

Brain mechanisms for preparing increasingly complex sensory to motor transformations

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Movements made in response to sensory cues require the brain to transform sensory information into an appropriate motor output. Sensorimotor mappings used in daily life range from direct or “standard” to highly complex. In “nonstandard” sensorimotor tasks, the visual stimulus guiding an action is often not the target of the action. A common example of such a nonstandard mapping is the use of a computer mouse on a horizontal surface to guide an object visible on a vertical monitor. The present study used event-related BOLD fMRI to examine how patterns of brain activity vary as sensorimotor mappings become progressively more complicated. We observed significantly different patterns of cortical activity depending on the level of dissociation between a sensory input and a required motor response. Our results suggest the presence of a functional network generally involved in performing the type of nonstandard sensorimotor tasks examined. This putative network includes regions of the primary motor cortex, medial motor areas, the superior parietal lobule (SPL), and the lateral premotor cortex. The extent of activity in active areas varied depending on the characteristics of the particular sensorimotor mapping used in performing a task. Furthermore, in addition to this putative network, specific task-related areas of activity were observed.

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Introduction

Movements are often made in response to sensory stimuli received from the environment. These movements require the integration and transformation of sensory information into a motor response (i.e., “sensorimotor transformation”). Motor responses to the same stimulus can vary depending on the requirements of a given task. Wise et al. (1996) have classified

sensorimotor mappings into categories that depend on the context of a task. A sensorimotor transformation is considered to use a “standard mapping” when the visual stimulus guiding an action is the target of the action. For example, reaching out to grasp a cup of coffee in front of you. In daily life, we also often perform “nonstandard” sensorimotor tasks, which include “transformational” mappings. A transformational sensorimotor mapping occurs when an algorithm relates visuospatial information to the direction of movement. An example of this type of mapping is the use of a computer mouse on a horizontal surface to control a cursor displayed on a vertical monitor. In this example, the operator must move the mouse “forward” horizontally to move the cursor “up” on the monitor. The present study uses fMRI to examine the neural correlates of transformational visuomotor tasks in the human brain.

Previous psychophysical studies have revealed that movement kinematics can change as the alignments of sensorimotor mappings are varied. Messier and Kalaska (1997) had subjects reach to locations on a horizontal workspace. In some trials, subjects touched targets directly using their index finger. In other trials, subjects displaced a cursor reflecting finger location to targets displayed on a vertical screen. Patterns of spatial errors (direction and extent) of final endpoint position were found to differ between the two conditions in spite of the fact that movements made in each condition were biomechanically identical. Others have observed changes in reaction time (Dassonville et al., 1999; Ghilardi et al., 2000), hand-path curvature (Goodbody and Wolpert, 1999), and learning processes (Clower and Boussaoud, 2000) when subjects were required to perform nonstandard sensorimotor tasks (compared to standard transformations). These changes may reflect differences in processing used by the brain to account for variation in the alignment of sensory input and motor responses. Patient studies also suggest that regions of the brain are differentially involved in sensorimotor transformations depending on the alignment of a given task. For example, compared to control subjects, the ability of individuals with Alzheimer disease to perform a transformational sensorimotor task can deteriorate (Ghilardi et al., 1999).

In this study, we used event-related BOLD fMRI to examine how patterns of activity in the human brain vary during

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progressively complex transformational visuomotor tasks. These tasks require increased cognitive processing and attention (relative to standard mappings), as they require the brain to take into account various amounts of task-specific information (such as how to use a particular tool or specific task-related rules). We hypothesized that different patterns of cortical activity would result from varying the level of dissociation between sensory input and required motor output. Specifically, we predicted that as sensorimotor tasks become progressively complex, additional areas of the brain would become active (relative to those active during a standard mapping task).

Examinations of human brain activity associated with sensorimotor transformations are fairly uncommon. In part, this is because imaging techniques, such as fMRI, are often sensitive to movement. Here, we minimize the contribution of movement artifacts to our data by using an event-related, instructed-delay paradigm. This protocol allowed us to examine the neural correlates of movement preparation for increasingly dissociated visuomotor transformations without having to include imaging volumes in which subjects performed an overt motor response in our analysis. In this study, subjects performed four progressively complex sensorimotor transformations. These tasks included a relatively direct reaching task, a rotated reaching task, a joystick task, and a rotated joystick task.

Materials and methods

Subjects

Nine right-handed females between the ages of 20 and 37 participated in the study. Females were used exclusively because pilot data demonstrated sex-related activity pattern differences in the tasks examined (ongoing study). All subjects provided informed consent, and handedness was verified using the Edinburgh inventory (Oldfield, 1971). None of the subjects had a history of neurological problems. All subjects had normal or corrected-to-normal (with contact lenses) vision.

Apparatus

BOLD fMRI was performed using a 4.0 Tesla, Varian/Siemens Unity INOVA whole-body scanner (Robarts Research Institute, London, Ontario). A birdcage RF head coil was used (Barberi et al., 2000). Subjects lay supine in the bore with their heads flexed forward approximately 30° using a “tilt-board.” A plastic screen was suspended vertically (approximately midway between the

waist and shoulders) at a distance that allowed subjects to directly see and touch back-projected targets. Motion about the wrist to acquire targets was approximately 30° for the hand movement conditions and 15° for the joystick conditions (see Description of conditions below). However, these values varied by subject from 10° to 20° depending on projection distance. Stimuli were generated using custom-written software (Matlab, Mathworks Inc.) run from a portable computer.

An interface was created which allowed subjects to control a modified joystick (Thrustmaster XL Action Controller) using their right index finger. The joystick was attached to the scanner bed such that subjects could control it with their arm resting comfortably beside them (Fig. 1).

Four bend sensors (Images SI, New York) were sewn into a thin, flexible glove (on the medial, lateral, dorsal, and ventral aspects), which subjects wore on their right hand. This allowed us to record kinematic details of hand movements made from within the bore of the magnet.

Training

Subjects were trained extensively at least 1 day before imaging data collection to ensure that activity reflected a learned paradigm rather than motor learning. Training was performed first at a desktop and then in a simulated scanner. The simulated scanner matched the dimensions of the actual imaging environment as closely as possible. Training lasted approximately 2 h per subject (or until subjects could perform all tasks repeatedly without error). Subjects also practiced all conditions from within the magnet immediately before scanning.

General paradigm

Each subject performed three consecutive imaging runs. Each run consisted of 30 s of baseline measurement (subjects were instructed to rest with their eyes open) followed by six conditions (described below—four experimental and two control presented in random order). Subjects performed five trials per condition per run (Fig. 2). Each imaging run was approximately 18 min long. T1-weighted anatomical images were collected immediately before collection of functional images.

Subjects performed instructed-delay tasks using both their eyes and/or right hand. Each condition began with an instruction period during which the name of the condition to be performed was projected onto the screen for 2 s. Subjects had previously memorized which condition each name was associated with during their training sessions. Following the instruction period,

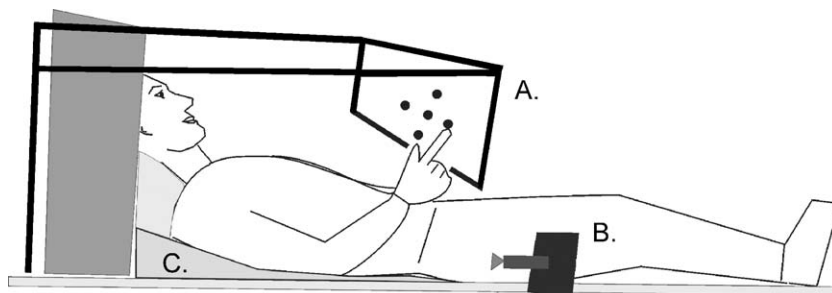


Fig. 1. Equipment setup. A schematic representation of a subject within the bore of the magnet. A represents the position of the screen onto which targets were projected; B, the position of the joystick; and C, the “tiltboard” used to flex subjects’ heads slightly forward.

Layout of a condition:

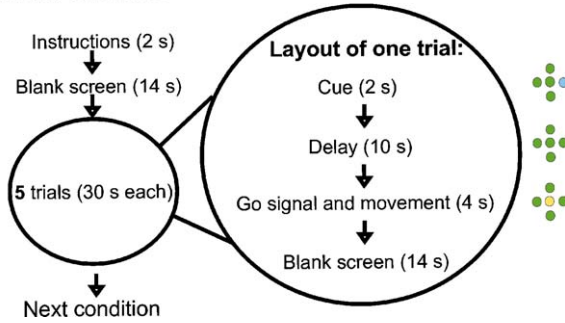


Fig. 2. The temporal layout of one condition within an imaging run. Each subject performed three consecutive runs. Each run contained all six conditions in random order as described in the Materials and methods.

subjects rested while the screen was darkened for 14 s to allow the hemodynamic response to return to baseline before beginning trials. Each trial was structured as an individual event (Rosen et al., 1998). A center target surrounded by four peripheral targets (at 0°, 90°, 180°, and 270°) appeared on the screen (“cue period”). Subjects were instructed to fixate on the center target. During the cue period, all targets (including the center target) were colored green except for one randomly selected peripheral target, which was blue. The blue color indicated the peripheral target for the trial. After 2 s, the peripheral target of interest changed from blue to green and all targets remained green for 10 s (“delay period”). Subjects were instructed to maintain central fixation during this delay period. The center target then turned from green to yellow providing subjects with a “go signal.” Subjects had 4 s in which to perform the required task. After this “movement period,” the screen was darkened again for 14 s before another trial (or another condition) began. Stimuli were identical for all conditions with the exception that a cursor was

visible after the go signal during the joystick conditions (see below).

Subjects’ heads were securely braced within the head coil using padding, and their upper arms were strapped to their torsos to minimize task-related head movements. Hand movements were kept as consistent as possible between conditions. In all cases, hand movements were made using motion at the wrist. Contact with both the screen and the joystick was made with the right index finger, and movement amplitude was kept small. Subjects were trained to make identical eye movements for all experimental conditions. However, eye movements were not monitored within the scanner as an MRI-compatible eye-tracking system was unavailable. Subjects were instructed to maintain fixation on the center target until receiving their go signal. At the go signal, subjects were trained to move their eyes from the center target to the cued peripheral target and then to keep their eyes on that target until the screen was darkened at the end of each trial.

Description of conditions (Fig. 3)

Condition 1—hand movement (HM)

At the go signal, subjects used their right index finger to touch first the center target and then the cued peripheral target. Subjects maintained contact with the peripheral target for approximately 1 s before returning their hand to a comfortable resting position immediately in front of the screen onto which targets were projected. Subjects were instructed to perform identical eye movements for each experimental condition (as described in the preceding section) (Fig. 3).

Condition 2—rotated hand movement (RHM)

As above except that at the go signal, subjects touched first the center target and then the peripheral target 180° opposite to the

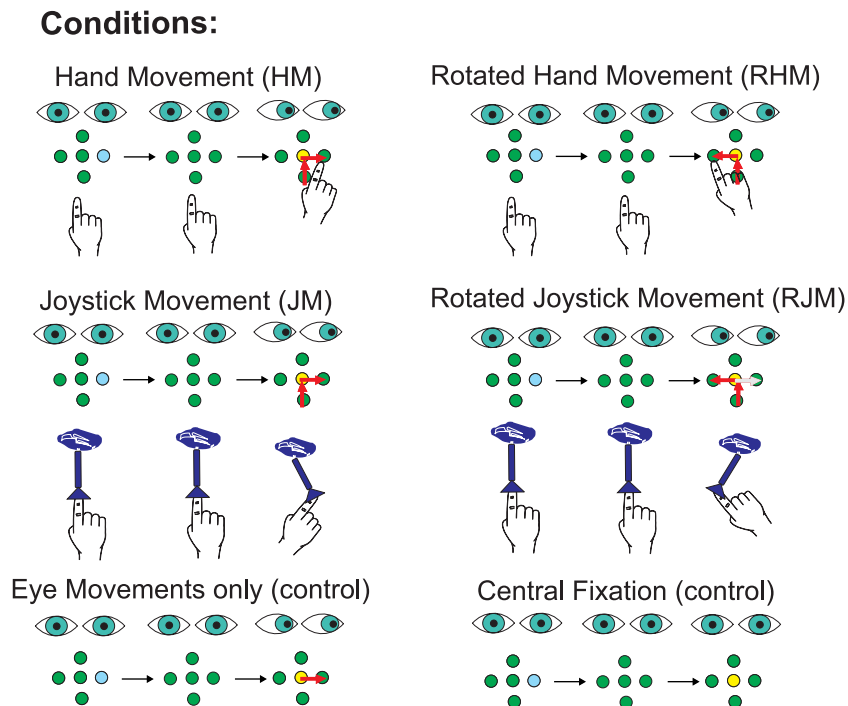


Fig. 3. An illustrated representation of hand/joystick and eye movements made during the six conditions examined in each imaging run.

cued peripheral target. In other words subjects were instructed to move their eyes to the cued target while moving their hand in the opposite direction.

Condition 3—joystick movement (JM)

Subjects used their right index finger to control a joystick. Movement of the joystick reflected movement of a cursor on the screen. At the go signal, subjects moved the cursor first to the center target and then to the cued peripheral target and held the cursor on target for approximately 1 s before lowering their hands to a comfortable resting position at their sides.

Condition 4—rotated joystick movement (RJM)

At the go signal, subjects used the joystick to move a cursor into the center target. After reaching the center target, the cursor reflected movement opposite to the direction of joystick handle movement (e.g., rightward movement of the joystick handle produced a leftward cursor movement). Subjects had to move the joystick handle 180° opposite to the direction of the cued location to move the cursor to the cued peripheral target.

Control 1—eye movements only

Subjects were instructed to only make eye movements to the cued peripheral target at the go signal.

Control 2—central fixation

Subjects were instructed to maintain fixation on the center target throughout the entire condition.

fMRI parameters

Functional imaging of the cortex was done using T2*-weighted, gradient echoplanar imaging, 64 × 64 resolution, time to echo (TE) = 12.0 ms, volume acquisition time = 2.0 s, flip angle = 40°. Fifteen 5-mm thick slices were used to collect data from the cortex, giving voxel dimension of 3 × 3 × 5 mm. Note that these parameters did not allow for collection of functional data from noncortical structures (including the cerebellum) in the majority of subjects. Acquisition of data from each slice was interleaved. Anatomical imaging was performed using turboFLASH, T1-weighted acquisition with 128 slices, TE = 5.5 ms, TR = 640 ms, flip angle of 11°, and a resolution of 0.8 × 0.8 × 1.25 mm.

Analysis of fMRI data

Data were analyzed using BrainVoyager 2000 (Brain Innovation). Time series for each data set were not concatenated to account for the effects of interrupting data acquisition between imaging runs. Preprocessing of functional data for each subject included motion correction using the first volume of each functional time series as a reference volume. Any data set in which a subject moved more than 1 mm was eliminated from further analysis. This criterion left a total of three imaging runs for seven subjects and two imaging runs for two subjects (i.e., 25 functional imaging runs). Temporal filtering applied to functional data included linear trend removal and high-pass filtering (0.0028 Hz) to remove drift in the time course. Each subject's functional data were coregistered to their corresponding high-resolution T1-weighted anatomical data. Both functional and anatomical data sets were normalized to Talairach space. The normalized func-

tional data were spatially smoothed using a 6-mm full-width half-maximum Gaussian kernel to compensate for intersubject anatomical differences. Localization of clusters of activity were confirmed using the Damasio Atlas (1995).

A general linear model (GLM) analysis was performed using a design matrix consisting of the stimulation protocol (boxcar design) for each subject. Predictors were defined for the instruction period, cue periods, delay periods, and movement periods of each condition. Each epoch was specified by a square wave time-locked to the epoch's onset and then convolved with a hemodynamic response function. For hypothesis testing, specific contrasts compared the BOLD signal between conditions at each voxel using paired Student *t* tests with Bonferroni correction for multiple comparisons (a corrected threshold of $P = 0.05$ was used for all comparisons). In all contrasts performed, the delay periods of each condition were examined. Presumably, signal changes during the delay period contain changes associated with both the cue period and the delay period since the delay followed immediately after the 2-s cue in each trial. Therefore, the analysis focuses on portions of the time course associated with preparation of the movement (i.e., patterns of activity associated with processes undertaken before production of the overt movement).

The hypothesis that activity in regions throughout the brain would increase as the sensorimotor tasks became increasingly dissociated was tested with individual contrasts of “more complex” conditions to “less complex” conditions (RHM > HM; JM > HM; RJM > HM; RJM > RHM; RJM > JM). To test if the converse of our hypothesis was ever true (i.e., that relatively less complicated conditions would show significantly greater activity than more highly dissociated conditions), we also performed the reciprocal contrasts to those described above (HM > RHM; HM > JM; HM > RJM; RHM > RJM; JM > RJM).

To reveal the specific cortical network involved in the preparation for the sensorimotor transformations, we examined activity associated with each experimental condition relative to the eye movement only and central fixation control conditions. Conjunction analyses were performed for the delay periods of each experimental condition (i.e., HM, RHM, JM, and RJM) contrasted with the delay periods of the two control conditions. Thus, we were able to describe BOLD signal changes associated with hand movement preparation “excluding” changes in signal intensity associated with preparation of eye movements and presentation of visual stimuli. The contrasts used were as follows: (1) HM > eye movements only; conjuncted with HM > central fixation, (2) RHM > eye movements only; conjuncted with RHM > central fixation, (3) JM > eye movements only; conjuncted with JM > central fixation, and (4) RJM > eye movements only; conjuncted with RJM > central fixation.

Behavioral data

Analog joystick and bend sensor data were sampled at 150 Hz (DAQ 6024-E, National Instruments Inc.) and stored on a portable computer.

However, collection of a full set of behavioral data was only found to be reliable from two of the nine subjects (due to equipment problems). Due to this small sample size, a statistical analysis of behavioral data is not included. However, the behavioral data were useful for verifying that subjects performed required hand movements correctly (e.g., subjects moved their hands at the correct time for each trial).

Results

Activity in “more complex” conditions over “less complex” conditions

We predicted that as sensory stimuli and motor responses became increasingly dissociated, greater activity would be observed throughout the cortex. Contrary to this hypothesis, no significant clusters of activity were detected for the RHM > HM, JM > HM, or RJM > JM contrasts. A small amount of activity was observed in the RJM > HM contrast (the contrast between the most indirect and the most direct condition). This activity included significant clusters in the left precuneus, the right superior frontal and middle temporal gyri, and bilaterally in the angular gyri. The RJM > RHM contrast also revealed some significant activity. In the left hemisphere, activity was observed in the precuneus, supramarginal gyrus, temporal lobe, and hippocampus. Activity in the right hemisphere included the superior and middle frontal gyri, the postcentral sulcus, and in a large area ranging from the angular gyrus to the lateral occipital gyrus (Fig. 4, Table 1).

Activity in “less complex” conditions over “more complex” conditions

Direct contrasts between experimental conditions revealed many regions of increased activity in less dissociated visuomotor tasks relative to tasks in which sensory and motor components were more greatly dissociated (Fig. 5, Table 2). In the HM > RHM contrast, significant activity was observed in the left primary sensorimotor region, right medial motor areas, right post central gyrus, left thalamus, left midbrain, and

bilaterally in the fusiform and lateral occipital gyri. Activity observed in the HM > JM contrast included left precentral, superior frontal, lateral occipital, and cuneus regions. The comparison of HM > RJM showed a great deal of activity in the left hemisphere which included regions of the primary sensorimotor area, medial motor area, middle frontal gyrus, paracentral gyrus, and the supramarginal gyrus. This contrast also revealed activity in the right hemisphere which included the middle temporal and fusiform gyrus regions. Activity was also apparent bilaterally in the cuneus, lateral occipital gyrus, caudate nucleus, and thalamus. The JM > RJM contrast revealed significant activity in the left precentral and middle frontal gyri, the right fusiform gyrus, and the left caudate nucleus. In the RHM > RJM contrast, clusters of significant activity were observed in the left superior frontal gyrus, left cuneus, left caudate nucleus, and in the right insula.

Experimental conditions relative to controls

Relative to control conditions (eye movement only and central fixation conditions), there were some areas of activity common to all or most of the experimental conditions (i.e., HM, RHM, JM, and RJM). Details of all significant clusters of activity are shown in Table 3, and Fig. 6 shows representative group results for each conjunction analysis. All of the experimental conditions included clusters of activity in the left sensorimotor area. Activity in the left medial frontal gyrus was apparent in the HM, RHM, and JM conditions relative to controls. The HM, JM, and RJM conditions had activity in the right superior frontal gyrus and right superior parietal lobule (SPL). Interestingly, throughout the cortex, the “rotated” conditions (i.e., RHM and RJM) appear to have less overall

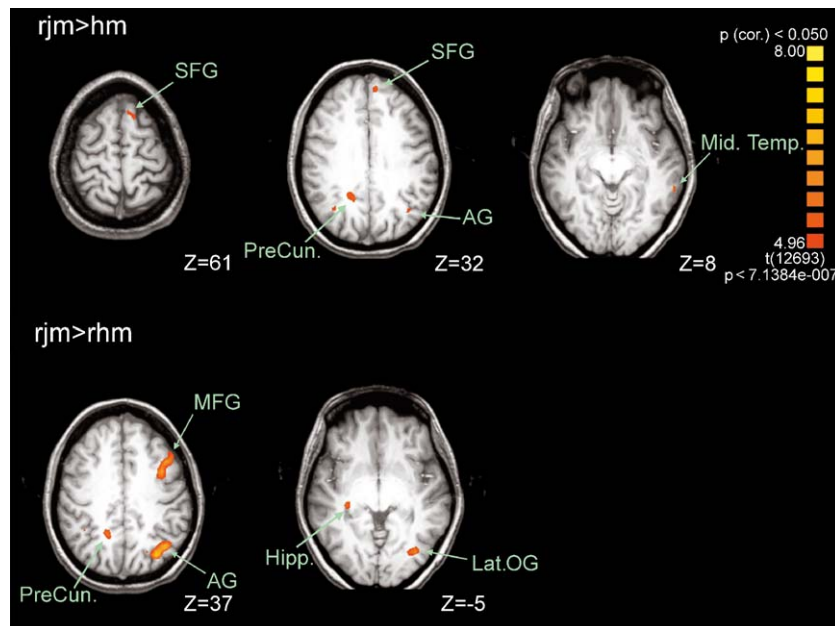


Fig. 4. Group results demonstrating significant clusters of activity in contrasts comparing “complex” conditions with “simpler” conditions. No activity was observed for the contrasts RHM > HM, JM > HM, or RJM > JM. Therefore, only results from the RJM > HM and RJM > RHM contrasts are shown. Group results are superimposed upon a normalized brain. Images are shown using neurological convention (left = left). Color bar represents corrected t value in significant voxels, P (cor.) = 0.05. SFG indicates superior frontal gyrus; PreCun., precuneus; AG, angular gyrus; Mid.Temp., middle temporal lobe; MFG, middle frontal gyrus; Hipp., = hippocampus; and Lat.OG, lateral occipital gyrus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Local maxima of significantly active regions in relatively “complex” experimental conditions compared to less complex conditions

Contrast	Anatomical region	Talairach coordinates of local maximum (x, y, z)	Extent (no. voxels)	t Value
RJM > HM	right superior frontal gyrus	9, 28, 61	77	5.43
		6, 40, 47	121	5.85
		5, 56, 29	272	5.94
	left angular gyrus	−34, −57, 31	67	5.41
	right angular gyrus	36, −58, 35	235	5.50
	left precuneus	−18, −45, 32	463	5.78
RJM > RHM	right middle temporal gyrus	57, −39, −6	67	5.60
	right superior frontal gyrus	11, 17, 63	26	5.37
	right middle frontal gyrus	38, 15, 41	2969	7.20
	right hemisphere from angular gyrus to lateral occipital gyrus	29, −62, 21	10,488	7.99
	left precuneus	−15, −47, 28	1884	6.94
	right postcentral sulcus	48, −36, 48	73	5.88
	left supramarginal gyrus	−38, −42, 35	35	5.28
	left temporal lobe	−27, −56, 24	1106	5.90
	left hippocampus region	−32, −24, −1	145	5.81

activity when compared to their “unrotated” counterparts (i.e., HM and JM).

Discussion

The progressively complex sensorimotor transformations examined here can be thought of as having increasing involvement of cognitive and attentional factors since they required subjects to implement task-related rules (e.g., moving in a direction opposite to a cued target) and they included tool use (the joystick tasks). The analyses performed in this study focused on activity related to the delay period between the cue and “go signal” in each trial. Much of the activity observed during this period of time is likely associated with preparatory set which includes activity related to the processing of the spatial location of the cue, preparation of the overt motor output, memory, and attentional processes (i.e., tasks associated with preparation of the required movement). Therefore, BOLD signal changes observed during this period of time likely arise from several sources, all of which are important to the successful performance of the visuomotor transformation tasks examined here. Thus, activity described here is associated with both movement output production itself and the cognitive factors involved in the context-specific aspects of this movement production.

We originally hypothesized that different levels of dissociation between sensory input and motor output in transformational sensorimotor tasks would result in different patterns of activity in the brain. Comparisons of experimental conditions both with controls and with one another produced evidence in support of this hypothesis. In other words, the different transformational tasks examined clearly produced different patterns of activity in the brain. However, we also made the specific prediction that as sensorimotor tasks became progressively complex, additional areas of the brain would become active (relative to those active during a more “standard mapping” task). Contrary to this prediction, our results demonstrated very little activity in contrasts of more highly dissociated sensorimotor transformations over less complex transformations (Fig. 4, Table 1). In fact, three of these contrasts (RHM > HM, JM > HM, and RJM > JM) did not reveal any

significant activity at all. Conversely, and contrary to our original prediction, contrasts designed to reveal activity in less dissociated conditions over more highly dissociated tasks revealed a large amount of activity. Our results are discussed in the following sections in the context of what previous studies have revealed concerning transformational sensorimotor tasks.

Greater overall activity associated with “less complex” tasks

As stated above, our results generally do not support our original prediction that greater activity would be observed in more complex tasks. One reason for this outcome may be the fact that we collected data from subjects who were extremely well trained and had therefore “overlearned” the tasks we examined. There is a great deal of evidence that the patterns of activity associated with motor skills change over the course of skill acquisition. For example, in a recent study by Morgen et al. (2004), fMRI was used to examine training-dependent changes in neural substrates underlying performance of simple thumb movements. Imaging data were collected before, during, and after training. The authors found that as subjects learned the task, there were reductions in activity in contralateral sensorimotor cortex and the inferior parietal lobule. In another study (Debaere et al., 2004), fMRI was used to examine changes in patterns of activity during acquisition of a complex bimanual wrist flexion and extension task. Learning-related decreases in activity were observed in the dorsolateral prefrontal, premotor, superior parietal lobule, and cerebellar regions of the brain. Interestingly, the authors also observed learning-related increases in areas of the primary motor cortex, superior temporal gyrus, bilateral cingulate cortex, premotor area, and cerebellum. Therefore, it might be interesting for us to also examine patterns of activity associated with our transformational tasks preceding and during training of subjects. Perhaps, the results of such an examination might reveal patterns of activity which more closely resemble our original predictions.

Among our results was the observation that “rotated” conditions (i.e., RHM and RJM) had significantly less activity in many regions than their “unrotated” counterparts (i.e., HM and JM). At present, functional imaging examinations of human subjects performing nonstandard, transformational tasks (especially those

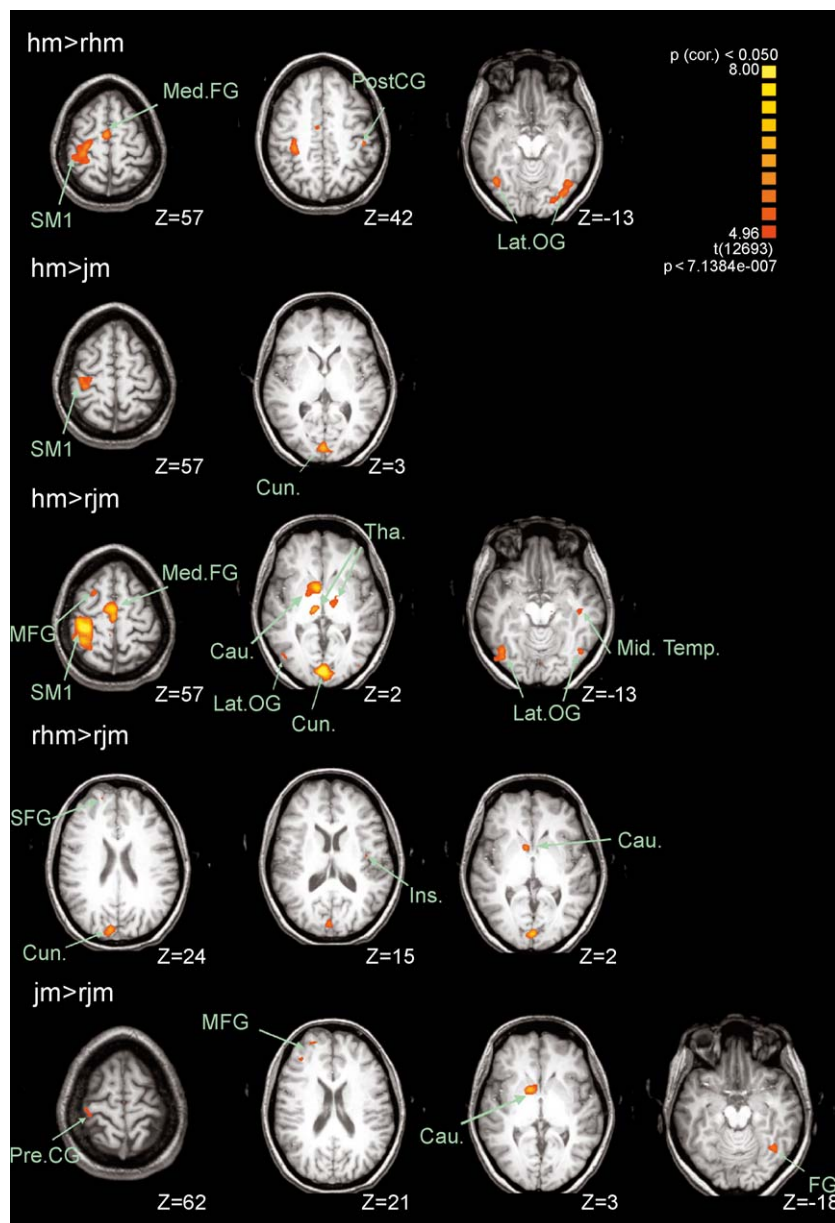


Fig. 5. Group results demonstrating significant clusters of activity in contrasts comparing "simpler" conditions with more "complex" conditions (i.e., HM > RHM, HM > JM, HM > RJM, RHM > RJM, and JM > RJM). Conventions as used in Fig. 4. SM1 indicates primary sensorimotor area; Med.FG, medial frontal gyrus; PostCG, postcentral gyrus; Lat.OG, lateral occipital gyrus; Cun, cuneus; MFG, middle frontal gyrus; Cau., caudate nucleus; Tha., thalamus; Mid. Temp., middle temporal lobe; SFG, superior frontal gyrus; Ins., insula; Pre.CG, precentral gyrus; and FG, fusiform gyrus.

requiring arm movements) are very rare. However, in general, imaging studies have demonstrated an increase in activity throughout the brain during nonstandard sensorimotor tasks (Connolly et al., 2002; DeSouza et al., 2003; Evdokimidis et al., 1996). Connolly et al. (2000) used fMRI to examine subjects performing nonstandard mapping tasks. In one condition (which was similar to the RHM condition examined here), subjects either pointed to a cued target with their finger or pointed 180° away from a cued target. In another condition, their subjects made saccades either toward or away from a cued target. In general, when subjects moved either their eyes or finger 180° away from cued targets, additional frontoparietal regions were recruited relative to movements made directly to the target. The authors concluded that, overall, the functional networks in the brain for

movements away from a target include the networks recruited for direct movements plus additional brain regions. Interestingly, the authors did note that there were three regions that did not follow this general trend. These areas (which were all located along the medial wall of the frontoparietal cortex) showed significantly less activity during movements opposite to cued targets relative to direct movements. These areas included cortex in the region of the SMA. We also observed decreased activity in medial frontal gyrus (i.e., around the SMA) in our HM > RHM and HM > RJM contrasts suggesting that medial motor areas could be involved in the process of "mental rotation" needed to compute an arm trajectory in a direction opposite to a target of interest.

A notable difference between the paradigms used in the present study and in the Connolly et al. study described above is that their

Table 2
Regions in which less complex transformational tasks have significantly greater activity than more complex tasks

Anatomical region		Contrast	Talairach coordinates of local maximum (x, y, z)	Extent (no. voxels)	t Value
Left precentral gyrus		HM > RHM	-26, -17, 54	10,737	6.90
		HM > JM	-33, -17, 54	1938	6.25
		HM > RJM	-35, -24, 59	13,439	10.33
		JM > RJM	-35, -19, 66	161	5.57
Postcentral gyrus	left	HM > RHM	-54, -18, 38	135	5.52
	right	HM > RHM	45, -21, 43	268	6.29
Lateral occipital and fusiform gyri	left	HM > RHM	-43, -61, -5	972	6.20
			-18, -82, -16	85	5.93
			-23, -65, -14	22	5.27
		HM > JM	-23, -90, 13	76	6.14
		HM > RJM	-21, -87, 14	444	5.93
			-44, -67, -6	1530	6.47
	right	HM > RHM	28, -74, -12	5023	7.39
		HM > RJM	39, -77, 0	95	6.11
			38, -62, -14	689	6.09
			30, -48, -14	111	5.82
Cuneus	left	JM > RJM	35, -55, -16	312	6.14
		HM > JM	-2, -84, 8	3056	7.72
			-14, -81, 30	43	5.56
		HM > RJM	-13, -83, 32	304	5.62
		RHM > RJM	-6, -83, 16	3491	8.56
	right	HM > RJM	10, -89, 31	197	5.76
		1, -86, 5	6195	10.24	
Medial frontal gyrus	left	HM > RJM	-4, -1, 53	6649	7.97
	right	HM > RHM	8, 3, 54	42	5.27
Left superior frontal gyrus		HM > JM	-6, 1, 66	58	5.85
		RHM > RJM	-19, 61, 23	22	5.29
Caudate nucleus	left	HM > RJM	-13, 7, 2	3629	7.86
		JM > RJM	-11, 10, 0	2230	7.53
		RHM > RJM	-9, 9, 3	208	6.26
	right	HM > RJM	8, 11, -1	75	5.18
	Thalamus	left	HM > RHM	-12, -16, 5	145
HM > RJM			-10, -16, 1	1106	7.21
right		HM > RJM	11, -6, 3	656	5.94
Left midbrain		HM > RHM	-8, -19, -8	71	5.47
Left middle frontal gyrus		HM > RJM	-23, 16, 56	290	5.91
			-42, 39, 18	153	5.54
Left paracentral lobule		HM > RJM	-6, -27, 51	567	6.79
Left supramarginal gyrus		HM > RJM	-63, -27, 41	737	6.86
Right middle temporal		HM > RJM	39, -18, -11	77	5.40
Left middle frontal gyrus		JM > RJM	-36, 43, 23	56	5.46
			-22, 61, 20	81	5.50
			-44, 55, 16	32	5.36
Right superior parietal lobule		RHM > RJM	23, -82, 38	44	5.48
Right insula		RHM > RJM	36, -7, 16	43	5.34

subjects were instructed to fixate on a central target while pointing. In contrast, during the rotated hand movement condition examined in the present study, subjects were instructed to move their eyes to the cued target. Therefore, to perform this task correctly, our subjects were required to make simultaneous eye and hand movements in opposite directions.

Previous work has demonstrated a very tight coupling between the eye and hand. For example, when presented with more than one target for eye and hand movements, subjects virtually always move both eyes and arm to the same target without specific instructions to do so (Gielen et al., 1984). In another study of eye-hand coordination by Neggers and Bekkering (2000), subjects were instructed to look and point at a target when it was presented. Subjects were further instructed to keep the pointing movement

directed to the initial target while making an additional saccade as quickly as possible to any other targets that appeared after the onset of the combined eye and hand movement. Subjects were unable to initiate a saccade away from the original fixated target during an ongoing pointing movement. This “gaze anchoring” effect during an ongoing arm movement provides further evidence of a strong link between control of hand and eyes. In the context of our study, to successfully perform the “rotated” hand and joystick conditions, in addition to calculating a 180° rotation, subjects would also have to suppress what could be a default tendency to move the eyes in the direction of their hand movement. This requirement that subjects dissociate eye and hand movements may account for our observation of an overall decrease in activity throughout the brain in our “rotated” conditions relative to their unrotated counterparts.

Table 3

Local maxima of significantly active regions in experimental conditions relative to control conditions (shaded areas represent regions significantly less active in experimental than control conditions)

Anatomical region	Condition	Talairach coordinates of local maximum (x, y, z)	Extent (no. voxels)	t Value
Left precentral gyrus (extending into left postcentral gyrus)	HM (including left medial frontal gyrus)	-27, -23, 57	37,115	18.22
	RHM	-32, -26, 62	12,733	13.16
	JM	-32, -28, 61	16,776	13.76
	RJM	-30, -24, 62	6675	8.64
Left medial frontal gyrus	HM (included in above)			
	RHM	-3, -10, 55	189	6.06
	JM	-3, -12, 55	2227	7.60
Right superior parietal lobule	HM	27, -41, 59	4186	8.60
	JM	21, -44, 62	1218	7.52
	RJM	20, -47, 65	87	5.87
Right superior frontal gyrus	HM	20, -6, 65	172	5.89
	JM	23, -5, 63	887	7.17
	RJM	8, 29, 62	140	6.42
Left lateral occipital and fusiform gyri	HM	-43, -62, -6	3064	9.39
	JM	-43, -59, -10	252	5.79
Right lateral occipital and fusiform gyri	HM	41, -61, -11	2837	8.17
	JM	41, -57, -14	1218	6.75
Left cuneus	HM	-1, -87, 1	1959	7.23
	RHM	-6, -79, 37	45	5.37
		-2, -84, 10	164	5.84
Left superior temporal gyrus	HM	-53, -22, 15	295	5.86
Right inferior parietal lobule	JM	35, -38, 54	2049	6.90
Left midbrain	JM	-13, -15, -5	523	7.60
Right supramarginal gyrus	RHM	41, -60, 36	244	5.81
Right lingual gyrus	RHM	18, -65, 11	821	6.37
Left superior frontal gyrus	RJM	-23, 59, 25	1121	6.06
Left caudate nucleus	RJM	-10, 12, 4	530	6.88

The decreased activity we observed in the RHM and RJM conditions relative to the HM and JM conditions could reflect the inhibition of a default reaction. However, a limitation of the current study is that we did not track subjects' eye movements. Thus, further study utilizing eye-tracking is currently being performed to test this hypothesis.

Activity related to specific conditions

Although our hypothesis that progressively dissociating the sensory and motor components of transformational tasks would result in increased cortical activity was generally not supported, we did observe some interesting task-specific activity in several cortical areas. A lengthy discussion of each observed area is not warranted here given the large number of comparisons undertaken in this study. However, a few regions of particular interest are discussed below.

Regions of the angular gyrus were more active in the RJM condition relative to the HM and RHM conditions. Damage to the angular gyrus results in a large variety of deficits (Mayer et al.,

1999; Mazzoni et al., 1990; Nagaratnam et al., 2002). In the case study of Mayer et al. (1999), they examined a patient with a focal ischemic lesion in the left angular gyrus. Included among this patient's deficits were finger agnosia, agraphia, right-left disorientation, and dyscalculia. Also, the patient was unable to perform a mental rotation task. The authors concluded that all of the patient's disorders (and those observed in other patients with similar lesions) had "impairment in mental manipulation" as a common psychoneurological factor. Interestingly, we observed angular gyrus activity in the rotated joystick condition over the two hand movement conditions (HM and RHM). Perhaps, activity in this area reflects a neural correlate of the mental rotation involved in the rotated joystick condition.

An anterior region of the right superior frontal gyrus was also more active in the rotated joystick condition than in either of the hand movement conditions. Interestingly, gray matter abnormalities have been observed in this region in individuals diagnosed with attention deficit hyperactivity disorder (ADHD) (Overmeyer et al., 2001), a condition associated with symptoms that include inattentiveness. Also, individuals diagnosed with ADHD have

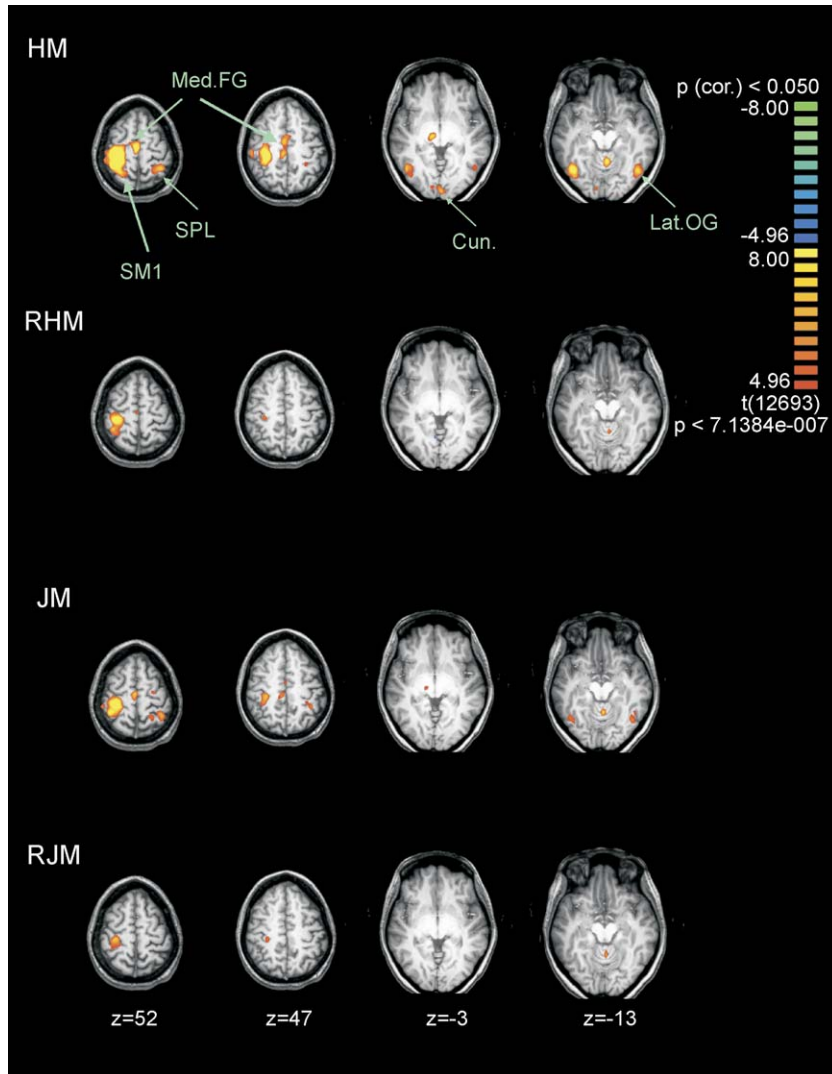


Fig. 6. Group results of experimental conditions HM, RHM, JM, and RJM contrasted with control conditions (eye movement only and central fixation) using conjunction analyses (described in Materials and methods). Conventions as used in Fig. 4. Med.FG indicates medial frontal gyrus; SM1, primary sensorimotor area; SPL, superior parietal lobule; Cun., cuneus; and Lat.OG, lateral occipital gyrus.

difficulty maintaining fixation and suppressing eye movements toward visual targets (Munoz et al., 2003). Since the RJM task required both tool use and simultaneous eye and hand movements in opposite directions, it was likely the most attention-intensive task of those we examined. The activity we observed in this region could in part reflect this high attentional demand.

Direct contrasts between experimental conditions revealed interesting condition-related differences in activity in the lateral occipital and fusiform gyri. Activity in these regions is often associated with perceptual processes such as visual recognition (see Grill-Spector et al., 2001). Furthermore, activity in this area can vary depending on the demands of a particular task (Tarr and Gauthier, 2000). In this study, depending on the current condition being performed, subjects were required to vary their motor responses to visual targets that remained identical between conditions. Subjects received information about which condition they were to perform in the form of written instructions presented before the onset of trials in each condition. Thus, to correctly perform each trial presented within each condition, subjects had to remember which transformation the current condition called for.

This recognition of the current context of a required motor output could be partially reflected in the variations of activity we observed in the fusiform and lateral occipital area. This activity in combination with that seen in the parietal and frontal cortices could represent an integration of the “ventral” and “dorsal” stream processes (see Milner and Goodale, 1995) necessary to perform context-specific sensorimotor transformations. Others have also observed activity within areas typically thought to be related to vision for perception during associative visuomotor tasks (Toni et al., 2002).

A functional network generally involved in transformational visuomotor tasks

Contrasting experimental conditions with control conditions (i.e., the eye movement and central fixation conditions) provided us with an overview of patterns of activity associated with preparation of the sensorimotor tasks. Several regions were observed to be active in all or most of the experimental conditions relative to controls. All of the conditions show a cluster of activity

in the left primary motor region. There is activity in the left medial frontal gyrus relative to controls in the HM, RHM, and JM conditions. The right superior parietal lobule (SPL) and the right superior frontal gyrus/precentral sulcus area show activity in the HM, JM, and RJM conditions. It is unclear why all of these areas were not significantly active in every case. [Indovina and Sanes \(2001\)](#) have also observed task-related activity changes within brain regions. The authors showed that the addition of a visual attention task to a concurrent finger-tapping task could either suppress or facilitate movement-related activation depending on the attentional requirements of the task. Thus, the variable attentional requirements of the progressively complex tasks examined in the current study could partially account for some of these variations in activity observed within areas. However, the overall consistency of activity in these areas could suggest that they are part of a functional network generally involved in transformational visuomotor tasks.

Clues to the specific roles of the areas involved in this putative network come from previous neurophysiological and imaging studies. The primary motor and medial motor regions have been shown to be involved in even the simplest voluntary movements ([Ball et al., 1999](#); [Kertzman et al., 1997](#)). Thus, that we saw activity in these regions is not surprising.

Cell recordings from area 5 in the monkey SPL indicate that this region plays a role in transformation of sensory information about the spatial location of a target into a body-centered representation used in goal-directed reaching ([Kalaska, 1996, 1997](#)). Furthermore, this activity in the monkey SPL is apparent during the delay period of instructed-delay reaching paradigms ([Kalaska and Crammond, 1995](#)). The significant increases in BOLD activity associated with movement preparation (relative to control tasks) that we observed in the SPL could indicate a similar role for this area in humans.

Given its physical location, the region of activity that we observed in the right superior frontal gyrus/precentral sulcus likely corresponds to part of the lateral premotor region. [Wise et al. \(1996\)](#) have argued convincingly that the premotor cortex is fundamental to the ability to perform nonstandard mapping tasks. Spatial information processing which has been observed in the premotor cortex during standard-mapping tasks may serve as a basis for nonstandard mapping computations. Thus, activity observed in the premotor cortex in the present study could be a necessary part of our subjects' ability to perform nonstandard sensorimotor transformations.

Conclusions

This study provides novel information about the neural correlates of nonstandard sensorimotor transformations in the human brain. Reaching tasks involving these types of transformations are common in daily life but have seldom been examined in human subjects. The results of the present study indicate that significantly different patterns of cortical activity are associated with each of the four progressively complex sensorimotor mappings examined here. Underlying these different patterns, we observed the existence of a putative functional network of areas (including the primary motor cortex, medial motor areas, superior parietal lobule, and lateral premotor cortex) thought to be of general importance for nonstandard sensorimotor mapping tasks. Surprisingly, in many of our comparisons,

progressively increased task complexity did not result in an overall increase in activity throughout the cortex. For example, "rotated" conditions generally demonstrated less activity than "unrotated" conditions. However, context-specific regions of activity, associated with different types of learned visuomotor transformations, were observed.

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