

# A voxel-by-voxel parametric fMRI study of motor mental rotation: hemispheric specialization and gender differences in neural processing efficiency

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**Abstract** Differences between men and women in brain size, cognitive performance and lateralization of brain activation have been perennial and controversial issues. Here we show that in a motor mental rotation task where women and men performed equally well, the slope of the functional magnetic resonance imaging (fMRI) blood oxygenation level dependent (BOLD) signal per degree of mental rotation was overall 2.4× higher in men than

in women. This was attributed to the much more inefficient engagement (i.e. higher slopes) of the right hemisphere by men (mainly the frontal lobe). These findings indicate that women process information much more efficiently than men, which could offset smaller brain size.

**Keywords** Mental rotation · fMRI · Gender · Cerebral cortex

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## Introduction

Paradigms involving mental rotation (MR) have been used extensively in cognitive psychology and brain research. The cardinal finding in these studies has been the monotonic increase of reaction time (RT) with the angle of MR (Shepard and Cooper 1982). Neurophysiological studies in monkeys have visualized the process of MR of an upcoming movement as a rotating neural representation of movement direction in motor (Georgopoulos et al. 1989; Lurito et al. 1991), premotor (Wise et al. 1996) and prefrontal cortical areas (Takeda and Funahashi 2004). On the other hand, functional neuroimaging studies in human subjects using functional magnetic resonance imaging (fMRI) (Cohen et al. 1996; Tagaris et al. 1997, 1998) and positron emission tomography (PET) (Alivisatos and Petrides 1997) have documented the engagement of a large number of brain areas in MR. Two common aspects of most functional neuroimaging studies are (a) that they analyzed signals averaged over whole regions of interest (ROI), and (b) that the analyses aimed to test whether a particular ROI showed a statistically significant activation during a MR period, as compared to a control period. More detailed analyses of the ROI activation were performed in

three series of studies using 3D wire-frame objects (Shepard and Metzler 1971). The first study showed that the intensity of the BOLD signal in the superior and inferior parietal lobules increased with errors in performance (Tagaris et al. 1996). The second study showed that the rate of MR was associated with activation of the right precen-tral gyrus (Tagaris et al. 1997). Finally, the third study showed that the width of the hemodynamic response was linearly related to the RT in single trials (Richter et al. 1997, 2000).

In summary, the various functional neuroimaging studies that have investigated the neural mechanisms of MR have shown the involvement of many brain areas and documented a more specific relation of particular areas with certain aspects of the process. However, several key questions remain to be answered: What is the relation of individual voxels to the process of MR? Specifically, is there a systematic relation between single voxel activation and the key parameter of MR, namely the rotation angle? What is the relative contribution of various brain areas to the process? Is there a differential involvement of the left or right hemisphere and/or of anterior or posterior areas? In the present study, we investigated these questions using a motor MR task (Georgopoulos and Massey 1987) and on a voxel-by-voxel basis.

A different but related issue concerns the effect of gender on MR, and on spatial abilities in general (see, e.g. Georgopoulos et al. 2001; Linn and Petersen 1985; Peters and Battista 2008; Voyer et al. 1995). Unfortunately, many studies on this subject are not very comparable because of substantial variation in the stimuli used, experimental design, task requirements, measures of performance, etc. On the other hand, studies of the brain mechanisms underlying visuospatial tasks, including gender differences, have to deal with hemispheric lateralization issues, which may differ by themselves between men and women. In the present study, we sought to compare men and women using a MR task that is visually simple, consisting of only two dots on a screen. Although a MR of an upcoming movement is involved in this task (Georgopoulos and Massey 1987), potential complications arising from processing of complex shapes (e.g. Shepard–Metzler diagrams) or body parts (e.g. hands) are avoided. In addition, we analyzed the data in great spatial detail (voxel-by-voxel) and compared the various brain areas across and within genders based on a most sensitive and specific measure, namely the slope of the BOLD versus MR angle regression line. This analysis provided a fine grain but also revealed systematic differences among brain areas, between the two genders, and a remarkable interaction between gender and hemispheric lateralization in the frontal lobe.

## Materials and methods

### Subjects

Four women and four men (mean age 26.8, SD = 4.2 years), in good health, participated in these experiments as paid volunteers. Informed consent was obtained from all participants prior to the experiment. All subjects were right-handed and performed the experiment using the right hand. The protocol of the study was approved by the relevant institutional review committees.

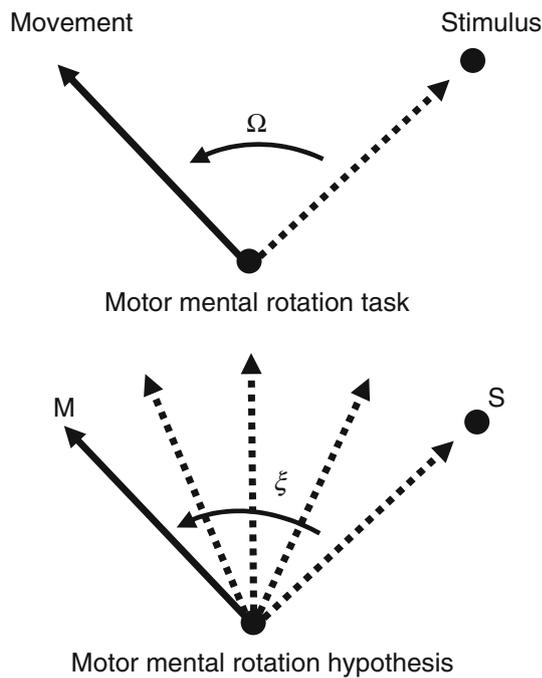
### Experimental paradigm

Subjects viewed stimuli on a display and operated a 2D joystick with their right hand. The joystick's position was shown as a feedback cursor on the screen. In the MR task (Fig. 1; Georgopoulos and Massey 1987), an instruction angle was shown for 900 ms. Then a trial started by the appearance of an open circle at the center of the screen, and the subject moved the joystick to bring its feedback cursor within the center circle. As soon as that was accomplished, a stimulus (red dot) appeared in 1 of 12 positions on a circle, every 30°; 12 stimuli were shown for each of 5 instruction angles (30°–150° counterclockwise, CCW, every 30°) in a randomized block design. The order of blocks was randomized across subjects. Subjects responded by moving a joystick-controlled cursor in a direction away from the stimulus at the instructed angle. The task and the MR hypothesis are shown in Fig. 1. In a control task, subjects moved the joystick in the direction of the stimulus. The control task was performed twice, before and after the MR task. Subjects familiarized themselves with the task in a brief session outside the magnet.

The MR angle was blocked in a randomized block design, thus allowing the measurement of the BOLD signal separately for each angle. This, in turn, allowed us to test the hypothesis that BOLD intensity may vary systematically with the MR angle.

### Image acquisition

fMRI data were acquired using a 4-Tesla system with head gradient and RF coil (SIS Co/Siemens) in a block design. Multislice, whole brain coronal anatomical images (T1-weighted) were obtained using a turbo-FLASH sequence with 5 mm slice thickness and in-plane spatial resolution of 1.88 mm × 1.88 mm. For functional imaging, a T2\*-weighted, single-shot echo-planar imaging (EPI) sequence was employed (TE = 25 ms). Imaging planes were coronal, with 5 mm slice thickness and in-plane spatial resolution of 3.75 mm × 3.75 mm. In total, 35–39



**Fig. 1** Upper panel: motor mental rotation task: movement (solid arrow) at an instructed angle  $\Omega$  away from the stimulus (dashed arrow), in a CCW departure. Lower panel: mental rotation hypothesis: movement direction is decided by mentally rotating the stimulus direction CCW by  $\Omega$  degrees. It is further hypothesized that angle  $\Omega$  is reached by steps of sequential partial increments of angular width  $\xi$  and successive comparisons of cumulative  $\xi$  to  $\Omega$

slices were collected, covering the whole brain. The acquisition time for a single slice was 30 ms, the repetition time 4.7–5 s. For each subject, 124 functional images were acquired continuously (Fig. 2). Of those, 60 images were collected during the task period; approximately 12 images were acquired per instruction angle block. Forty and 24 multi-slice images were acquired during the first and second control periods, respectively.

**ROIs**

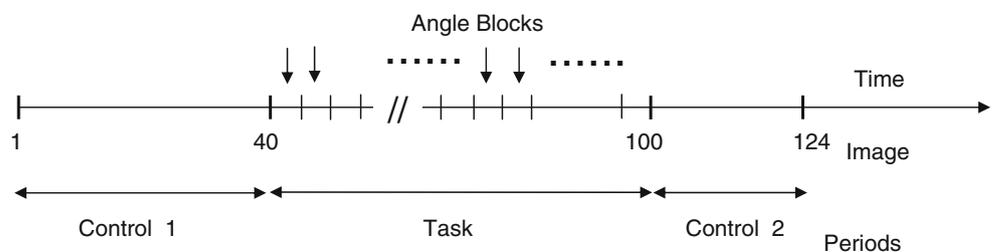
Based on brain anatomy (pattern of sulci and gyri) and Talairach coordinates, ROI were drawn on the multislice anatomical images. A total of 37 ROIs were drawn in frontal, parietal, and occipital lobes, the medial wall of the cerebral hemispheres and the cerebellum. Data from

temporal lobe areas were not analyzed. All voxels were studied within a given ROI. The following criteria were used to demarcate ROIs.

The superior frontal gyrus is defined anteriorly by the frontomarginal sulcus, posteriorly by the precentral sulcus, laterally by the superior frontal sulcus, and medially by the interhemispheric fissure. The middle frontal gyrus is defined anteriorly by the frontomarginal sulcus, posteriorly by the precentral sulcus, laterally by the inferior frontal sulcus, and medially by the superior frontal sulcus. The inferior frontal gyrus is defined anteriorly by the inferior frontal sulcus, posteriorly by the precentral sulcus, laterally by the sylvian fissure, and medially by the inferior frontal sulcus. The precentral gyrus is defined anteriorly by the precentral sulcus, posteriorly by the central sulcus, laterally by the sylvian fissure, and medially by the interhemispheric fissure. The postcentral gyrus is defined anteriorly by the central sulcus, posteriorly by the postcentral sulcus, laterally by the sylvian fissure, and medially by the interhemispheric fissure. The superior parietal lobule is defined anteriorly by the postcentral sulcus, posteriorly by the lateral extension of the parieto-occipital sulcus, laterally by the medial border of the intraparietal sulcus, and medially by the interhemispheric fissure. The inferior parietal lobule is defined anteriorly by the postcentral sulcus, posteriorly by the lateral extension of the parieto-occipital sulcus, laterally by the sylvian fissure, and medially by the lateral border of the intraparietal sulcus. The intraparietal sulcus is defined anteriorly by the postcentral sulcus, posteriorly by the lateral extension of the parieto-occipital sulcus, laterally by the inferior parietal lobule, and medially by the superior parietal lobule. The superior occipital lobule is defined anteriorly by the lateral extension of the parieto-occipital sulcus, posteriorly by the occipital pole, laterally by a lateral extension of the calcarine sulcus, and medially by the interhemispheric fissure. The inferior occipital lobule is defined anteriorly by the coronal plane containing the intersection of the parieto-occipital sulcus and the calcarine sulcus, posteriorly by the occipital pole, laterally by the inferior margin of the hemisphere, and medially by a lateral extension of the calcarine sulcus.

The calcarine sulcus is defined from the occipital pole to its intersection with the parieto-occipital sulcus. The lingual gyrus is the medial gray matter inferior to the

**Fig. 2** Schematic diagram of the experimental design



calcarine sulcus extending anteriorly to the plane containing the intersection of the parieto-occipital sulcus and the calcarine sulcus. The cuneus is the medial gray matter superior to the calcarine sulcus, extending anteriorly to the parieto-occipital sulcus. The precuneus is the medial gray matter defined anteriorly by the marginal ramus of the cingulate sulcus, posteriorly by the parieto-occipital sulcus, and inferiorly by the subparietal sulcus. The paracentral lobule is the medial gray matter defined anteriorly by the paracentral sulcus, posteriorly by the marginal ramus of the cingulate sulcus, and inferiorly by the cingulate sulcus. The medial frontal gyrus is the medial gray matter defined anteriorly to the medial extension of the frontomarginal sulcus, posteriorly to the paracentral sulcus, and inferiorly to the cingulate sulcus. The cingulate gyrus is defined anteriorly by the cingulate sulcus, posteriorly by the subparietal sulcus, superiorly by the cingulate sulcus and subparietal sulcus, and inferiorly by the corpus callosum. The sub-genu area is not included. The cerebellum is divided into the vermis, left hemisphere, and right hemisphere.

#### General data analysis

Standard statistical methods (Snedecor and Cochran 1989; Zar 1999), were used to analyze the data and display the results, including ANOVA and linear regression. All data analyses were done on a voxel-by-voxel basis (see below). The SPSS statistical package for Windows XP (version 2002) and the IMSL statistical library (in FORTRAN programs) were used for data analysis.

The statistical significance of single proportions (against the null hypothesis of zero) and of a comparison between two proportions were tested using the binomial theorem (Fleiss 1981). When an ANOVA was performed on proportions,  $p$ , the data were first arcsine transformed to  $p'$  to normalize their distribution (Snedecor and Cochran 1989; Zar 1999):

$$p' = \arcsin \sqrt{p} \quad (1)$$

Finally, a laterality ratio, LR, was calculated for each lateralized ROI as follows:

$$LR = \frac{\frac{R_L}{N_L}}{\frac{R_R}{N_R}} = \frac{R_L N_R}{R_R N_L} \quad (2)$$

where  $R$  and  $N$  indicate the number of voxels with a significant regression slope and total number of voxels in a given area, respectively. The effect of gender was assessed using an analysis of variance (ANOVA) on the log-transformed LR. This transformation of the LR ratio was needed to normalize its distribution and stabilize the variance (Snedecor and Cochran 1989; Zar 1999):

$$LR' = \ln(LR) \quad (3)$$

#### fMRI data analysis

##### General

As mentioned above, for each subject, 124 functional images were acquired continuously (Fig. 2), yielding 124 BOLD data values for each voxel. BOLD signal intensity was extracted for each voxel using the fMRI analysis program STIMULATE (Center for Magnetic Resonance Research, University of Minnesota Medical School, Minneapolis, MN, USA). This program also provided image-based coordinates for each voxel.

The BOLD data were log-transformed to confer normality, stability of variance and additivity, as explicated in a previous paper (Lewis et al. 2005). The elementary unit for data analysis was a voxel: all analyses (e.g. regression of BOLD on MR angle) were done on a voxel-by-voxel basis. Further statistical analyses (e.g. ANOVA,  $t$ -tests, etc.) were performed on aggregates of voxels, such as ROI, hemispheres, etc.

##### Detrending

The presence of a linear trend was assessed for each voxel using a linear regression of the BOLD values during the first and second control periods against elapsed time, and the BOLD data during the task period were detrended accordingly. (The first 7 points of both control periods were rejected to allow for stabilization of the hemodynamic response.)

##### Dependence of voxel-by-voxel BOLD signal on instructed angle of mental rotation

This was assessed by performing, for every voxel, a linear regression, where the detrended BOLD signal in the  $k$ th voxel was the dependent variable and the instructed angle of MR,  $\Omega$ , was the independent variable:

$$BOLD_k = a_k + b_k \Omega \quad (4)$$

The threshold for statistical significance in this regression analysis was set to  $P < 0.01$ .

##### Permutation analysis

In the analysis above, many regressions were carried out, on data from each voxel. Therefore, it is possible that the percentage of significant relations to the instructed angle thus identified might be inflated. We evaluated this problem by performing a permutation analysis, as follows. For each voxel, the values of BOLD data corresponding to

instructed angles were randomly permuted and the regression performed in the identical manner, as it was performed on the original, non-permuted data. This was done for all voxels, and the percentage of statistically significant regressions ( $P < 0.01$ ) was calculated for each ROI. This process was repeated 1,000 times. Descriptive statistics of the percentages of significant regressions (minimum, maximum, and mean) were retained as indicators of what can be expected by chance.

### Spatial gradients in BOLD versus rotation angle slopes

This analysis was aimed to find out whether voxel-by-voxel slopes varied in a regular fashion in the anteroposterior and mediolateral dimensions within selected ROIs. Since the location of a voxel was coded in image coordinates (see above), we computed standardized coordinates for the  $k$ th voxel of the  $i$ th subject to enable pooling of voxels across subjects.

$$AP_{i,k} = \frac{AP_{i,k} - AP_{i,\min}}{AP_{i,\max} - AP_{i,\min}} \quad (5)$$

$$ML_{i,k} = \frac{ML_{i,k} - ML_{i,\min}}{ML_{i,\max} - ML_{i,\min}}. \quad (6)$$

Then, for a given ROI, the presence of a spatial gradient along those two dimensions was assessed by performing a voxel-by-voxel multiple regression analysis, where the BOLD versus MR angle slope was the dependent variable and the standardized AP and ML coordinates were the independent variables.

### Standardized BOLD signal

Average detrended BOLD values for Control 1 and Task periods (Fig. 2) were computed to evaluate, for each voxel, the overall change in the BOLD signal during the whole period of the MR task  $T$  (Task period), with respect to the preceding control task  $C$  (Control 1 period). For that purpose, we computed a standardized BOLD signal change  $S$  (Lewis et al. 2003) as follows:

$$S = \frac{T - C}{C} \quad (7)$$

## Results

### Behavior

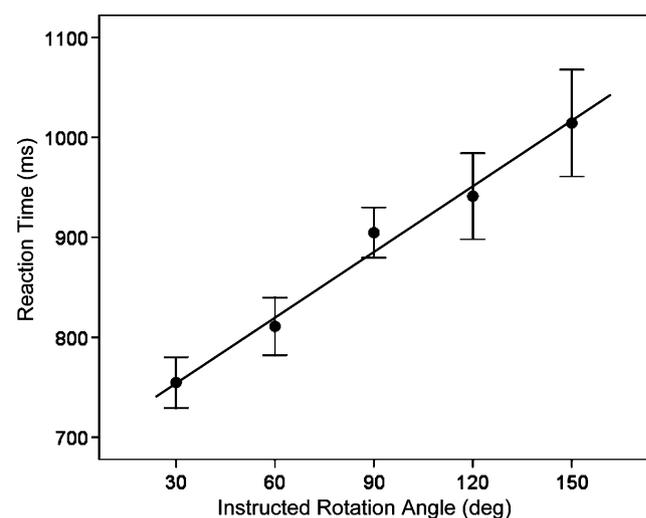
Subjects performed the motor MR task very well. The mean absolute angle between instructed and performed angle (variable error) was  $10.6^\circ \pm 0.31^\circ$  (mean  $\pm$  SEM,

$N = 662$  trials) and did not differ significantly between men and women ( $P = 0.65$ ,  $t$ -test). The mean RT ( $904.5 \pm 15.2$  ms) also did not differ significantly between men and women ( $P = 0.6$ ,  $t$ -test). Finally, RT increased as a linear function of the instructed angle,  $\Omega$  (Fig. 3). The regression equation was  $RT \text{ (ms)} = 689 + 2.187\Omega \text{ (deg)}$  ( $P < 10^{-7}$ ,  $t$ -test on the slope) corresponding to a mean rate of MR of  $457^\circ/\text{s}$ . Mean regression slopes did not differ significantly between men and women ( $P = 0.6$ ,  $t$ -test).

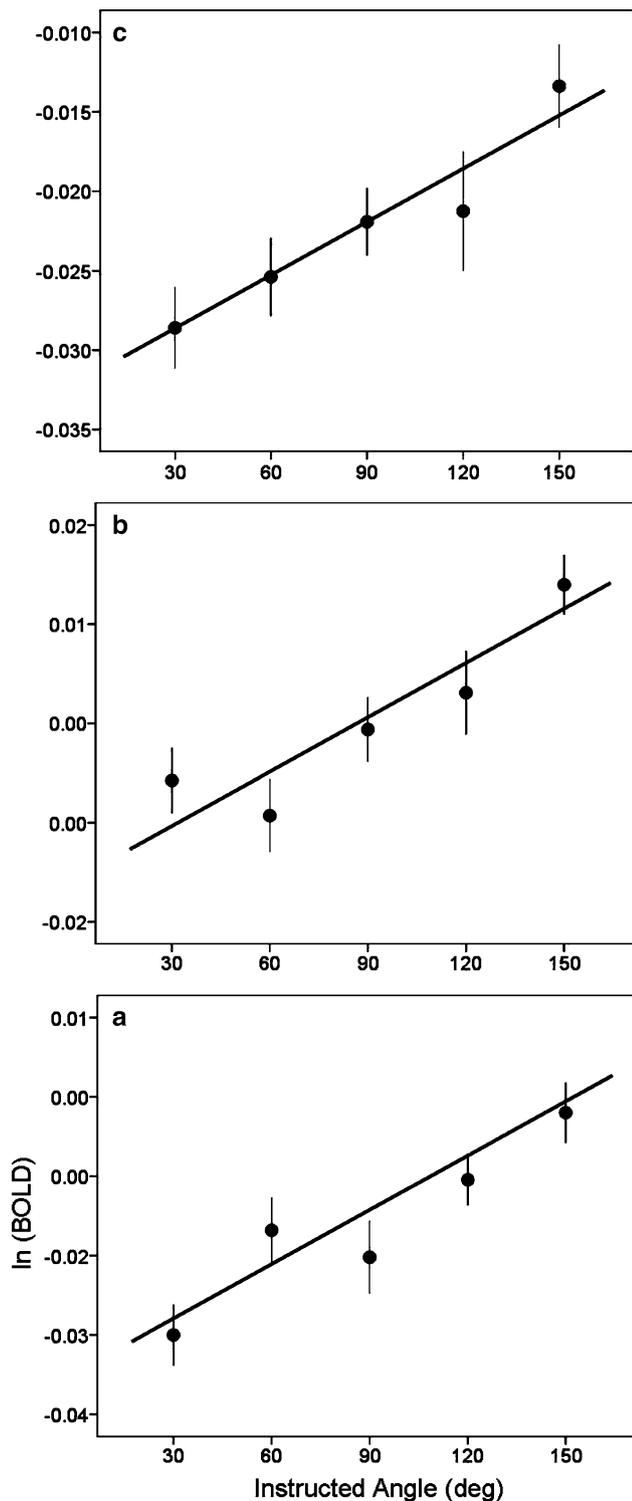
### Relation of BOLD signal to angle of mental rotation

Data from 188,593 voxels of 37 areas (17 in the left cerebral hemisphere, the same 17 in the right hemisphere, and the cerebellar hemispheres and midline) were analyzed. We found a statistically significant relation between BOLD intensity and MR angle in 10.5% of the voxels (on the average), where BOLD varied as a linear function of the MR angle. Examples are shown in Fig. 4 and the results per ROI are given in Table 1. With respect to expected chance effects on these percentages, none of 1,000 permutations yielded percentages that were equal or higher than those observed in any area (Table 1). Therefore, all of the observed percentages exceeded chance by  $P < 0.001$ .

Next we analyzed the value of the voxel-by-voxel slope of BOLD intensity versus MR angle. For that purpose, we performed an ANOVA for each lateralized ROI ( $N = 18$ ) to assess the effect of Gender, Hemisphere, and their interaction ( $G \times H$ ) on that slope. The results are shown in Table 2. A significant effect of Gender was found in 9/18 (50%), of Hemisphere in 3/18 (16.7%), and of  $G \times H$  in 4/18 (22.2%) of ROIs. A more detailed analysis of these effects were carried out by comparing, for each ROI, the



**Fig. 3** Reaction time of motor mental rotation (mean  $\pm$  SEM) is plotted against instructed angles. Linear increase of RT with the angle is statistically significant ( $P < 10^{-7}$ )



**Fig. 4** Single voxel BOLD activation (mean  $\pm$  SEM) is plotted against mental rotation angle. **a** superior parietal lobule, right hemisphere,  $P < 10^{-5}$  ( $t$ -test on linear regression slope). **b** precentral gyrus, right hemisphere,  $P < 10^{-5}$ . **c** left cerebellum,  $P < 10^{-5}$

slopes between the two genders within each hemisphere (Table 3). It can be seen that men had significantly higher slopes than women in 11 ROIs (mostly in the right frontal

and parietal lobes), whereas women had higher slopes in 5 ROIs. Table 4 shows that there was a strong right hemispheric preponderance (higher slopes) in the frontal lobe of men but hardly any hemispheric difference in women. This effect in men was further analyzed by testing for the presence of statistically significant spatial gradients in the BOLD versus MR angle slopes in lateral frontal (superior, middle and inferior frontal gyri, and precentral gyrus) areas. In general, there were strong spatial gradients in the frontal areas. Since the slopes of these gradients were in same direction (higher slopes anterior and lateral) in all areas above, we performed a multiple regression analysis (see “Materials and methods”) after pooling the voxels of these areas together, in order to an estimate of the overall effect. We found highly significant anteroposterior ( $P = 5.9 \times 10^{-14}$   $t$ -test on the AP regression coefficient) and mediolateral ( $P = 0.00017$ ,  $t$ -test on the ML regression coefficient) gradients. The regression equation was:

$$\text{BOLD versus angle slope} = -0.034 - 0.150\text{AP} - 0.115\text{ML} \quad (8)$$

It can be seen that the AP gradient was steeper than the ML gradient. The direction of the AP gradient was from anterior (higher slopes) to posterior (lower slopes); the direction of the ML gradient was from lateral (higher slopes) to medial (lower slopes).

We performed the same analysis on lateral parietal areas (postcentral gyrus, superior parietal lobule, intraparietal sulcus, and inferior parietal lobule) that are known to be interconnected with the frontal ones in an orderly fashion (Caminiti et al. 1985; Petrides and Pandya 2006, 2007). No significant gradients were found in the parietal cortex.

#### Differences between women and men

We carried out four analyses to assess possible differences between men and women. First, the change in the standardized BOLD signal (see “Materials and methods”) during task performance from the control task did not differ significantly between men and women ( $P = 0.23$ ,  $t$ -test). Second, the proportions of voxels that showed a significant regression slope ( $P < 0.01$ ,  $t$ -test on the slope, see “Materials and methods”) did not differ significantly between women and men in any of the areas studied ( $t$ -test). Third, the left–right laterality index (see “Materials and methods”) did not differ significantly between men and women in any area studied ( $t$ -test). Together, these results indicated that the proportions and lateralization of voxels related to motor MR did not differ significantly between women and men.

A fourth analysis was performed on the regression slope itself (i.e. BOLD vs. MR angle). This slope reflects the efficiency of the neural mechanism underlying MR (BOLD

**Table 1** Percentages of voxels that showed a significant relation to motor mental rotation angle ( $P < 0.01$ ,  $t$ -test on regression slope, see “Materials and methods”)

ROI	Mean %	% left	% permutation	% right	% permutation	Right $\neq$ left
Superior parietal	14.6	13.3	0.997 (0.54, 1.54)	15.8	0.997 (0.55, 1.44)	0.001 (R > L)
Superior occipital	12.8	12.5	0.996 (0.59, 1.40)	13.0	0.995 (0.52, 1.46)	NS
Superior frontal	12.5	11.8	0.995 (0.63, 1.37)	13.2	0.991(0.69, 1.39)	0.010 (R > L)
Lingual gyrus	12.4	13.3	0.984 (0.35, 1.78)	11.5	1.005 (0.38, 1.82)	NS
Intraparietal sulcus	12.1	12.8	0.995 (0.53, 1.65)	11.4	1.004 (0.43, 1.63)	NS
Inferior parietal	11.9	12.4	0.992 (0.55, 1.52)	11.3	0.999 (0.60, 1.52)	0.001 (L > R)
Inferior occipital	11.6	10.5	0.987 (0.54, 1.48)	12.7	0.994 (0.58, 1.65)	NS
Calcarine sulcus	11.2	11.8	0.987 (0.36, 1.80)	10.6	1.003 (0.34, 1.71)	NS
Middle frontal gyrus	11.2	10.8	0.988 (0.64, 1.40)	11.6	0.990 (0.61, 1.32)	NS
Postcentral gyrus	10.9	9.0	0.992 (0.64, 1.45)	12.7	0.991 (0.59, 1.39)	$10^{-10}$ (R > L)
Medial frontal gyrus	9.9	9.0	0.993 (0.57, 1.49)	10.8	0.995 (0.58, 1.59)	0.005 (R > L)
Inferior frontal gyrus	9.4	8.9	0.978 (0.52, 1.49)	9.8	0.973 (0.43, 1.53)	NS
Cingulate gyrus	9.3	8.7	0.993 (0.63, 1.51)	9.9	0.990 (0.60, 1.41)	0.03 (R > L)
Precuneus	9.3	8.0	0.987 (0.44, 1.64)	10.5	0.991 (0.52, 1.49)	0.001 (R > L)
Cuneus	9.2	9.0	1.002 (0.45, 1.72)	9.3	0.988 (0.35, 1.59)	NS
Paracentral lobule	9.1	9.0	1.002 (0.56, 1.65)	9.1	0.990 (0.45, 1.60)	NS
Lateral cerebellum	8.6	8.8	0.989 (0.72, 1.27)	8.3	0.994 (0.71, 1.32)	NS
Precentral gyrus	7.8	8.5	0.996 (0.52, 1.40)	7.1	0.990 (0.61, 1.40)	0.003 (R < L)

Areas are ranked according to mean percentage. For the permutation test, the *mean (minimum, maximum)* percentage of significant ( $P < 0.01$ ) regressions (out of 1,000 permutations) are given. The column on the far right gives the probability values (and the hemispheric preponderance) for rejecting the null hypothesis that the Left and Right proportions are equal (see “Materials and methods”). For non-lateralized midline cerebellum, the percentage of significant regressions observed was 6.6% and the permutation values were: 0.995 (0.51, 1.56)

NS Not significant

signal per degree of rotated angle): the smaller the slope the higher the efficiency of neural MR. This analysis revealed striking differences between the two sexes. First, the overall slope (i.e. across all ROIs) was significantly higher (by 2.4 $\times$ ) in men than in women (Fig. 5;  $P < 10^{-8}$ ,  $t$ -test), indicating a higher efficiency in neural processing of MR by women. And second, an analysis of hemispheric differences (ROIs pooled) showed that the regression slopes were practically the same in the right and left hemisphere of women but were much higher in the right (than the left) hemisphere of men (Fig. 6;  $P < 10^{-10}$ ,  $t$ -test). The difference in the left hemisphere between men and women did not reach statistical significance ( $P = 0.077$ ,  $t$ -test).

## Discussion

In this study we investigated systematically the relations between BOLD activation and angle of motor MR on a voxel-by-voxel basis in 37 brain areas from 8 subjects. To our knowledge this is the first such detailed study. There were three major findings. First, we found voxels with a significant relation to the angle of motor MR in all areas, with a preponderance in the superior parietal lobule; this

finding demonstrates the distributed nature of the process of MR. Second, the average slope of BOLD activation versus the angle of MR was substantially higher in men than in women; this result documents a higher efficiency of neural information processing in women than men. And third, there was a clear hemispheric asymmetry in the frontal lobe of men (but not of women), such that BOLD versus rotation angle slopes were significantly higher in the right than left hemisphere. We discuss these findings below.

## Task considerations

In this study we used a direct MR task without a visual object to be rotated (Georgopoulos and Massey 1987) to avoid BOLD activation stemming from visual processing of well formed objects (e.g. 3D wire frame drawings, 2D alphanumeric stimuli, pictures of familiar objects and tools, human body parts, etc.). Such processing might interact with the MR process itself and thus might obscure those brain mechanisms more specific to that process. For example, MR of visual objects, as in the Shepard and Metzler (1971) experiment, possess four major component processes, namely (a) perceptual encoding of the apparent shape of the object and its orientation, (b) MR of one object

**Table 2** Results of ANOVA regarding the magnitude of voxel-by-voxel BOLD slopes for mental rotation (dependent variable) in individual areas (Gender and Hemisphere were fixed factors)

ROI	Gender	Hemisphere	G × H
Cingulate gyrus	0.0004	NS	0.004
Medial frontal gyrus	NS	0.025	NS
Superior frontal gyrus	0.00005	NS	NS
Middle frontal gyrus	NS	$6 \times 10^{-8}$	$2.9 \times 10^{-9}$
Inferior frontal gyrus	0.01	0.042	0.0001
Precentral gyrus	NS	NS	NS
Postcentral gyrus	NS	NS	0.0015
Superior parietal lobule	0.0001	NS	NS
Intraparietal sulcus	0.0015	NS	NS
Inferior parietal lobule	NS	NS	NS
Paracentral lobule	NS	NS	NS
Cuneus	0.038	NS	NS
Precuneus	0.006	NS	NS
Lingual gyrus	NS	NS	NS
Superior occipital gyrus	0.022	NS	NS
Inferior occipital gyrus	NS	NS	NS
Calcarine sulcus	NS	NS	NS
Lateral cerebellum	0.01	NS	NS

Numbers are *P* values (*F* test)

NS Not significant ( $P \geq 0.05$ )

**Table 3** Gender differences in specific areas regarding the magnitude of BOLD slopes for mental rotation in individual areas

ROI	Left hemisphere		Right hemisphere	
	<i>P</i>	Gender	<i>P</i>	Gender
Cingulate gyrus	NS		0.00006	M > W
Medial frontal gyrus	NS		0.028	M > W
Superior frontal gyrus	NS		0.00002	M > W
Middle frontal gyrus	0.000004	W > M	0.00005	M > W
Inferior frontal gyrus	NS		0.001	M > W
Precentral gyrus	0.015	W > M	NS	
Postcentral gyrus	0.036	W > M	0.001	M > W
Superior parietal lobule	0.026	M > W	0.001	M > W
Intraparietal sulcus	NS		0.001	M > W
Inferior parietal lobule	NS		NS	
Paracentral lobule	NS		NS	
Cuneus	NS		0.041	W > M
Precuneus	NS		0.003	W > M
Lingual gyrus	NS		NS	
Superior occipital gyrus	NS		NS	
Inferior occipital gyrus	NS		NS	
Calcarine sulcus	0.013	M > W	NS	
Lateral cerebellum	0.002	M > W	NS	

*P* *P*-values (*t*-test), NS not significant ( $P \geq 0.05$ ), *M* and *W* gender preponderance

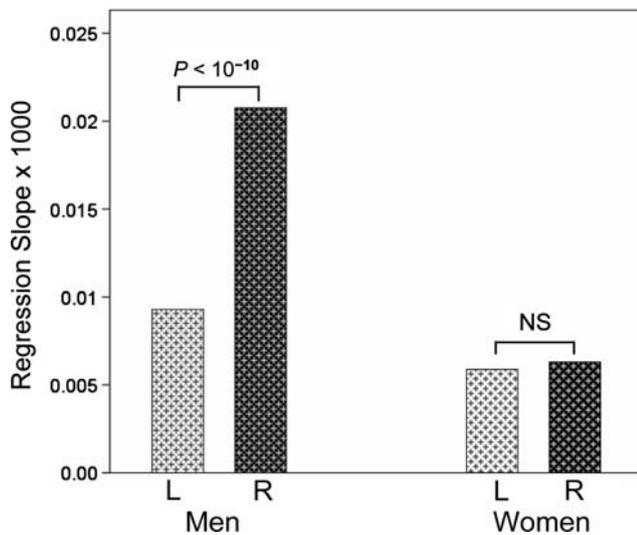
**Table 4** Evaluation of hemispheric differences between men and women regarding the magnitude of voxel-by-voxel BOLD slopes for mental rotation in individual areas

ROI	Men		Women	
	<i>P</i>	Hem	<i>P</i>	Hem
Cingulate gyrus	0.015	R > L	0.049	L > R
Medial frontal gyrus	$2.2 \times 10^{-7}$	R > L	NS	
Superior frontal gyrus	0.001	R > L	NS	
Middle frontal gyrus	$2.2 \times 10^{-17}$	R > L	NS	
Inferior frontal gyrus	0.0001	R > L	NS	
Precentral gyrus	0.008	R > L	NS	
Postcentral gyrus	0.00002	R > L	NS	
Superior parietal lobule	NS		NS	
Intraparietal sulcus	NS		NS	
Inferior parietal lobule	NS		NS	
Paracentral lobule	NS		NS	
Cuneus	NS		NS	
Precuneus	0.007	L > R	NS	
Lingual gyrus	NS		NS	
Superior occipital gyrus	NS		NS	
Inferior occipital gyrus	NS		NS	
Calcarine sulcus	0.029	L > R	NS	
Lateral cerebellum	NS		0.047	R > L

*P* *P*-values (*t*-test), *Hem* hemisphere, *L* left, *R* right, NS not significant ( $P \geq 0.05$ )

**Fig. 5** Linear regression slopes of BOLD versus mental rotation angle are shown as mean  $\pm$  SEM for men and women

from its perceived orientation to the orientation of its mate, (c) serial comparisons between the mentally rotated object's shape and the perceived unrotated object's shape, and (d) a decision on whether the shapes match or not (see, e.g. Hugdahl et al. 2006; Parsons 2001).



**Fig. 6** Mean linear regression slopes (BOLD vs. mental rotation angle) for men and women for left (L) and right (R) hemispheres. *P* value is from *t*-test, *NS* not significant

#### Relations of fMRI activity to MR angle

This problem was investigated by Carpenter et al. (1999) using the Shepard and Metzler (1971) MR paradigm. It was found that fMRI activation in the intraparietal sulcus increased as a linear function of the disparity angle between the two wire-frame objects. This result was attributed to increased computational demands with increasing disparity angle. In our results, individual voxels parametrically related to the angle of motor MR were spread across several areas in the brain. There was a general antero-posterior cerebrocortical trend where the percentage of such voxels increased from frontal to parietal areas (Table 1). The highest percentage was found in the superior parietal lobule, in keeping with the results of previous studies based on whole ROI analyses (Tagaris et al. 1998).

It is worth noting that, from a theoretical point of view, the process of MR has been conceptualized, almost exhaustively, as a rotating mental visual image of a neural representation. Accordingly, MR has been considered exclusively in the time domain. However, there is an aspect of the process, in addition to the rotation itself, that deserves considering, namely the decision to stop the rotation and emit the response. A plausible hypothesis would suppose that a comparison is being performed at some regular interval during the rotation between the (partial) angle by which the image has already been rotated and the full angle specified by the requirement of the trial. The number  $N$  of such comparisons in a trial would depend on the total angle specified  $\Omega$  and the angular increment  $\zeta$  (Fig. 1):  $N = \frac{\Omega}{\zeta}$ . In that case, neural activity would be

expected to vary (increase or decrease) in a systematic fashion with  $N$ . With respect to neurophysiological studies, this hypothesis predicts that the frequency of single cell discharge during MR trials would differ from that observed during control trials. Indeed, this was observed in the study of Lurito et al. (1991) where a statistically significant main “Task” effect in an analysis of variance (ANOVA) was found in 14.7% of cells recorded in the motor cortex of monkeys; in 48% of those cells mean activity increased during the MR task, as compared to the control task, whereas it decreased in 52%. With respect to the BOLD signal, this hypothesis predicts that while its time course would be a function of the rotation angle or RT (Richter et al. 2000), reflecting the time-consuming rotation process, its intensity would also vary with the same parameters, reflecting the number of postulated comparisons. The findings of the present study are compatible with this prediction.

#### Neural processing efficiency: differences between men and women

The regression slope of BOLD activation versus angle of MR can be regarded as a quantitative measure of the efficiency of neural processing per angular unit (e.g. degree) of MR: the higher the slope, the lower the neural processing efficiency, and vice versa. Our findings revealed a clear overall higher efficiency in women than in men and, in addition, a remarkable interaction between gender and hemispheric lateralization in the frontal lobe. Specifically, neural processing efficiency was systematically lower (i.e. higher BOLD vs. rotation angle slopes) in frontal (lateral and medial) areas in the right hemisphere of men, as compared to the same areas of the left hemisphere, whereas no such effect was observed in women. This finding is similar to another one observed in a previous study of mental object completion (Georgopoulos et al. 2001). In that study, the right temporal lobe was activated in the task in men but not in women. The effects in different lobes probably reflect the nature of the tasks, where the visual mental object completion engaged the temporal lobe and the motor MR engaged the frontal lobe. Thus, depending on the task, different areas of the right hemisphere are engaged in men, as compared to women.

This preferential involvement of the right hemisphere in men was further characterized by identifying statistically significant spatial gradients in the BOLD versus MR angle slopes in lateral frontal (superior, middle and inferior frontal gyri, and precentral gyrus) areas. The strong AP gradient found (higher slopes anterior  $\rightarrow$  lower slopes posterior) indicates a gradually increasing neural processing efficiency from anterior to posterior. Remarkably, no such gradient was found in the parietal cortex.

The value of these results rests on the fact that the behavioral performance did not differ between men and women. This was indeed the case in this study. Previous studies have yielded different results with respect to gender differences in mental rotation, too numerous to discuss them here in detail. Instead, we deem it most appropriate for the purpose of this study to summarize the most pertinent evidence to the task we used. (a) The same subjects who performed the motor MR task in the present study also performed a 2D visual MR task (Shepard and Cooper 1982) in the same study (Tagaris et al. 1998). An analysis of the RT versus angle of rotation slopes showed that the two genders did not differ significantly (P. Christova, S. M. Lewis, G. Tagaris, A. P. Georgopoulos, unpublished observations,  $P < 0.28$ , *t*-test). (b) Shepard and Cooper (1982) did not observe gender differences in visual MR. Specifically, they state that “no consistent differences were observed in the performances of the two sexes.” (Shepard and Cooper 1982, p 76). (c) No gender differences in MR slopes have been found in other studies of MR using the Shepard and Metzler (1971) objects (Butler et al. 2006, 2007; Hugdahl et al. 2006; Jordan et al. 2002; Thomsen et al. 2000; Weiss et al. 2003). However, gender differences have been observed in other studies (Halari et al. 2006; Linn and Petersen 1985; Voyer et al. 1995, 2006).

#### Gender differences in brain mechanisms of visuospatial tasks

The discussion in the preceding section dealt with behavioral and/or functional neuroimaging studies. However, a substantial fund of knowledge concerning gender differences and brain mechanisms (including hemispheric lateralization of function) has come from the study of people with brain damage; typically, gender differences have been explored in the context of visuospatial tasks and language-related functions. With respect to hemispheric lateralization of visuospatial function, it is generally believed that the right hemisphere plays a crucial role in that function (Benton 1967; Gott 1973; Mack and Levine 1981; Nebes 1978; Piercy et al. 1960; Smith 1969). However, there is substantial controversy regarding this matter (see, e.g. De Renzi 1982; Gainotti 1985). This mainly stems from the fact that potential differences between women and men could be confounded by the fact that the effects of right or left hemispheric lesions may depend on gender. Specifically, with respect to men, right hemispheric lesions seem to be more effective in producing visuospatial deficits, as compared to either left-hemispheric lesions in men or right hemispheric lesions in women (Lewis and Kamptner 1987; McGlone and Kertesz 1973). On the other hand, with respect to women, the effects of left hemispheric lesions on visuospatial functions are

similar to those of right hemispheric lesions in women (Lewis and Kamptner 1987; McGlone and Kertesz 1973) but similar (McGlone and Kertesz 1973) or worse (Lewis and Kamptner 1987) than left hemispheric lesions in men. Now, with respect to hemispheric specialization, the right and left hemispheres have been traditionally regarded as relating mainly to visuospatial and language skills, respectively. Since women are regarded more expert in language skills (Hobson 1947; Meyer and Bentig 1961; Wechsel 1958), it has been proposed that they may tend to use preferentially verbal strategies in task performance (Kimura 1969), hence their smaller dependence on the right hemisphere. Then, gender differences are explained by postulating that men and women employ fundamentally different strategies to perform visuospatial tasks based on spatial or verbal operations, respectively. A variant of this idea makes use of the concept of synthetic (non verbal) and analytic (verbal) functions for which the right and left hemispheres are thought to be specialized, respectively (Levy 1969). Specifically, it has been proposed that tasks involving perceptual synthesis rely on the right hemisphere (in men), whereas tasks involving perceptual analysis or language skills rely on the left hemisphere (in women) (Tucker 1976). The argument, then, can be formulated as follows: men tend to use spatial/synthetic strategies, hence their right hemisphere preponderance in solving visuospatial problems; in contrast, women tend to employ verbal/analytic strategies, hence their left hemispheric preponderance. Although this is a plausible scheme with reasonable support (see literature above), it is nevertheless quite speculative. What seems to be especially weak is the supposed reliance of women on verbal strategies in solving visuospatial tasks. Although this could be the case for fairly complex tasks, it does not seem plausible for simple ones. And, specifically, it would seem difficult to believe that a verbal strategy would be the strategy employed to perform our motor MR task in which the individual visual stimuli were simple dots. Indeed, there were no systematic differences between men and women with regard to left hemispheric processing, whereas there was a major systematic preponderance of the right frontal lobe in men. A simple hypothesis is that indeed visuospatial tasks involve mostly right hemispheric mechanisms for which women seem to be most efficient.

#### Conclusions

These results demonstrate, for the first time, the higher efficiency of women in processing MR information overall, and by both cerebral hemispheres. In contrast, men showed a more than twofold decrease in efficiency (i.e. increase in the BOLD versus MR angle) accounted for by frontal and

pericentral regions. A stronger engagement of the right hemisphere in men than in women was found previously in another visuospatial task involving mental figure completion (Georgopoulos et al. 2001).

Finally, these findings may bear on the more general issue pertaining to the smaller brain size found in women (Good et al. 2001). Even in our current sample, the total number of voxels in the areas analyzed were more in men ( $N = 97,525$ ) than in women ( $N = 91,068$ ). The results of this and a previous study (Georgopoulos et al. 2001) suggest that women's brains process information much more efficiently, for equivalent behavioral performance. Therefore, less brain tissue might be needed by women than men.

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