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Preliminary sex differences in human cortical BOLD fMRI activity during the preparation of increasingly complex visually guided movements

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Abstract

In the past it has often been assumed that the cortical networks for visually guided movement are the same for males and females. Here we use functional magnetic resonance imaging (fMRI) to show significant sex-related differences in human brain activity during visual-to-motor transformation tasks. Although the behavioural performance of the male and female groups did not differ, sex-related differences in levels of blood oxygen level-dependent fMRI activity are apparent in several cortical areas that have previously been demonstrated to be important for visually guided movements. These areas include the primary sensorimotor, dorsal premotor, superior parietal and lateral sulcus regions. Furthermore, the data indicate that the nature of these sex differences depends on the spatial mapping between a visual cue and the motor response that it guides.

Introduction

The ubiquitous nature of visually guided reaching in daily life makes gaining a more complete understanding of how the brain controls these movements both fundamentally important and clinically relevant. To our knowledge, there has not yet been a direct examination of how the processes underlying the control of visually guided reaching may differ in males and females. However, an increasing amount of indirect evidence is beginning to point to the possibility that sex-related differences are likely to exist in the brain processes involved in visuomotor control. For example, data suggesting that the motor systems of males and females differ can be seen anatomically ranging from a molecular level to a larger, overall structural level in the brain. Grachev & Apkarian (2000) found sex differences in metabolite levels in the brain. The authors observed that compared with males, females had greater levels of *N*-acetyl asparate in the primary sensorimotor cortex (i.e. the primary motor and somatosensory cortices surrounding the central sulcus). Structural sex differences have also been observed around the region of the central sulcus. For example, whereas an interhemispheric asymmetry in the depth of the central sulcus region that controls arm movement is present in male subjects, this asymmetry was not found in females (Amunts *et al*., 2000). Also, sex differences in the proportion of grey and white mater adjacent to the central sulcus are known to exist (Good *et al*., 2001). In addition, there is evidence that sex hormones influence anatomical characteristics of the primary motor cortex. For example, gonadectomy in male rats decreased the span of horizontal neuronal connections within the primary motor cortex, whereas this decrease was significantly lessened in animals that received exogenous testosterone (Venkatesan & Kritzer, 1999). Both the primary motor and the primary somatosensory cortices are known to have important roles in the control of reaching movements. The primary motor cortex has well-documented roles in the execution of reaching movements (see Kalaska *et al*., 1997; Sergio *et al*., 2005) and inactivation of the primary somatosensory cortex results in serious deficits in the control of arm movements (e.g. Hikosaka *et al*., 1985). The presence of anatomical sex-related differences within these cortical areas suggests that sex differences in their functions (such as the control of reaching movements) may also exist.

Evidence of sex-related differences in the motor system is also suggested by behavioural studies. For example, in a study by Chaudhury *et al*. (2004), female subjects made larger errors than males when a visual illusion guided a target-directed walking path. By contrast, male subjects showed a greater impairment than females when vision was occluded during praxic tasks (Chipman *et al*., 2002). These examples of sex differences in the behavioural responses to manipulation of the visuomotor system suggest (albeit indirectly) that the visuomotor systems of men and women may differ.

Although functional imaging has not been used to look directly for sex differences in visually guided reaching movements, imaging experiments have revealed sex differences in brain activity during processes that are vital to normal motor control (such as spatial and somatosensory processing). For example, Sadato *et al*. (2000) observed that premotor activity was lateralized in males during tactile discrimination but was symmetric in females. Also, sex differences during mental rotation tasks are evident even when male and female participants are equally good at the task (Jordan *et al*., 2002; Weiss *et al*., 2003; Seurinck *et al*., 2004). In addition, Gron *et al*. (2000) demonstrated sex differences in hippocampal, parietal and premotor activity as subjects used button presses to navigate through virtual mazes.

The results of the studies described in the preceding sections demonstrate the existence of anatomical sex-related differences in

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brain regions that are highly important for motor control, behavioural sex differences in response to visuomotor manipulations, and functional differences in brain activity associated with processes closely related to normal motor control. Taken together, these findings suggest the possibility of sex differences in the brain activity underlying visuomotor function itself. In the current study, we directly tested the hypothesis that the neural correlates underlying the control of visually guided arm movements differ in males and females.

In this study, we compared patterns of cortical activity in males and females while subjects performed a series of progressively complex visuomotor tasks. Wise *et al*. (1996) have classified visuomotor tasks into categories that depend on the nature of the mapping used. A visuomotor task is considered to use a 'standard' mapping when the visual stimulus guiding the action is also the target of the action (e.g. reaching out to grasp a glass of water). In contrast, a visuomotor task is considered to use a non-standard, transformational mapping when an algorithm is used to relate visuospatial information from a cue to the direction of the required movement (e.g. pushing a computer mouse 'forward' on a desk to move a cursor 'up' on a screen). Non-standard visuomotor tasks can require subjects to learn context-dependent rules and novel spatial mappings and can involve tool-use. Therefore, non-standard mappings contain 'cognitive' components beyond those that are associated with standard mapping tasks. There is evidence that sex differences exist in cognitive processes such as working and spatial memory, spatial attention and spatial perception (Gur *et al*., 2000; Bell *et al*., 2006; Frings *et al*., 2006; Haut & Barch, 2006). Thus, along with the prospect that the neural correlates of standard visually guided reaching differ in males and females (as suggested by the anatomical, behavioural and functional sex differences described in the preceding sections), it is also reasonable to hypothesize that sex differences in visuomotor tasks will also depend on the complexity of the mapping examined. Therefore, in the current study, we not only test the hypothesis that sex-related differences in the brain activity associated with visually guided reaching exist, but also that the nature of these differences is dependent on the complexity of the task.

Materials and methods

Subjects

Nineteen right-handed subjects participated in the experiment. The subjects included ten males, mean (±SD) age 26.8 ± 3.4 years, and nine females, mean age 25.3 ± 4.1 years. There were no significant differences in the mean ages of the male and female groups ($t = 0.512$, $P = 0.62$). The subjects performed visually guided reaching movements while cortical activity was imaged using event-related blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI). Handedness was verified using the Edinburgh inventory (Oldfield, 1971). Subjects filled out questionnaires detailing their computer and video game experience. None of the subjects had a history of neurological problems. All subjects had normal or corrected-to-normal (with contact lenses) vision. The York University Research Ethics Board human participants subcommittee approved the experimental protocol. All subjects provided informed consent prior to data collection.

Apparatus

BOLD fMRI was performed using a 4.0-T, Varian/Siemens Unity INOVA whole-body scanner (Robarts Research Institute, London, Ontario, Canada). A birdcage RF head-coil was used during data collection (Barberi *et al*., 2000). Subjects lay supine in the scanner with their heads tilted forward approximately 30° so that they could directly see and touch targets which were back-projected onto a plastic screen suspended in front of them. Subjects' heads were securely braced within the head coil using padding to minimize task-related head movements. Subjects' right upper arms were also secured in place (using straps) to help minimize the translation of lower arm movements to the head.

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

An interface was created that allowed subjects to control a non-magnetic joystick using their right index finger. The joystick was attached to the scanner bed so that subjects could control it with their arm resting beside them.

General paradigm

Subjects were thoroughly trained to perform the required tasks (training generally occurred 2–3 days before imaging). Training was performed first at a desktop and then in a simulated scanner that mimicked the configuration of the actual MRI scanner as closely as possible. All subjects received the same amount of training (approximately 2.5 h). After this time, individuals who had any obvious difficulty with any of the tasks were not included in the study. Subjects also practised all conditions from within the magnet immediately before scanning.

On the day of scanning, each subject performed three consecutive imaging runs. Each run consisted of 30 s of baseline measurement (the screen remained blank for the entire period and subjects were instructed to rest with their eyes open) followed by six conditions (four experimental and two control) presented in pseudo-random order. Subjects performed five trials for each of the six conditions in each of the three functional imaging runs. Individual trials in each condition were event-related. Each trial was 30 s long including a 14-s intertrial interval to allow the haemodynamic response to return to baseline between trials. Each trial commenced with a 2-s cue period during which a centre target surrounded by four peripheral targets appeared on the screen. All of the targets were green except for one random peripheral target that was blue, indicating that it was the target of interest for the trial. Following the cue period, there was a 10-s delay period during which all of the targets were still visible on the screen but were all coloured green. After this instructed-delay, subjects received a 'go-signal' in the form of the centre target turning from green to yellow. After this signal, subjects had 4 s in which to perform the required motor response. Note that a 2-s instruction period preceded the onset of each condition (during which the name of the condition to be performed was shown on the screen followed by 14 s of blank screen to allow the haemodynamic response to return to baseline).

Experimental conditions (Fig. 1)

Subjects performed four different visuomotor mappings (numbers 1–4 below). Motor responses were increasingly dissociated from visual information. Visual information was identical for all conditions except for the two joystick tasks (see below) where a small cross-shaped cursor was visible during the movement period of each trial. Two control conditions (nos. 5 and 6 below) also examined BOLD activity

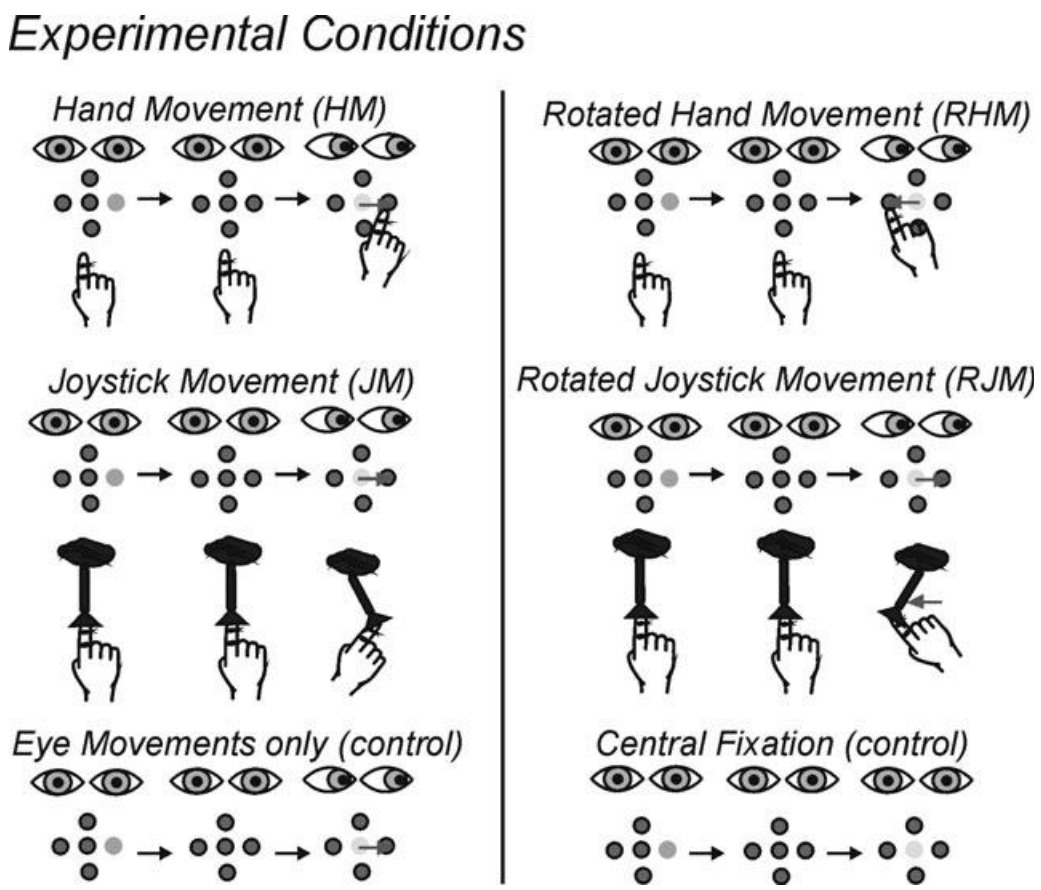

FIG. 1. An illustrated representation of the experimental conditions.

associated with eye movements and the presentation of visual stimuli. During all conditions, subjects were instructed and trained to remain still during the cue and delay periods of each trial with their eyes fixed on the centre target. Upon receiving the 'go-signal' for each trial, subjects were instructed to make identical eye movements for all of the conditions (except the central fixation control condition described below). During the movement period of each trial, subjects were to move their eyes from the centre target to the cued peripheral target while simultaneously performing the required hand movements. Subjects were then to maintain fixation on the peripheral target until the end of each trial. Hand movements made in all of the experimental conditions were similar; all used motion at the wrist and forearm, and contact with either the screen or the joystick was made with the right index finger.

1. Hand movement (HM) condition

Subjects lay supine in the bore with their right arm resting comfortably on their chest in front of the screen. After receiving the 'go-signal', subjects used movement of their right forearm and wrist to position their right index finger first onto the centre target and then onto the cued peripheral target (i.e. subjects touched the screen directly).

2. Rotated hand movement (RHM) condition

As in the HM condition above, except that at the 'go-signal' subjects touched first the centre target then the peripheral target 180° opposite to the cued peripheral target. Therefore, to perform this task correctly, subjects were required to move their eyes to the cued target while moving their hand in the opposite direction.

3. Joystick movement (JM) condition

Rather than touching the screen directly, subjects used their right index finger and movement of the forearm and wrist to move a joystick handle that controlled movement of a cursor on the screen. The cursor was only visible after the 'go-signal' (i.e. during the movement period) of each trial. At the 'go-signal', subjects moved the cursor first to the centre target and then to the cued peripheral target.

4. Rotated joystick movement (RJM) condition

After receiving the 'go-signal', subjects used the joystick to move the cursor onto the centre target. Once the cursor reached the centre target, it was programmed to move opposite to the direction of the joystick handle (e.g. rightward movement of the joystick handle produced leftward cursor movement). Subjects were required to move the joystick handle 180° opposite to the direction of the cued peripheral target in order to move the cursor onto the cued target.

5. Eye movement (EM) condition

Subjects were instructed to make only eye movements to the cued target locations.

6. Central fixation (CF) condition

Subjects were instructed to maintain fixation of their eyes on the centre target throughout each trial.

fMRI parameters and data analysis

Functional images of the cerebral cortex were obtained 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 (acquisition of data from each slice was interleaved) with a voxel dimension of 3 × 3 × 5 mm. These imaging parameters allowed us to collect functional data from the entire cortex except for the orbital frontal region. Functional data collected also included subcortical structures such as the basal ganglia and thalamus. However, these parameters did not allow us to collect data from the cerebellum. T1-weighted anatomical images were collected using turbo-FLASH acquisition with 128 slices, TE = 5.5 ms, TR = 640 ms, flip angle = 11°, and a resolution of 0.8 × 0.8 × 1.25 mm. T1-weighted images were collected for each subject immediately prior to collection of functional data.

Data were analysed using Brain Voyager 2000 and Brain Voyager QX (Brain Innovation, Maastricht, The Netherlands). Each subject's data were corrected for motion using the first volume of each functional time-series as a reference. Any imaging run in which a subject moved more than 1 mm in any direction was eliminated from further analysis. In total, six runs were eliminated (three runs from three female subjects and three runs from two male subjects) leaving a total of 51 functional time-series for analysis. Temporal filtering was applied to the functional data (linear trend removal and high-pass filtering at 0.0028 Hz) to remove drift in each time-course.

Each subject's functional data were co-registered to their corresponding T1-weighted anatomical data for individual analyses. For group data analysis, each data set (functional and anatomical) was normalized to Talairach space and functional data were spatially smoothed using a 4-mm full-width half-maximum Gaussian kernel to compensate for intersubject anatomical differences. A general linear model (GLM) analysis was initially performed separately for each subject's data for individual subject analyses. Another GLM analysis with a design matrix containing all subject data (from both males and females) was run both to examine male and female groups separately and to compare directly the male and female subject groups using fixed- and random-effects approaches (see below). Design matrices consisted of each subject's stimulation protocol convolved with a haemodynamic response function. Trials were event-related and therefore predictors were defined for the instruction period, cue periods, delay periods and movement periods of each condition. In all contrasts performed, the delay periods of each condition were examined. Due to the haemodynamic response lag associated with fMR imaging, signal changes during the delay period presumably contain changes associated with both the cue period and the delay period as the delay period immediately followed the 2-s cue in each trial. Therefore, the analyses described below focused on portions of the time course associated with the preparation of the movement (i.e. patterns of activity that were associated with processes undertaken before production of the overt movement). By using the delay period as the predictor of interest in these analyses, we were able to minimize task-related movement artefacts associated with arm movements made after the 'go signal'.

To examine the cortical networks involved in the preparation of the visuomotor transformations, activity in each condition vs. baseline was initially examined separately for the male and female groups. Activity associated with the delay periods of each condition was contrasted with baseline data (where baseline data consisted of the initial 30 s of each run in which subjects were instructed to relax with their eyes open and to not make any movements).

The hypothesis that males and females showed different patterns of cortical activity while preparing visually guided movements was directly tested using a whole-brain fixed-effects approach for statistical comparisons of activity in the male and female groups. For the fixed-effects comparisons, each of the contrasts used compared the BOLD signal between the male and female groups for the delay period of each trial in each of the conditions using Student *t*-tests with Bonferroni correction ($P_{cor} = 0.05$). The locations of activity clusters revealed by all analyses were confirmed using the *Atlas* of Damasio (1995).

Fixed-effects analyses do not take between-subject variability into account. Thus, in order to better apply our results to the general population, a region of interest (ROI) random-effects analysis was also performed. ROIs were chosen in part based on the results of the fixed-effects analysis. Areas that showed significant sex-related differences using the fixed-effects approach were used to guide the creation of ROIs for the random-effects comparison. However, to account for individual anatomical variability, a visual inspection was performed to ensure that each ROI was located within the desired anatomical location in each subject's individual normalized anatomical data. Each ROI examined here consisted of a 729-voxel cube centred near the local maximum of significant clusters observed in the fixed-effects analysis. Thus, each ROI included the approximate local maximum of significant regions observed in the fixed-effects analysis and a small region of grey matter around this locus. Brain areas tested in the ROI analysis included regions of the bilateral sensorimotor cortices in the arm and hand region, the premotor cortex anterior to the hand region of the primary motor cortex, superior parietal lobules around area 5, intraparietal sulci, lateral sulci around the region of the parietal operculum, medial motor cortices and the thalamus. Within Brain-Voyager QX, a random-effects analysis is performed by running a multisubject, subject-separable GLM. For the resulting GLM, a random-effects analysis is performed using a summary statistics approach and two groups are then compared by computing the mean of the summary statistic for each group followed by a two-sample *t*-test to compare the group means.

Behavioural data

The direction of hand movements made by each subject during each trial was determined offline by examining voltage changes within individual bend sensors in the glove worn on each subject's right hand during data collection. Trials in which a subject moved their hand in an incorrect direction or failed to make a movement were considered error trials. Note that movement amplitudes were small and made at the wrist. Also, reaction times were not recorded as all subjects were encouraged to move slowly (to avoid introducing movement artefacts into the data). Therefore, assessment of hand movement direction was used to determine whether individual trials were performed correctly or not.

Results

Behavioural data

Assessment of handedness

The assessment of handedness for each subject was performed according to Oldfield (1971). In this assessment, handedness is calculated based on subjects' self-reported preference of hand for ten different activities (e.g. writing, drawing, throwing). A score of −10 indicates that a subject is entirely left-handed, a score of +10 indicates

that a subject is entirely right-handed and a score of 0 indicates ambidexterity. In the current study, all subjects were found to be very right-handed and there were no significant differences in handedness between the male and female groups. The mean score for males was 9.0 ± 0.24 and the mean score for females was 9.0 ± 0.41 ($P = 0.99$).

Task proficiency

The kinematic characteristics of movements made from within the bore of the magnet were recorded using bend-sensors sewn into a thin, black glove that subjects wore on their right hand. Hand movements made during each trial were examined. Example bend-sensor data are presented in Fig. 2A. Trials were considered incorrect if the subject moved their hand in the wrong direction or failed to make a hand movement. Reaction times were not examined as all subjects were instructed to move slowly to ensure that arm movements did not translate to the head. The mean number of errors made by the male and female groups during the experimental conditions are shown in Fig. 2B. In general, error rates for all subjects were low with means in the range of 0–1 error per condition in each run. The number of errors made by males and females were not significantly different in any of the conditions (*t*-test: HM $P = 0.20$, RHM $P = 0.89$, JM $P = 0.27$, RJM $P = 0.80$).

Male and female groups examined separately

Table 1 details clusters of activity observed in the male and female groups (analysed separately) during the experimental and control conditions. In general, similar regions are active in both sexes (such as the primary sensorimotor cortex, lateral and medial premotor regions, superior parietal cortex, basal ganglia and thalamus). However, some differences are notable even prior to statistical comparisons. An example of these empirical differences within the lateral sulcus region is shown in Fig. 4A and discussed below.

Whole-brain fixed-effects analysis

The whole-brain comparison of the male and female group data revealed significantly different BOLD signals for males vs. females in areas that included the primary sensorimotor, premotor, medial motor, superior parietal, lateral sulcus and thalamus regions (Table 2 and partially illustrated in Fig. 3). Significant sex-related differences in particular areas were only apparent in some conditions. Specifically, the contrasts of male and female subjects' data revealed significantly greater activity in the left primary sensorimotor region in females in the Hand Movement and Joystick Movement conditions. Similarly, there was more activity in females in the right superior parietal lobule (Hand Movement, Joystick Movement and Rotated Joystick Movement conditions), in the right premotor cortex (Joystick Movement condition) and left medial motor cortex (Joystick Movement condition). There was greater activity in male subjects than in females in the left lateral sulcus (Rotated Hand Movement and Rotated Joystick Movement conditions) and the right lateral sulcus (Rotated Hand Movement condition). There were no significant differences between males and females in either control condition (Eye Movement and Central Fixation).

Region of interest random-effects analysis

The ROI analysis revealed significant sex-related differences in several regions (Table 3). There was greater activity in females than in males in the left primary sensorimotor region (Hand Movement and Joystick Movement conditions), the right dorsal premotor cortex (Hand Movement, Joystick Movement and Rotated Joystick Movement conditions), and the right superior parietal lobule and intraparietal sulcus (Hand Movement and Joystick Movement conditions). There was more activity in males than in females bilaterally in the lateral sulcus in the Rotated Hand Movement condition (demonstrated in Fig. 4B and C). There were no significant differences in either control condition (Eye Movement and Central Fixation).

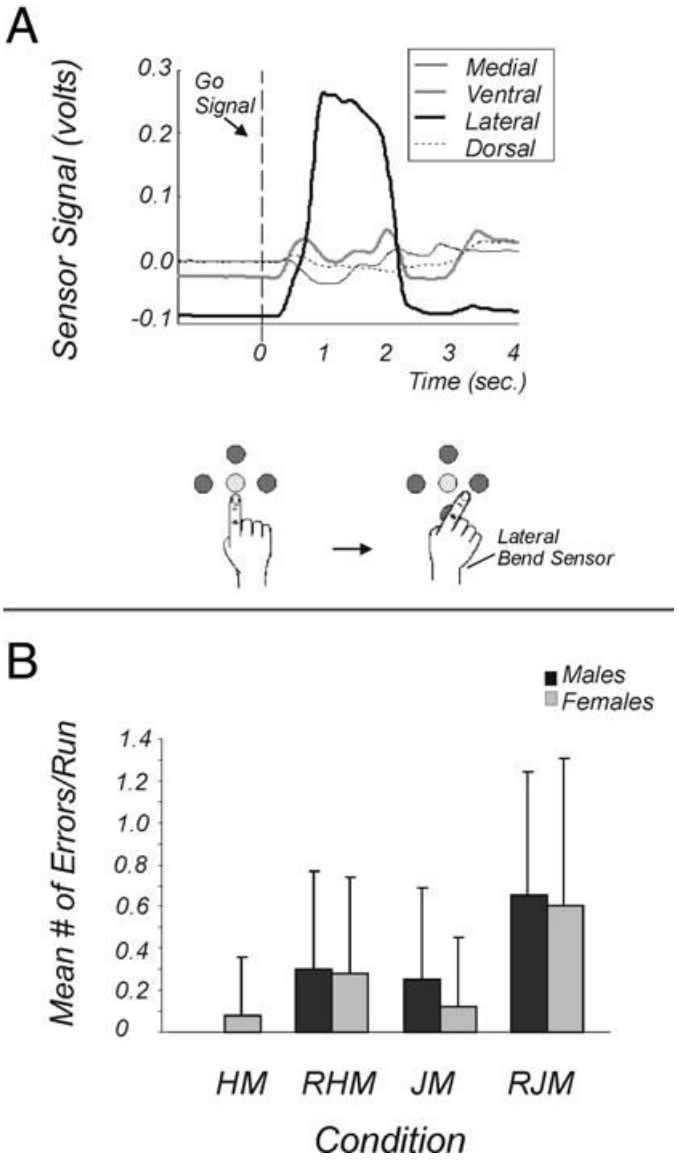

FIG. 2. (A) Sample bend-sensor data from a single subject during one trial. After receiving the 'go-signal', the subject correctly moved their hand in a rightward direction resulting in an increase in the signal received from the bend sensor placed on the lateral side of the subject's wrist and hand. (B) The mean number of errors made by the male (black bars) and female (grey bars) groups during performance of the experimental conditions. Error rates were low for all subjects. The number of errors made by males and females was not significantly different. Error bars represent standard deviation. HM represents the Hand Movement condition, RHM the Rotated Hand Movement condition, JM the Joystick Movement condition, and RJM the Rotated Joystick Movement condition.

TABLE 1. Local maxima of significantly active regions for male and female subject groups analysed separately. Data shown for each experimental condition for the two subject groups are relative to baseline. Negative *t*-values represent areas with significantly more BOLD activity during baseline.

		Talairach coordinates of local maxima (*x*, *y*, *z*)		Extent (no. of voxels)		*t*-value	
Anatomical region	Condition	Males	Females	Males	Females	Males	Females
Left primary sensorimotor region (extending into lateral premotor and superior parietal lobule regions)	HM	−33, −29, 54	−38, −24, 53	49246	63012	13.99	28.31
	RHM	−33, −25, 55	−34, −26, 57	40194	32791	15.28	22.89
	JM	−32, −27, 57	−36, −25, 55	25839	47915	13.51	22.89
	RJM	−35, −30, 53	−33, −25, 56	40463	35993	12.63	17.51
Left medial motor region (extending into right medial motor region)	HM	−1, −11, 48	−2, −8, 52	13321	40071	16.46	20.62
	RHM	1, −13, 49	−2, −7, 49	22610	14193	14.59	14.81
	JM	−2, −14, 48	0, −9, 50	9471	22831	14.59	16.75
	RJM	−3, −16, 47	−5, −6, 54	7027	10912	12.11	11.72
	EM	None	−2, 0, 49	None	6710	None	9.38
	CF	None	−1, 0, 54	None	2163	None	6.91
Right precentral and/or superior frontal gyrus	HM	None	35, −8, 59	None	6981	None	12.8
	RHM	None	30, −6, 67	None	779	None	8.33
	JM	46, −1, 54	27, −5, 62	579	6470	7.06	13.37
	RJM	None	26, −6, 63	None	2611	None	11.62
	CF	None	42, −10, 59	None	4103	None	8.15
Left middle frontal gyrus	HM	None	−33, 39, 34	None	3636	None	7.91
	RHM	None	−37, 40, 41	None	2040	None	8.31
	CF	None	−32, 45, 35	None	2530	None	6.87
Right middle frontal gyrus	JM	None	45, 8, 40	None	2340	None	7.56
	CF	47, 1, 53	39, 44, 39	1028	5790	7.63	7.15
Right superior parietal/ intraparietal sulcus region	HM	39, −40, 50	34, −38, 54	16260	23644	8.82	15.98
	RHM	23, 53, −50	30, −45, 60	23116	10566	11.18	12.32
	JM	39, −46, 55	35, −39, 52	4457	27487	9.49	15.68
	RJM	26, −59, 58	38, −37, 50	2512	24586	7.43	13.47
	CF	None	29, −48, 62	None	2359	None	6.61
Left and right cuneus and lingual gyri	HM	1, −80, 19	−2, −76, 11	40844	75207	14.43	23.06
	RHM	2, −76, 20	−1, −75, 13	65199	61110	15.81	19.69
	JM	2, −83, 18	0, −70, 19	26368	97892	11.9	18.67
	RJM	0, −80, 22	−1, −72, 9	29618	70892	11.83	16.85
	EM	2, −82, 17	0, −72, 11	21739	69715	10.98	19.44
	CF	1, −82, 14	0, −71, 8	17737	59103	11.48	18.13
Left lateral sulcus (including superior temporal gyrus and parietal operculum)	HM	−51, −19, 7	−54, −23, 18	3943	6593	8.65	10.18
	RHM	−51, −13, 10	None	27176	None	11.7	None
	JM	−54, −18, 11	−55, −25, 20	6667	3205	10.25	7.41
	EM	−56, −19, 9	None	1731	None	7.47	None
Right lateral sulcus (including superior temporal gyrus and parietal operculum)	HM	51, −22, 20	53, −25, 20	9240	5019	9.55	9.6
	RHM	50, −16, 17	None	11299	None	9.87	None
	JM	53, −24, 21	57, −26, 22	9917	1548	10.02	7.64
	RJM	54, −26, 20	None	3938	None	8.06	None
	EM	43, −24, 16	None	863	None	6.3	None
Right insula	RHM	None	37, 1, 12	None	1791	None	7.52
	RJM	None	32, 24, 5	None	3008	None	8.9
Left thalamus	HM	−15, −14, 4	−15, −11, 6	304	7556	6.16	16.52
	RHM	−17, −16, 7	−14, −16, 2	6472	1246	9.41	9.53
	JM	None	−14, 14, 6	None	3938	None	11.71
	RJM	None	−15, −16, 0	None	902	None	9.16
Right thalamus	HM	None	10, −14, 1	None	872	None	8.28
Left caudate nucleus	EM	−10, 21, 9	−12, −1, 16	585	807	7.02	6.8
Right caudate nucleus	EM	None	10, 0, 17	None	500	None	7.53
Left lentiform nucleus	RJM	None	−29, −18, 0	None	1365	None	7.67
Left anterior cingulate gyrus	HM	−1, 30, 11	None	4023	None	−4.9	None
	JM	None	0, 32, 6	None	885	None	−6.91
Left posterior cingulate gyrus	RHM	−4, −56, 29	None	3277	None	−6.93	None
Right medial frontal gyrus	EM	3, 46, 39	None	4972	None	−7.22	None
Left superior frontal gyrus	RHM	−6, 14, 60	None	785	None	−7.35	None
	JM	−3, 38,55	None	153	None	−6.57	None
Right superior frontal gyrus	JM	14, 27, 57	7, 50, 41	408	178	−6.89	−6.75
	EM	17, 29, 56	15, 56, 10	1337	2316	−7.01	−8.46
Right middle frontal gyrus	RHM	None	30, 12, 47	None	2059	None	−7.84
Left angular gyrus	HM	None	−39, −68, 38	None	4148	None	−8.61
	JM	None	−37, −74, 36	None	978	None	−7.62
Right angular gyrus	HM	None	45, −65, 36	None	4246	None	−8.97
	RHM	None	35, −59, 30	None	9825	None	−9.52
	JM	None	45, −67, 34	None	971	None	−7.18

TABLE 2. Local maxima of significantly active regions for fixed-effects comparison of male and female group data

Conditions and anatomical regions	Talairach coordinates of local maxima (x, y, z)	Extent (voxels)	t-value
Regions significantly more active in female subjects relative to male subjects			
HM			
Left primary sensorimotor region	−34, −21, 57	9290	10.70
Right superior parietal lobule	27, −42, 60	3095	8.74
JM			
Left primary sensorimotor region	−38, −25, 60	9387	13.17
Right premotor region	26, −5, 62	1510	7.06
Left medial motor region	−3, −7, 66	1223	9.17
Right superior parietal lobule	21, −44, 61	6122	11.12
RJM			
Right superior parietal lobule	17, −49, 65	1133	7.97
Regions significantly more active in male subjects relative to female subjects			
RHM			
Left lateral sulcus (including superior temporal gyrus and parietal operculum)	−50, −24, 7	15327	8.84
Right lateral sulcus (including superior temporal gyrus and parietal operculum)	52, −12, 16	4320	8.84
RJM			
Left lateral sulcus (including superior temporal gyrus and parietal operculum)	−60, −22, 2	439	6.95

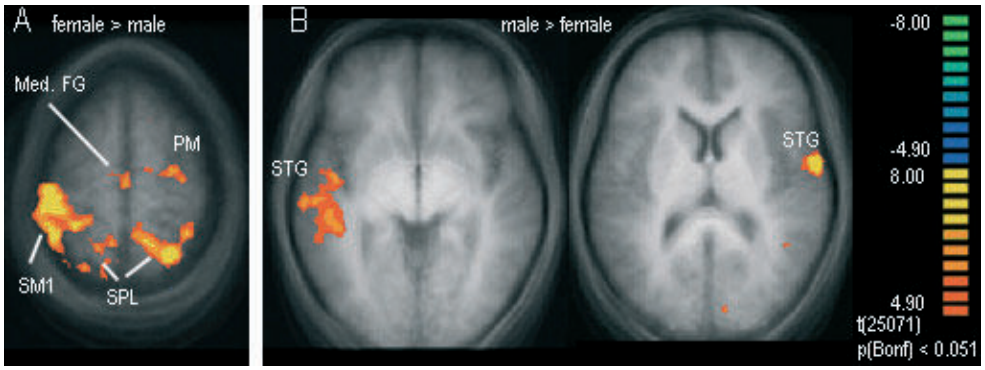

FIG. 3. A partial illustration of the results of the whole brain fixed-effects comparison of male and female group data. Functional data are superimposed on a normalized, 'averaged' brain constructed from all subjects. Colour bar represents corrected t-values in significant voxels, P (cor) = 0.05. Med. FG indicates medial frontal gyrus; PM, premotor cortex; SM1, primary sensorimotor cortex; SPL, superior parietal lobule; STG, superior temporal gyrus. Images are shown using neurological convention (left = left). (A) Regions with significantly higher BOLD activity in females relative to males in the Joystick Movement (JM) condition (z = 61). (B) Regions with significantly higher BOLD activity in males relative to females in the Rotated Hand Movement (RHM) condition (z = −3 on left side of panel and z = 12 on right).

Discussion

The motor response to a single visual cue can vary depending on the context and requirements of the task. Visuomotor mappings where the motor response is spatially dissociated from the guiding visual cue are considered to be 'non-standard' (Wise *et al*., 1996). These types of visuomotor dissociations are becoming increasingly common components of daily life and include such tasks as using a computer mouse, playing a video game, driving a vehicle and even laparoscopic surgery. In the current study, we provide evidence of sex-related differences in the brain activity associated with the preparation phase of visually guided reaching movements. The data presented here demonstrate that these differences exist in both 'standard' reaching movements (i.e. when the motor response is spatially congruent with the sensory cue guiding it) and in 'non-standard' reaching movements. In the following sections, we discuss what these sex-related differences may indicate about non-standard mapping in the human brain, the specific brain regions in which sex differences were observed, and the limitations of the study.

The effect of different visuomotor mappings on observed sex differences

In a previous study (Gorbet *et al*., 2004), we demonstrated that patterns of activity in the brain during preparation of visually guided movements depend on the context-specific requirements of particular visuomotor mappings. The current study extends these findings by demonstrating that the pattern of brain activity associated with non-standard visuomotor transformations may also depend on the sex of an individual. The comparisons of male and female subject groups performed in this study revealed significantly greater activity in females relative to males in the left primary sensorimotor cortex, the right dorsal premotor cortex, the right

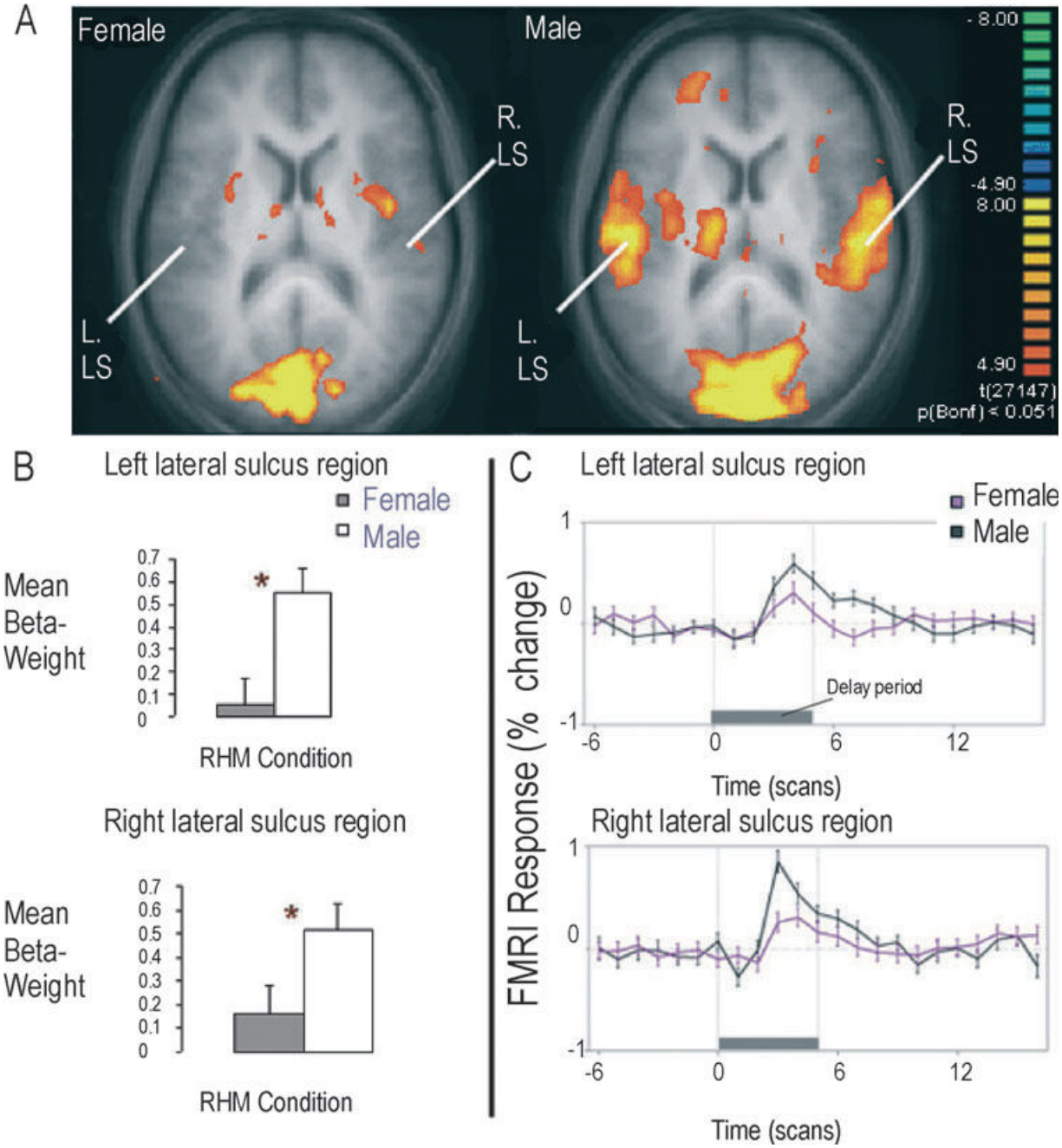

FIG. 4. Data illustrating sex-related differences within the left and right lateral sulcus region during the Rotated Hand Movement (RHM) condition. (A) Female (left) and male (right) group data (groups examined vs. baseline separately) during the RHM condition relative to baseline. Functional data are superimposed on a normalized, 'averaged' brain constructed from all subjects (both male and female) ($z = 14$). The colour bar represents corrected t-values in significant voxels, P (cor) $= 0.05$. Activity is apparent bilaterally in the lateral sulci [including the superior temporal gyri (STG) and parietal operculum (OP)] region of the male subjects but not the female subjects. (B) Direct statistical comparison of male and female group data (*$P < 0.05$). Mean beta-weights for the male (white bar) and female (grey bar) groups within regions of interest (ROI) in the lateral sulci. The ROIs each consist of a 729-voxel cube. Talairach coordinates for the ROIs are 52, −20, 9 and −52, −20, 9. (C) Time course of changes in activity in the ROIs described above during the RHM condition in males (black) and females (purple).

superior parietal lobule, and significantly greater activity in males relative to females bilaterally in the lateral sulci. However, the occurrence of these differences depended on the nature of the spatial mapping between the motor response and the visual cue that guided it. In particular, regions showing greater activity in the female group were much more commonly observed during the Hand Movement and Joystick Movement conditions (rather than the Rotated Hand Movement or Rotated Joystick Movement conditions). Thus, female subjects showed greater amounts of BOLD activity relative to males during conditions in which the eye and arm movement components of the task were made in the same spatial direction. By contrast, greater activity in the male group was seen in the Rotated Hand Movement condition (random- and fixed-effects comparisons) and in the Rotated Joystick Movement

TABLE 3. Regions of interest (ROI) showing significantly different mean beta weights for male and female groups

ROI location	Talairach coordinates of centre ROI (*x*,*y*,*z*)	Contrasted condition	Mean beta weight		*t*-value	Corrected *P*-value
			Female	Male		
Left primary sensorimotor cortex	−33, −27, 56	HM	1.11	0.50	4.10	< 0.001
		JM	0.88	0.37	2.90	< 0.01
Right premotor cortex	30, −7, 60	HM	0.45	0.19	2.17	< 0.05
		JM	0.45	0.08	2.78	< 0.05
		RJM	0.36	0.08	2.14	< 0.05
Right superior parietal lobule	31, −46, 56	HM	0.59	0.21	2.34	< 0.05
		JM	0.55	0.15	2.44	< 0.05
Right intraparietal sulcus	29, −37, 57	HM	0.69	0.07	4.02	< 0.001
		JM	0.61	0.08	3.12	< 0.01
Left lateral sulcus (including superior temporal gyrus and parietal operculum)	−52, −20, 9	RHM	0.06	0.56	4.67	< 0.001
Right lateral sulcus (including superior temporal gyrus and parietal operculum)	52, −20, 9	RHM	0.16	0.52	2.96	< 0.01

condition (fixed-effects comparison). Thus, greater amounts of activity were observed in male subjects in 'rotated' conditions in which the directions of eye and arm movements were made in opposite directions. These findings suggest the existence of differences in the ways in which the male and female brains produce non-standard motor responses.

In general, the ability to dissociate the directions of eye and arm movements is an important component of many non-standard visuomotor transformations. In non-standard tasks, one may often need to look at a visual cue in one location while guiding the arm to a different location. The motor control literature contains a large amount of evidence indicating that there is a very close relationship between the control of eye and arm movements within the brain. This evidence comes from both behavioural observations (e.g. Neggers & Bekkering, 2001; Snyder *et al*., 2002; Scherberger *et al*., 2003) and physiological and clinical examinations (e.g. Carey *et al*., 1997; Boussaoud & Bremmer, 1999; Stuphorn *et al*., 2000). Some of these observations regarding overlapping control of the eyes and arm suggest that the brain may contain a network that acts to guide the two effectors to the same spatial location. If such a putative network that couples the directions of movements of the eyes and the arm does exist, this network may need to be suppressed in order to dissociate the spatial directions of eye and arm movements. The fact that the sex-related differences observed here seem to be associated in part with the spatial relationship between the directions of eye and arm movements indicates that if there are indeed shared brain networks involved in the control of both the eyes and the arm, this circuitry may differ in males and females.

In the following sections, the specific regions in which sex-related differences were observed in this study are discussed with respect to what these differences may suggest about the control of visually guided reaching.

Regions in which sex differences were observed in the current study

The parietal and premotor cortices

The superior parietal and premotor cortices form part of a network known to be essential to the performance of visually guided movements. The superior parietal association cortex plays an important role in integrating sensory information regarding where objects of interest are in the environment (relative to the observer and to other objects), and the location of the arm relative to the other segments of the body (for example, see Scott *et al*., 1997; Graziano, 2001). The dorsal premotor cortex receives a great deal of input from the parietal cortex and is involved in the selection and planning of non-standard visually guided movements (see Wise *et al*., 1996).

In the current study, examinations of the male and female groups separately indicated that both the left and the right superior parietal lobules (SPL) were active in male and female subjects in all of the experimental conditions. However, statistical comparisons revealed that activity in the right SPL was significantly greater in females than in males in both the Hand Movement and the Joystick Movement conditions. Examinations of activity in the two groups separately also revealed that the left dorsal premotor (PMd) region is active in the male and female groups in all of the experimental conditions. By contrast, the right PMd region is active in the female group but not active in males (with the exception of the Joystick Movement condition). Direct statistical comparisons between the sexes revealed significantly more activity in right PMd in females than in males in the Hand Movement, Joystick Movement and Rotated Joystick Movement conditions. Thus, our analyses suggest that activity in SPL and especially in PMd activity tends to be more prominent in the contralateral hemisphere in males and more bilateral in females during visually guided arm movements. However, these sex differences in cerebral lateralization appear to be dependent on the nature of the visuomotor transformation performed.

Sex differences related to which hemisphere is active in the parietal and premotor regions have been reported previously in tasks that are involved with normal control of movement (such as cognitive spatial and somatosensory processing). For example, sex-related differences in the laterality of SPL activity have been observed during mental rotation (Johnson *et al*., 2002; Jordan *et al*., 2002; Roberts & Bell, 2003) as well as during navigation through a virtual environment (Gron *et al*., 2000). Similarly, Sadato *et al*. (2000) observed lateralized PMd activity in men during tactile discrimination and bilateral PMd activity in women. Observations of bilateral patterns of activity in women and unilateral activity in men have also been observed in several other regions of the brain during tasks less related to motor function such as language processing (for examples see Shaywitz

et al., 1995; Ortigue *et al*., 2005), and during responses to fear signals (Williams *et al*., 2005). Thus, a pattern of symmetric activity in females and lateralized activity in males could be a general property of human brain function. These differences could be due in part to differences in interhemispheric connectivity in men and women. Sex differences in the structure of the human corpus callosum have been noted in the scientific literature for many years. Although this literature is considered by many to be controversial, sex differences in the structure of the corpus callosum continue to be reported (for recent examples see Dubb *et al*., 2003; Suganthy *et al*., 2003; Westerhausen *et al*., 2004; Shin *et al*., 2005; Tuncer *et al*., 2005). The corpus callosum is the main route of interhemispheric cerebral connectivity in the brain, and therefore could be involved in the sex differences in the symmetry of activity observed both here and in other studies.

The sex-related differences observed in PMd in this study are also of particular interest with respect to known information regarding this region's roles in non-standard mappings. This region of the brain has a well-documented role in the preparation of reaching responses based on context-dependent information such as that used to guide non-standard visuomotor mapping tasks (for example, see Wise *et al*., 1996). Damage to PMd impairs both the acquisition of new non-standard mappings and the performance of previously learned mappings (see Hadj-Bouziane *et al*., 2003). Our findings of sex differences in PMd activity during non-standard tasks suggest both acquisition of new non-standard mappings and performance of learned mappings may differ in males and females.

The primary sensorimotor cortex

Both the fixed-effects and the random-effects analyses used in the current study revealed greater activity in female subjects relative to males around the central sulcus in the left hemisphere. This significantly increased BOLD response in females occurred in the Hand Movement and Joystick Movement conditions and encompassed an area including regions of the primary somatosensory and primary motor cortices (i.e. primary sensorimotor cortex), in areas typically representing the hand and arm (Yousry *et al*., 1997; Pizzella *et al*., 1999).

As mentioned in the introductory section of this study, several previous studies have documented anatomical sex differences in the region of the primary sensorimotor cortex. The presence of anatomical sex differences in this region of the brain suggests that sex differences might also be present in the functions these regions govern. However, few studies have looked for functional differences in this area of the brain. No sex-related differences were found in the primary sensorimotor area during a simple finger-tapping reaction time task (Mikhelashvili-Browner *et al*., 2003). By contrast, Jordan *et al*. (2002) observed sex-related differences in a region including the primary motor cortex during a mental rotation task. Interestingly, the sex differences observed in the current study occurred in the two 'unrotated' conditions (i.e. Hand Movement and Joystick Movement) in which subjects' hand movements were made in the same direction as the guiding visual cue. We did not observe any significant sex differences in the primary sensorimotor cortex in either the Rotated Hand Movement or the Rotated Joystick Movement conditions. Thus, the sex differences in the primary sensorimotor cortex presented in the current study are probably not related to the mental rotation aspects of the conditions examined. Indeed, it is not clear from the data presented in the current study why the female group showed more activity than the male group in this particular region in the Hand and Joystick Movement conditions. However, it is of interest that the observed sex-related differences depended on the nature of the spatial association between the visual cue and the motor response that it guided. The relationships between sex differences in the primary sensorimotor cortex activity and the spatial congruity of the visual and motor components of a task require further exploration.

The lateral sulcus

In this study, we observed sex-related differences in activity within the lateral sulcus. This activity occurred within a large area ranging from the superior temporal gyrus (STG) to the parietal operculum (OP). Male subjects showed significantly greater bilateral activity in this region than females in the Rotated Hand Movement condition (both fixed- and random-effects analyses) and greater left hemisphere activity in the Rotated Joystick Movement condition (fixed-effects analysis only). Both of these conditions required subjects to make hand movements 180° opposite to the direction of a cued visual location. In this sense, these conditions required subjects to perform a 'mental rotation'. Although sex differences in brain activity during mental rotation have been observed in several other studies, none that we know of has reported differences in this region of the brain (Roberts & Bell, 2000, 2003; Johnson *et al*., 2002; Jordan *et al*., 2002; Weiss *et al*., 2003; Seurinck *et al*., 2004). Thus, it is unclear whether the sex-related differences we observed in this cortical region are truly associated with the mental rotation aspects of the tasks.

Interestingly, the lateral sulcus regions in which we observed these sex differences during the rotated conditions included regions of the posterior insular cortex and temporal–parietal junction. These regions are known to be active during multimodal sensory processes that include vision and somatosensation (Downar *et al*., 2000). In addition, Balslev *et al*. (2005) observed greater activity in the temporal–parietal junction in a condition where somatosensory and visual information provided conflicting information regarding the position of the arm when compared with a condition in which somatosensory and visual information were congruent. The sex differences in the lateral sulcus region activity observed in this study might suggest differences in processing of multimodal sensory information in males and females. In particular, these processing differences in males and females may be most evident when visual information guiding the arm is spatially dissociated from the arm movement, and therefore from the somatosensory feedback from the arm.

Limitations and future directions

Given the potential importance of sex-related differences in a task as fundamentally important as visually guided reaching, it is necessary to acknowledge and discuss some of the limitations of the current study. The results presented were obtained using several different analytic approaches including random-effects ROI comparisons of the two groups, fixed-effects comparisons, analysis of male and female group data separately, and examinations of individual subject data. All of these approaches provided similar results. However, although we are very confident in the data we have presented, we would like to stress that these results should be considered to be preliminary until they are backed up by further examinations of larger data sets. When attempting to demonstrate the existence of differences between two groups of subjects, it is preferable to include as many individuals in each group as possible. However, given the large financial cost associated with functional imaging using MRI, it was not feasible for us to include any additional subjects. The variability associated with individual subjects can create problems when insufficient numbers of subjects are used. These problems can include thresholding effects that

can potentially lead to artificial differences between groups. Indeed, some individual variability was observed in our results such that the sex-related patterns of activity noted in the group results were apparent in most, but not all, individual subjects. For example, the activity in the right PMd region observed in the female group data was only apparent in approximately 70–80% of individual female subjects in the conditions in which significant sex-related differences were observed. The absence of activity in this region in a few of the female subjects could be due in part to the relatively poor statistical power of examining the time-series of individual subjects (for this reason, individual analyses are not included in the results section of the current paper). However, it is also very likely that individual variability also contributes to these within-group differences. Thus, the dimorphic patterns of activity in males and females described here are unlikely to be universal. Individual variation should be expected and taken into account during any examination of the human brain. In spite of the problems associated with individual variation when comparing groups of subjects, the fact that the random-effects analysis (which is not highly biased by cases of large individual variability) provided similar results to our other analyses helps strengthen our certainty in the results presented here in spite of a limited number (i.e. 19) of subjects.

In addition to the importance of examining as large a group of subjects as possible, it is also important to eliminate possibly confounding differences between the two groups being compared. In the current study, we have tried to eliminate as many non-sex-related differences between the groups as possible. The mean ages of the male and female groups did not differ. In addition, all subjects were thoroughly trained prior to imaging and were very proficient in all of the tasks. The numbers of errors made by the male and female groups were not statistically different. Limitations of the experimental set-up did not allow us to track subjects' eyes during imaging. However, there were no significant sex-related differences in BOLD activity in the Eye Movement control condition. Therefore, it is unlikely that sex differences result from the male and female groups making different eye movements. Also, because two of the motor tasks required the use of a joystick, subjects completed questionnaires detailing their experience with video and computer games. The large majority of subjects had very little or no 'gaming' experience. Of the subjects who occasionally played video games (one female and two males), none played for more than 1 h per week for the 6 months prior to data collection. It is difficult to assess overall athletic ability in a questionnaire, but all subjects included in the study were young and physically healthy. Thus, while we acknowledge that it is difficult to eliminate completely all non-sex-related differences between the groups, we argue that the majority of the data presented here are probably attributable to sex-related group differences.

Despite the limitations of the study presented in this paper, we believe that this study represents an important starting point and generates many testable hypotheses for subsequent investigations. For example, if the differences in the laterality of activity seen in areas such as PMd are indeed attributable to sex differences in the functional organization of the brain, stimulation of these regions via techniques such as transcranial magnetic stimulation should evoke different behavioural consequences in males and females (ongoing study).

The possibility of sex-related differences in a task as fundamental to daily life as visually guided reaching could have profound implications on both basic research practices and on the clinical treatment of motor deficits. We hope that these results will stimulate further study of this very important possibility.

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Abbreviations

BOLD fMRI, blood oxygen level-dependent functional magnetic resonance imaging; CF, Central Fixation condition; EM, Eye Movement condition; GLM, general linear model; HM, Hand Movement condition; JM, Joystick Movement condition; PMd, dorsal premotor cortex; RHM, Rotated Hand Movement condition; RJM, Rotated Joystick Movement condition; ROI, region of interest; SPL, superior parietal lobule.

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