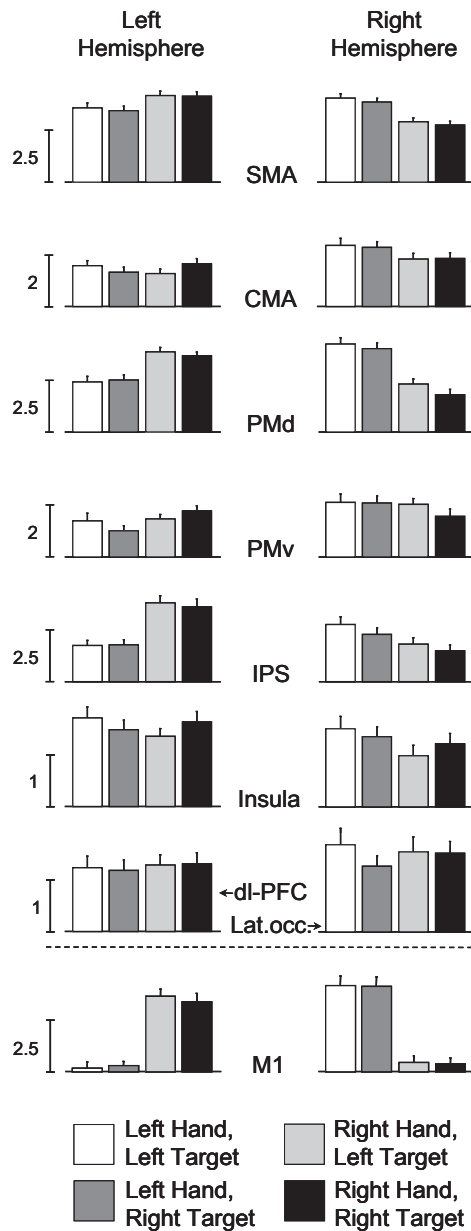


FIG. 7. Spatial and effector selectivity in response to cue2. Mean beta weights (in arbitrary units) of 16 subjects during the preparation phase of each of the 4 possible reaching movements, defined by a combination of either the left or right hand with either a leftward or rightward target. PMd and IPS show significant modulations in relation to both selected hand and target location ($P < 0.05$). SMA, CMA, and PMv show only effector-specific modulations ($P < 0.05$). For comparison, M1 shows a very strong preference for the contralateral hand ($P < 0.001$), irrespective of the location of the target for action. Error bars: SE.

a GLM analysis the metabolic demands for three separate and successive stages in the sensorimotor process for reaching. We determined the BOLD activation at the information-processing stage (cue1), the retrieval-and-integration stage to prepare a reach plan (cue2), and at the movement-execution phase (after the go-signal). In our analysis, we capitalized on the idea that regions that integrate spatial and effector signals not only should show significant activation to each of the two cues, but also should respond more strongly to the second cue than to the first, resulting from the increased metabolic demands for the

integrative processing of the two cues. As a result, we found bilateral regions in the posterior parietal cortex (IPS), the premotor cortex (PMd, PMv), the medial frontal cortex (SMA, CMA), and the insular cortex (Ins) involved in target–arm integration. Unilateral involvement was observed for the left dorsolateral prefrontal cortex (dl-PFC) and a lateral occipital region (Lat.Occ.) in the right hemisphere. These regions were generally more active during movement preparation than during movement execution. Moreover, all of these regions could be activated not only by spatial information without a motor plan, but also by the plan to use a specific effector without spatial information. Using a region-of-interest analysis, we further determined their functional properties in sensorimotor control in terms of spatial and effector specificity. This showed that the posterior parietal cortex and dorsal premotor cortex specify both the spatial location of a target and the effector selected for a forthcoming action.

As far as we are aware, no other fMRI studies have tested human subjects using the two-stage reach-instruction task of this study. However, our behavioral design borrowed heavily from previous studies in monkey neurophysiology, which has the benefit of making it possible to place the results in the context of a large body of related research in monkeys. We previously showed that the bilateral regions of the posterior parietal cortex (IPS), premotor cortex (PMd, PMv), medial frontal cortex (SMA, CMA), and insular cortex (Ins) are central to the process of reach planning based on the association of sensory signals. These regions were also observed in monkeys performing similar tasks (Calton et al. 2002; Hoshi and Tanji 2000, 2002, 2004a,b,c, 2005, 2006; Hoshi et al.

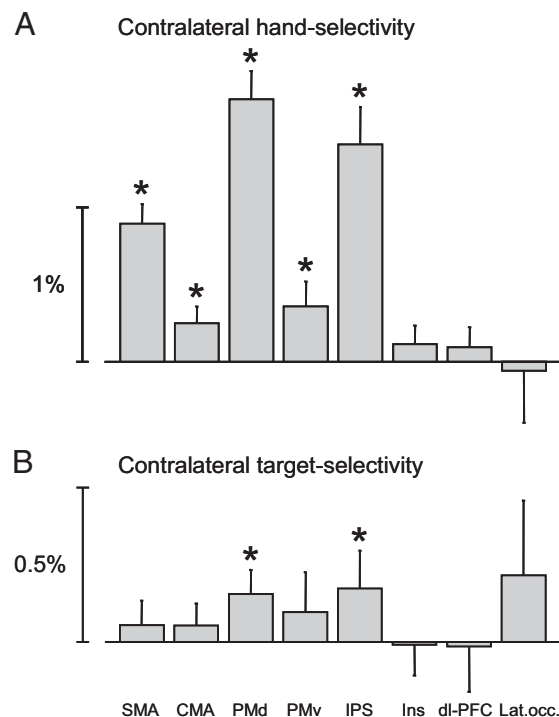


FIG. 8. Spatial and effector-specific modulations pooled across hemispheres during the reach preparation phase. *A*: difference in activation between planning a reach with the contralateral hand and a reach with the ipsilateral hand. *B*: difference in activation between a reach planned toward a remembered target in the contralateral hemifield and a target in the ipsilateral hemifield. Stars indicate a significant difference ($P < 0.05$). Error bars: SE.

2005). One difference between the present paradigm and the monkey experiments by Hoshi and colleagues relates to the memory components of the effector and target cues. In the monkey studies, both cues were presented as a brief flash of a square in the periphery, the putative instructions of which were to be remembered for some time and then integrated into a movement plan. In our study, effector cues were presented centrally and remained on until the next cue appeared, whereas target cues were brief visual dots in the periphery and had to be stored in memory. Because our paradigm consisted of effector–target and target–effector trials, however, differences in memory components were balanced across epochs in the computation of the integration contrast, which resulted in virtually the same regions as observed in the monkey. Various other studies in the monkey, using slightly different paradigms, reported reach-planning activity in these regions as well (Cisek et al. 2003; Shen and Alexander 1997; Snyder et al. 2000). Thus our results highlight the synergy between primate neurophysiology and human functional imaging as to the neural mechanisms for reach planning.

Our event-related design allowed the identification of BOLD activity related to specific epochs of the task, enabling the dissection of the mere sensory and motor responses from activity that might be related to integrative processes for movement planning. This would be impossible in a block design. The present results corroborate the findings of previous human imaging studies that isolated preparatory activity for reaching movements (Astafiev et al. 2003; Connolly et al. 2003; Medendorp et al. 2003, 2005). Prado et al. (2005) recently demonstrated a more widespread pattern of brain activity for reaching to peripheral targets than to foveal targets, showing additional activation at the parieto-occipital junction (area PO) and more rostral regions of PMd for peripheral reaches. The present observation of activation in a region in the parieto-occipital sulcus during both reach planning and execution is in line with these findings as reaches were always aimed at targets flashed onto the retinal periphery.

We also observed activation in the insular cortex and lateral occipital cortex in this two-stage reach-instruction paradigm, for which, to our knowledge, corresponding experiments in monkeys have not been made. The observed activation of the insular cortex may not be surprising given its connections to parietal and premotor areas (Augustine 1996). Also, recent human neuroimaging studies reported activity in the insula during reaching movements (Desmurget et al. 2001; Grefkes et al. 2004; Kertzman et al. 1997). The activation observed in the lateral occipital cortex fits well with observations by Astafiev et al. (2004) demonstrating that activity in this region is modulated by reaching movements, even in the absence of visual feedback from the movement.

Importantly, although all parietofrontal regions we identified within the visuomotor integration network responded primarily bilaterally (Nirkko et al. 2001), they also demonstrated a contralateral organization for the hand used to reach (Cisek et al. 2003; Medendorp et al. 2005). Thus each hemisphere seems functionally specialized in the processing of visual information for the planning of a movement with the contralateral hand. In contrast, we observed a lesser degree of laterality for target location (spatial selectivity) within the network. That is, contralateral spatial selectivity was observed only in the posterior parietal cortex (IPS) and dorsal premotor cortex (PMd) during

the second delay period, in the integration phase. The fact that only a trend toward spatial selectivity was found in the first delay period may simply reflect a lack of statistical power because that analysis was based on only half of the trials. Importantly, in the integration phase, the representations in regions IPS and PMd contained information about both the selected hand and target location (Medendorp et al. 2005). In terms of target selection and effector selection, it can be argued that only these regions within the integration network reflect the specific action that is to be performed. IPS and PMd were able to retrieve selective information about the effector or the spatial target, retain the fragment of information given first until receiving the second fragment, and then integrate the two sets of information to specify the forthcoming action (Calton et al. 2002; Hoshi and Tanji 2006). Along the same lines, then, it could be argued that the other regions identified here fulfill a more general, global role in the visuomotor integration for reaching movements, perhaps involved in monitoring and simulating behavior (Hoshi et al. 2005; Picard and Strick 2001).

Although we are confident in concluding that the massed activation in the regions PMd and IPS reflects a demonstration of sensorimotor integration, there may be limits to this interpretation. For example, one may regard the observed BOLD changes as representing a neural correlate of a decision-making process for response selection. Various studies indicated that the primate brain can simultaneously specify several likely alternative movement directions, before making a decision between them, with the neuronal activity depending on the probability that a particular movement will be selected (Basso and Wurtz 1998; Cisek and Kalaska 2005; Cisek et al. 2003). However, in these studies, the effector was known and the number of potential target locations was varied. It is therefore difficult to determine whether the results of these studies examined the preparation of multiple movement plans or the mere representation of multiple target locations for a single effector. In the present study, the brain may have simultaneously encoded the four potential target locations when the effector cue was presented to formulate four movement plans. Likewise, when the target was cued first, the brain may at the same time have derived internal information about the two effectors to develop two concurrent effector-specific movement plans. Our fMRI study does not allow differentiation between decision-making and motor-planning mechanisms, and it seems plausible that the network that we probed is involved in both processes. Further experiments may be useful to assess in more detail the possibility of contingency plans for multiple potential movements in the regions.

In natural situations, a reaching movement toward an object is often accompanied by a movement of the eyes to the same goal. The present study, however, was restricted to reaching with the eyes fixating centrally. Although we did not record eye movement information during scanning, previous work showed that subjects are quite able to perform such a task (Medendorp et al. 2005), although some subjects may maintain better fixation than others. Could (part of) the activation be confounded by unwanted eye movements? Perhaps. Neither can we exclude that subjects made plans for both eye and arm movements, with the eye movement plan cancelled at the moment of execution. Moreover, it is well established that there is no complete segregation between eye and arm movements for the activation in many regions in parietal and frontal

cortex (Lawrence and Snyder 2006). However, the presence of arm-effector-specific signals in most of the integration regions is not consistent with an explanation of our results by eye movements only. That said, many of these regions were shown to play important roles in coordinating the hand with the eye (Buneo et al. 2002; Pesaran et al. 2006). It would be useful to perform experiments that explicitly dissociate eye movement planning from reaching movements to further address this issue (Snyder et al. 1997).

In line with previous studies (Batista and Andersen 2001; Buneo et al. 2002; Calton et al. 2002; Hoshi and Tanji 2000, 2002, 2004c, 2006; Kertzman et al. 1997; Medendorp et al. 2005), our results suggest that both IPS and PMd play crucial roles in the integration of the target's location with information about the selected effector. This interpretation of the data hinges critically on the fact that these regions show bilateral but differential responses to target locations and effector instructions. Note, however, that we cannot discern whether the differential response to the effector instructions reflects a neural correlate for the current position of the hand or a correlate for the selection of the hand. This would require further experiments, with the hand put at different starting positions within the workspace.

Related to this, human psychophysics has suggested that a reaching movement is planned in terms of a vector (Shadmehr and Wise 2005; Vindras and Viviani 2005), in eye-centered coordinates (Beurze et al. 2006; Henriques et al. 1998). To compute this vector, the locations of the target and hand must be expressed in the same reference frame. Taking this to the neural level, this means that common coordinates are required to facilitate the integration of target and effector information for the computation of the hand-to-target difference vector. Consistent with the psychophysics, Buneo et al. (2002) suggested that this vector is computed in the monkey posterior parietal cortex, in eye-centered coordinates. Here, in the human, the region in posterior parietal cortex that we have identified exhibits some overlap with region "retIPS," which was previously shown to code reach representations in eye-centered coordinates (Medendorp et al. 2003, 2005).

Based on this, we would suggest that the IPS region identified here begins the neural computations required for an accurate reach by integrating target and hand information in eye-centered coordinates. It is also known that information about initial hand position is coded in the postcentral sulcus, in a somatotopic map, as relative joint angles (Gardner and Costanzo 1981; Helms Tillery et al. 1996). Note that we observed activation in the postcentral sulcus after the second cue (see Fig. 3), which could be interpreted as a readout of this map. This activation is then "transferred" into more posterior regions and recoded to represent the position of the hand relative to the eye to facilitate the integration with the eye-centered target location information.

Obviously, because muscles need to contract to make a reaching movement, further processing is required to transform an eye-centered reach representation into a more intrinsic limb-centered muscle-based motor command. The further implementation of this coordinate transformation must occur downstream from the eye-centered IPS region. Based on the present results, we cannot make any claims about the exact role of the PMd region in this transformation because we did not test between reference frames. However, because PMd is

generally accepted to be a motor area, it is likely to be involved in this transformation, also given its sensitivity for the initial position and orientation of the arm (Caminiti et al. 1991; Pesaran et al. 2006; Scott et al. 1997) and for eye position signals (Boussaoud et al. 1998). A crucial experiment to be performed therefore would be to investigate the activity in these integration regions with respect to the reference frames they deploy (Beurze et al. 2006; Buneo et al. 2002; Pesaran et al. 2006).

In summary, the present study revealed a distributed network of motor regions engaged in the integration of target and effector information for the planning of a human reach. Although these findings impose significant insights in reach planning in general, as well as in the relationship between primate neurophysiology and human functional imaging, future work should address the functional properties of nodes in this network in more detail.

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