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Sex differences in mental rotation: Top–down versus bottom–up processing

Tracy Butler,[a,*] Julianne Imperato-McGinley,[b,1] Hong Pan,[a] Daniel Voyer,[c] Juan Cordero,[b] Yuan-Shan Zhu,[b] Emily Stern,[a,1] and David Silbersweig[a,1]

[a]*Functional Neuroimaging Laboratory, Department of Psychiatry, Weill Medical College of Cornell University, Box 140, 1300 York Avenue, New York, NY 10021, USA*
[b]*Department of Endocrinology, Weill Medical College of Cornell University, New York, NY 10021, USA*
[c]*Department of Psychology, University of New Brunswick Fredericton, NB, Canada*

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Functional MRI during performance of a validated mental rotation task was used to assess a neurobiological basis for sex differences in visuospatial processing. Between-sex group analysis demonstrated greater activity in women than in men in dorsalmedial prefrontal and other high-order heteromodal association cortices, suggesting women performed mental rotation in an effortful, "top–down" fashion. In contrast, men activated primary sensory cortices as well as regions involved in implicit learning (basal ganglia) and mental imagery (precuneus), consistent with a more automatic, "bottom–up" strategy. Functional connectivity analysis in association with a measure of behavioral performance showed that, in men (but not women), accurate performance was associated with deactivation of parieto-insular vestibular cortex (PIVC) as part of a visual–vestibular network. Automatic evocation by men to a greater extent than women of this network during mental rotation may represent an effective, unconscious, bottom–up neural strategy which could reasonably account for men's traditional visuospatial performance advantage.

Introduction

The biological basis for possible cognitive differences between men and women remains a topic of great interest and controversy. Mental rotation is a visuospatial task which gives rise to robust sex-based differences in performance, with men performing more accurately than women on average (Voyer et al., 1995). It therefore serves as a valuable probe for investigating the neurobiological underpinnings of sex differences in cognition. Several prior studies aimed at determining the neural basis for this male advantage have shown that men and women both activate regions of prefrontal, parietal, and temporal–occipital regions during mental rotation, with no (Dietrich et al., 2001; Tagaris et al., 1996; Unterrainer et al., 2000) or variable (Fink et al., 2003; Jordan et al., 2002; Seurinck et al., 2004; Thomsen et al., 2000) between-sex differences, though greater activity in frontal brain regions has been detected in women in a majority of studies (Seurinck et al., 2004; Thomsen et al., 2000; Weiss et al., 2003). One limitation of these prior studies, likely to account in part for discrepant results, is the use of variable, study-specific mental rotation paradigms created by each set of investigators for use during fMRI scanning. None of these study-specific tasks gave rise to significant male behavioral performance advantages in scanned subjects (perhaps due to small sample sizes typical of neuroimaging studies), and none were known to do so in larger populations, calling into question the usefulness of results in explaining a neural basis for this advantage. We therefore utilized a computerized mental rotation task optimized for use during fMRI scanning, which we have previously shown to be a valid measure of mental rotation abilities and to produce the expected pattern of sex-based performance in a large sample of normal subjects (Voyer et al., 2006), to investigate the neural basis for sex differences in mental rotation performance. In addition to standard between-sex group analysis of imaging data, we incorporated performance accuracy at each level of task difficulty into correlational analyses in order to assess contributions of sex, level of behavioral performance, and interaction effects to fMRI results, in accordance with studies emphasizing the importance of this approach (Seurinck et al., 2004; Shelton and Gabrieli, 2004; Tagaris et al., 1996; Unterrainer et al., 2000). Functional connectivity analyses were performed in order to explore brain networks engaged during accurate mental rotation, and how they might differ by sex.

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* Corresponding author. Fax: +1 212 746 5818.
E-mail address: tab2006@med.cornell.edu (T. Butler).

[1] Senior authors.

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Materials and methods

Subjects

32 healthy subjects underwent fMRI scanning as part of the present study, which was approved by the New York Presbyterian Hospital–Weill/Cornell Institutional Review Board. Acceptable data were obtained from 25 subjects: 13 women (mean age 28.6, std 7.5) and 12 men (mean age 30.1, std 5.9). All subjects were strongly right-handed according to the Edinburgh Handedness Inventory, free from medical, neurological and psychiatric disease, and taking no medications. Reasons for excluding subjects from final analyses were MRI ghosting artifact greater than 5% (one woman, two men); head movement greater than 1/3 of a voxel based on examination of realignment parameters (two women, one man); and failure to perform the task in the scanner (one man).

Stimuli

Redrawn versions of Shepard and Metzler original cube figure (Peters et al., 1995) were presented in pairs (Fig. 1). Figures were white on a black background. Stimuli pairs were either the same but rotated with respect to one another (“same” trials), or they were mirror images of each other (“different” trials). Stimuli were rotated with respect to one another around their vertical axis. Presentation of stimuli in the scanner was controlled by the Integrated Functional Imaging System (IFIS; MRI Devices Inc. Gainesville, FL) by means of Eprime software (Psychology Software Tools Inc., Pittsburgh, PA). Each pair of figures subtended a visual angle of approximately 6.3° horizontally and 2.5° vertically as displayed on an MRI-compatible LCD screen attached to the scanner’s head coil.

Experimental conditions

The Rotate activation conditions consisted of pairs of figures which were either identical (same) or mirror images (different) rotated by 40°, 80°, 120° or 160° with respect to one another. Subjects were instructed to mentally rotate figures into alignment in order to decide if they were the same or different.

The Compare activation condition consisted of pairs of figures which were either identical or mirror images which were *not* rotated (i.e., rotated 0°) with respect to one another. Subjects were instructed that in this condition, there was no need to try to rotate figures into alignment. This condition controlled for visual properties of the stimuli, the saccades and evaluation process required to reach a same or different decision, and the motor act of pressing a button.

Practice

Immediately preceding scanning, to familiarize subjects with the task and ensure they understood instructions, subjects performed a brief (approximately 5 min) practice version of the task on a computer. They were required to attain at least 60% correct in the easiest Rotate condition, in which figures were rotated 40° with respect to one another, as well as in the Compare condition. No subject required more than two practice runs to reach this criterion.

Experimental task

In the context of a block design paradigm, stimuli pairs at each angle of rotation (including the 0° compare condition) were grouped into blocks of five trials each. Each trial lasted 7.5 s, resulting in blocks lasting 37.5 s. Each trial consisted of an orienting signal (a fixation cross in the center of the screen) for 500 ms, followed by a pair of stimuli presented for 7 s. Subjects responded to stimuli by pressing a button with their right index finger for a same response or right middle finger for a different response. Response accuracy and latency were recorded. Stimuli remained on-screen even when a response was produced faster than 7 s (in order to equalize visual stimulation across conditions and subjects). A dot appeared for 250 ms upon a subject’s response, to indicate to the subject that the button press

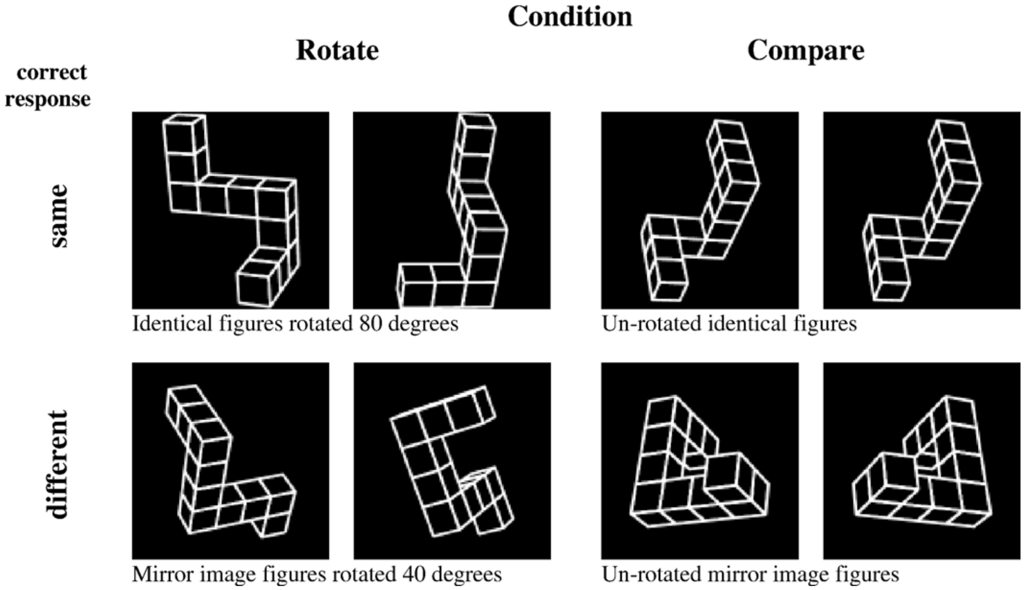

Fig. 1. Examples of stimuli pairs derived from Shepard and Metzler (1971) used in the present study.

had been recorded. If subjects did not respond within 7 s, the next trial began. Within each block of five trials, there were three same trials and two different trials presented in pseudo-random order.

An epoch (run) consisted of four 37.5-s active blocks, each followed by a 24-s rest block during which subjects looked at the center of the screen, which was marked by a dash. There were four Rotate epochs and three Compare epochs. Within each Rotate epoch, there was one block for each of the four angles of rotation. This resulted in 4 blocks (20 trials) of stimuli at each of the four angle of rotation, for a total of 16 Rotate blocks (80 trials.) Within each Compare epoch, all four active blocks were composed of unrotated pairs of stimuli, resulting in a total of 12 Compare blocks (60 trials.) The rationale for separating Rotate and Compare trials into different epochs was to distinguish these two conditions and to allow for a reminder of task instructions prior to stimuli presentation in order to ensure that subjects did not mistakenly engage in mental rotation during the compare condition (as had been noted in preliminary testing). Thus, the word “rotate” appeared on the screen immediately before each Rotate epoch, and the word “compare” appeared on the screen immediately before each Compare epoch.

The order of epochs and of blocks within epochs was the same for each subject, and was counterbalanced to control for systematic bias due to time and/or order effects.

After scanning, subjects completed a questionnaire about their experience.

Behavioral data analysis

Average accuracy (proportion of correct responses) and reaction time (RT) were calculated for each subject at each angle of rotation (0°, 40°, 80°, 120°, 160°). Rotate trials to which a subject responded in less than 250 ms were excluded from analysis. Accuracy was calculated both with and without omitted trials (when no subject response was recorded.) RT was calculated only for correct trials. Using SAS (Cary, NC, USA), separate two-way repeated measures analyses of variance examined the dependent measures of accuracy and RT, with sex as the between-subjects factor and degree of rotation as the within-subjects factor. Results at the $P < 0.05$ threshold were considered significant.

Image acquisition

Image data were acquired on one of two identical GE Signa 3 T MRI scanner (max gradient strength 40 mT/m, max gradient slew rate 150 T/m/s; General Electric Company, Waukesha, WI) using blood oxygen level-dependent (BOLD) fMRI. Approximately equal numbers of men and women were scanned on each scanner (6 women, 6 men on scanner #1; 7 women, 6 men on scanner #2). After shimming to maximize homogeneity, a series of fMRI scans was collected using gradient echo echo-planar imaging (EPI) (TR-2000; TE-30; flip angle = 70°; FoV = 240 mm; 27 slices; 5 mm thickness with 1 mm inter-slice space; matrix = 64 × 64). Images were acquired over the whole brain parallel to the AC–PC plane. The first six volumes of each epoch were discarded. A reference T1-weighted anatomical image with the same slice placement and thickness and a matrix of 256 × 256 was acquired immediately preceding the EPI acquisition. A high-resolution T1-weighted anatomical image was acquired using a spoiled gradient (SPGR) sequence with a resolution of $0.9375 \times 0.9375 \times 1.5$ mm^3.

Image processing and data analysis

Image processing performed within a customized Statistical Parametric Mapping (SPM) 99 software package (Frackowiack et al., 2004) included manual AC–PC re-orientation of all anatomical and EPI images; realignment of functional EPI images based on intracranial voxels to correct for slight head movement between scans; co-registration of functional EPI images to corresponding high-resolution anatomical image for each subject; stereotactic normalization to the standardized coordinate space of Talairach and Tournoux (Montreal Neurological Institute, MNI average of 152 T1 brain scans) based on the high-resolution anatomical image; and spatial smoothing of the normalized EPI images with an isotropic Gaussian kernel (FWHM = 7.5 mm).

A voxel-by-voxel univariate multiple linear regression model at the subject level determined the extent to which each voxel’s activity correlated with the principal regressor, which consisted of stimulus onset times (onset of active blocks) convolved with a prototypical hemodynamic response function. The temporal global fluctuation estimated as the mean intensity within brain region of each volume was removed through proportional scaling. The first order temporal derivative of the principal regressor (to compensate for slight latency differences in individual hemodynamic response from the prototypical response), temporal global fluctuation, realignment parameters, and scanning periods were incorporated as covariates of no interest. This first-level analysis resulted in a set of contrast images of condition-specific effects for each subject, which were entered into second-level random effects analyses to best account for inter-subject variability and allow population-based inferences to be drawn (McGonigle et al., 2000).

Voxel-by-voxel univariate group-level random effects analyses examined within-group between-condition effects (Rotate versus Compare in men and women separately), between-group within-condition effects (women versus men during Rotate) and interaction effects using these contrast images, with subject age and scanner entered as covariates of no interest in an ANCOVA

Table 1
Mean accuracy (ACC) and reaction time (RT) in ms in women ($n = 13$) and men ($n = 12$) for each experimental condition

		Compare (0°)	40°	80°	120°	160°	Average rotation
ACC (std)	Women	0.99 (0.02)	0.83 (0.14)	0.74 (0.18)	0.76 (0.13)	0.68 (0.17)	0.75 (0.16)
	Men	1.0 (0.01)	0.92 (0.13)	0.82 (0.18)	0.86 (0.12).	0.72 (0.18)	0.83 (0.17)
RT (std)	Women	1336.4 (270.6)	3531.4 (512.2)	3980.7 (519.5)	4045.9 (638.9)	4289.7 (708.8)	3961.9 (645.0)
	Men	1398.3 (492.6)	3762.8 (697.9)	4224.9 (733.1)	4240.3 (653.7)	4226.0 (600.9)	4113.5 (682.8)

Trials in which no response was recorded, or a response with RT <250 ms was recorded, were excluded from analysis. RT was calculated only for correct trials.

Table 2
Brain regions differentially active during mental rotation in men and women

	Volume (mm^3)	x	y	z	P_{unc}	$PFDR_{corr}$	z score
Greater in women							
L dorsalmedial prefrontal cortex/superior frontal gyrus (BA 8)	594	−9	27	51	<0.0001	0.01	4.01
R dorsalmedial prefrontal cortex/superior frontal gyrus (BA 8)[a]	162	15	30	54	<0.0001	0.011	3.41
L inferior occipito-temporal cortex (area LOC)	27	−39	−69	−9	0.001	0.012	3.29
R temporal pole (BA 21)	27	54	9	−30	0.001	0.012	3.15
Greater in men							
R postcentral gyrus (BA 5)	810	24	−42	66	<0.0001	0.005	−4.19
L ventral globus pallidus	270	−15	−3	−6	<0.0001	0.006	−3.87
L medial parietal/paracentral lobule (BA 5)	189	−15	−36	51	<0.0001	0.006	−3.77
L postcentral gyrus (BA 3)	81	−18	−42	66	<0.0001	0.006	−3.34
L precuneus	162	−9	−69	51	<0.0001	0.006	−3.3
Bilateral peri-midbrain	81	−3	−36	3	0.001	0.006	−3.22

[a] This is the only cluster that in part reflects differences in deactivation (see text for explanation).

setting. Regionally specific results were considered statistically significant if the P value was less than 0.01 for the F statistic of the ANCOVA and the peak voxel-wise P value was less than 0.001 for the effect-specific T statistic and survived correction over the whole brain for false discovery rate at $P < 0.05$ (Genovese et al., 2002).

To identify brain areas most active in association with accurate performance of the mental rotation task in men, in women, and in men as compared to women, a voxel-by-voxel univariate correlational analysis was performed using a multiple regression model in an ANCOVA setting, with each subject's contrast image from each Rotate condition (40°, 80°, 120°, 160°) as the independent variable, the z-transformed percentage of correct responses in the corresponding condition as the regressor of interest, and the subject factor, subject age, and scanner as covariates of no interest. For this supplemental analysis, results were considered statistically significant if the P value was less than 0.01 for the F statistic; voxel-wise $P < 0.0001$; and cluster size was greater than three voxels (81 mm^3).

To identify brain networks associated with accurate mental rotation performance in men and women, a voxel-by-voxel univariate correlational analysis was performed using a multiple regression model in an ANCOVA setting, with each subject's contrast image from each Rotate condition as the independent variable, the condition-specific activation level in "seed" voxels (identified through the above-described accuracy correlational analysis) in the corresponding condition as the regressor of interest, and the subject factor, subject age, and scanner as covariates of no interest. Again, for these supplemental analyses, results were considered statistically significant at a stringent threshold of $P < 0.05$ corrected for multiple comparisons over the entire brain, with cluster size greater than six voxels (162 mm^3).

Results

Behavioral results

For both accuracy and RT, there was an expected main effect of degree of rotation, with greater degree of rotation associated with lower accuracy [$F(4,92) = 29.10$, $P < 0.0001$] and longer RT [$F(4,92) = 240.5$, $P < 0.0001$] in both men and women. There was a weak trend towards a main effect of sex on performance accuracy, with men performing non-significantly better than women [$F(1,23) = 2.04$, $P = 0.17$], though this trend was not apparent when omitted trials were counted as incorrect and included in the analysis [$F(1,23) = 0.29$, $P = 0.59$]. There was no main effect of sex on RT [$F(1,23) = 0.48$, $P = 0.5$], and no interaction between degree of rotation and sex for either accuracy [$F(4,92) = 0.81$, $P = 0.52$] or RT [$F(4,92) = 0.71$, $P = 0.6$]. See Table 1 for mean accuracy and reaction times.

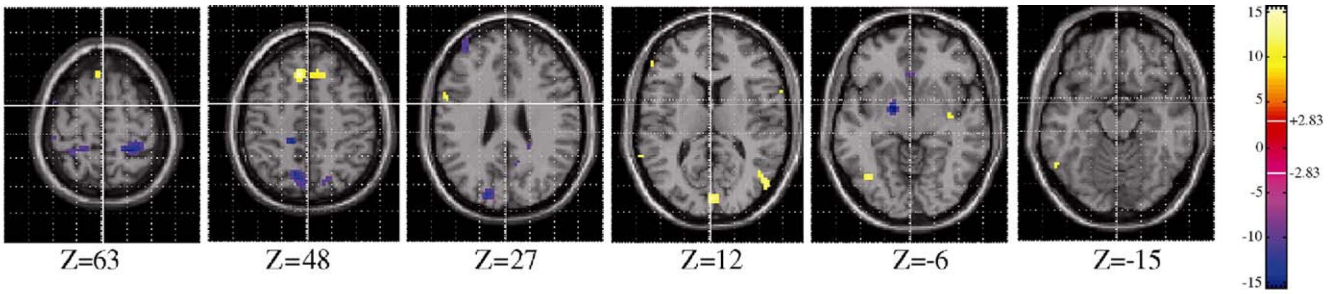

Fig. 2. Areas of significantly different activation between men and women performing mental rotation. Greater activity in women is displayed in yellow/red; greater activity in men in blue/purple. Note greater activity in women in bilateral dorsalmedial prefrontal cortex, left temporal pole, right temporal–parieto-occipital cortex (near angular gyrus), and left temporal–occipital cortex (area LOC). Note greater activity in men in bilateral postcentral gyri, precuneus, and left ventral basal ganglia. BOLD fMRI results are displayed as a T-map at a $P_{UNC} < 0.01$ threshold (for illustration purposes), overlaid onto canonical T1 axial sections [left = left, right = right] selected to illustrate areas of sex differences.

Table 3
Brain regions in which activity was positively correlated with accurate mental rotation performance in women, men, women versus men, and men versus women

	Volume (mm^3)	x	y	z	P_{unc}	z score
Regions correlated with accurate mental rotation performance in women						
L middle/superior frontal gyrus	2538	−27	21	45	<0.0001	5.02
L parietal (precuneus) (BA7)	432	−9	−51	36	<0.0001	4.28
L middle temporal gyrus (BA22)	243	−54	−36	3	<0.0001	4.09
Regions correlated with accurate mental rotation performance in men						
L posterior insula/claustrum (PIVC)	135	−33	−3	9	<0.0001	4.01
Regions more correlated with accuracy in women than in men						
L middle/superior frontal gyrus	945	−27	21	45	<0.0001	4.17
	567	−15	36	51	<0.0001	4.14
	135	−36	12	54	<0.0001	4.14
Regions more correlated with accuracy in men than in women						
L insula	324	−36	6	12	<0.0001	−4.33

All regions represent areas of deactivation, less active during mental rotation than during a resting baseline.

fMRI results

Rotate versus compare

During mental rotation (all angles) as compared to the Compare control condition (0 degree), both men and women activated bilateral prefrontal cortices, bilateral parietal (inferior and superior lobules), bilateral temporal–occipital regions and visual association cortices, and bilateral diencephalic structures, including thalamus and basal ganglia (see Supplementary Fig. 1 and Table 1 online).

Rotate, women versus men

Between-sex comparisons during mental rotation (see Table 2 and Fig. 2) revealed greater activity in women in bilateral (left greater than right) dorsalmedial prefrontal cortex (DMPFC), right anterior temporal pole and a region in the left inferior occipital lobe corresponding anatomically to lateral occipital cortex (area LOC) (Grill-Spector et al., 1999). At a threshold of $P < 0.005$, women also demonstrated greater activity in the region of the right angular gyrus ($x = 51$, $y = -72$, $z = 15$; z score = 2.95.) It should be noted that these regions were predominantly areas of true activation, i.e., areas in which activity was greater during mental rotation than during rest. The exception was the superior portion of the right DMPFC cluster, which reflected greater deactivation in men as compared to women.

Areas more active in men as compared to women during mental rotation consisted of right greater than left bilateral post-central gyri, left paracentral lobule, left precuneus, and left ventral basal ganglia.

Between-sex results obtained using the interaction term (Rotate versus Compare) were similar to results described above obtained via direct comparison between men and women during the Rotate condition; only the latter are reported.

Correlation with accuracy

For both women and men, all brain areas in which activity correlated significantly with performance accuracy were areas of deactivation (i.e., brain regions in which activity was *decreased* during mental rotation as compared to rest). Better performance was associated with less deactivation, resulting in the positive correlation between performance and BOLD activity. In women, accurate mental rotation performance was most correlated with brain activity in left (extending to right) middle frontal gyrus (MFG), with activity in this region significantly more correlated with accuracy in women than in men. In men, the only brain region significantly correlated

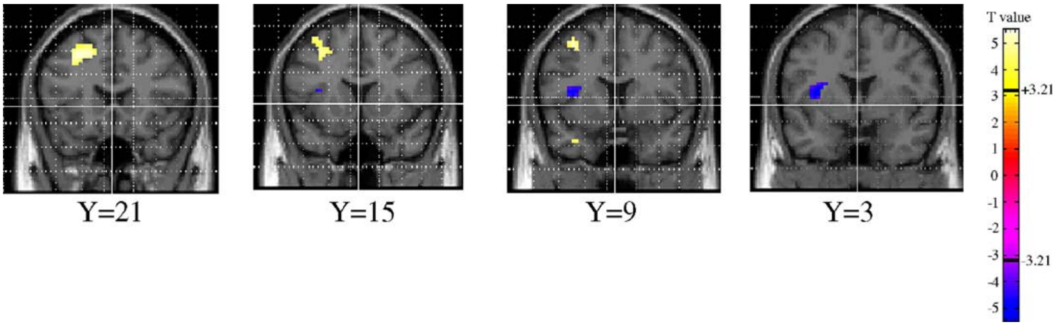

Fig. 3. Brain areas differentially associated with accurate performance in men and women. Note that all of these areas correspond to areas of deactivation that are less active during mental rotation than during a resting baseline. Brain areas in which activity is significantly more correlated with accurate mental rotation performance in women than in men are displayed in yellow/red (left middle frontal gyrus near dorsolateral prefrontal cortex); areas in which activity is significantly more correlated with accurate mental rotation performance in men than in women are displayed in blue/purple (left posterior insula corresponding to parieto-insular vestibular cortex, PIVC.) BOLD fMRI results are displayed as a T-map at a $P_{UNC} < 0.001$ threshold, overlaid onto canonical T1 coronal sections [left = left, right = right] selected to illustrate areas of sex differences.

with accurate performance was left posterior insula bordering on claustrum. Activity in this region was significantly more correlated with accuracy in men than in women, with the point of maximal sex difference located slightly anteriorly. This posterior insula/claustrum region appears to correspond anatomically to the cortical projections of the vestibular system, referred to as parieto-insular vestibular cortex (PIVC) (Brandt and Dieterich, 1999; Guldin and Grusser, 1998) and further discussed below. PIVC correlation with accurate performance in men was bilateral, with weaker right-sided activation also detected ($x = 33$, $y = -12$, $z = 6$; z score = 3.11). Table 3 lists brain regions significantly associated with accurate mental rotation performance in men, women, in women as compared to men, and in men as compared to women. Fig. 3 shows brain areas differentially associated with accurate performance in men and women.

Examination of sex- and condition-specific activity in these two regions found to be most associated with accurate performance in women and men (left MFG and left PIVC, respectively) shows *decreased* activity in both of these regions during mental rotation as compared to a resting baseline, as noted above (Figs. 4A, B). Increasing task difficulty (operationalized by increasing angle of rotation) was associated with further linear decreases in left MFG activity in women (but not men) and further linear decreases in left PIVC activity in men (but not women).

Functional connectivity analyses

The two brain regions found to be most associated with accurate performance in women and men (left MFG and left PIVC, respectively) were used as seed voxels in separate functional connectivity analyses to inform interpretation of results and to identify brain networks differentially associated with accurate mental rotation performance in men and women.

Left MFG functional connectivity

Brain regions identified as correlating positively with left MFG activity during mental rotation are listed in Table 4 and depicted in Supplementary Fig. 2 online. Networks were similar for both men and women and included bilateral frontal regions, bilateral angular gyri, bilateral temporal association cortices, and most prominently, bilateral posterior cingulate. In women, positive correlation also identified left pulvinar of the thalamus and left cerebellum. In men, positive correlation identified dorsal anterior cingulate, right parahippocampal gyrus, and right postcentral gyrus. In general, these regions appear to correspond to a “default” brain network previously shown to be active when subjects are not engaged in any particular task (Greicius and Menon, 2004; Raichle et al., 2001). Brain regions *inversely*

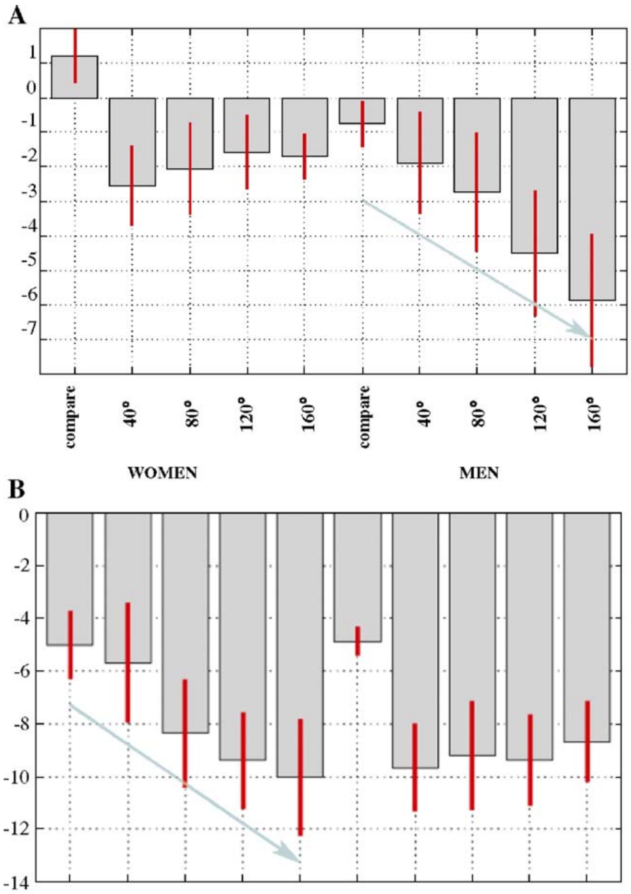

Fig. 4. (A) Bar plot of sex- and condition-specific activity in left posterior insula corresponding to parieto-insular vestibular cortex (PIVC; $x = -33$, $y = -3$, $z = 9$), the region most correlated with accurate mental rotation performance in men. Note that PIVC is deactivated during mental rotation (i.e., PIVC activity is significantly below baseline activity for all mental rotation conditions), with further linear decrease in PIVC activity associated with increasing angle of rotation in men (gray arrow), but not women. (B) Bar plot of sex- and condition-specific activity in left middle frontal gyrus (MFG; $x = -27$, $y = 21$, $z = 45$), the region most correlated with accurate mental rotation performance in women. Note that MFG is also deactivated during mental rotation, with further linear decrease in MFG activity associated with increasing angle of rotation in women (gray arrow), but not men. Zero corresponds to a resting baseline. Vertical bars indicate standard error.

Table 4
Brain regions in women and in men functionally connected (positive correlation) to left middle frontal gyrus (MFG; $x = -27$, $y = 21$, $z = 45$), the region most correlated with accurate mental rotation performance in women

Region in women	Volume (mm^3)	x	y	z	z score	P_{corr}	Region in men	Volume (mm^3)	x	y	z	z score	P_{corr}
Frontal													
Seed voxel and surrounding b/l frontal regions	50,868	−27	21	45	>8	<0.0001	Seed voxel and surrounding L frontal region	11,502	−27	21	45	>8	<0.0001
							L mid/superior frontal gyrus	2052	−36	12	27	6.77	<0.0001
								378	−18	48	42	5.31	0.002
							R middle frontal gyrus	324	27	9	45	5.18	0.003
							R dorsal anterior cingulate	1215	18	24	42	6.75	<0.001
Temporal													
R middle temporal gyrus	1755	63	−36	−3	>8	<0.0001	R middle temporal gyrus	594	48	−60	6	5.95	<0.0001
	378	51	0	−10	6.18	<0.0001							
	162	66	−51	0	5.21	0.003							
L mid/superior temporal gyrus	1836	−69	−18	−12	7.62	<0.0001	L middle temporal gyrus	4833	−54	−57	18	7.14	<0.0001
	1539	−57	−39	0	7.61	<0.0001		3294	−48	−45	0	6.87	<0.0001
							R posterior parahippocampal gyrus	3942	36	−48	−6	6.89	<0.0001
Posterior cingulate													
b/l posterior cingulate	24,948	−6	−39	39	>8	<0.0001	L posterior cingulate	729	−15	−51	27	5.43	0.001
Parietal													
L inferior parietal lobule	7317	−39	−66	39	>8	<0.0001	L parietal	648	−18	−5	64	5.53	0.001
	405	−30	−27	8	5.74	<0.0001							
R angular gyrus	3942	48	−60	33	>8	<0.0001	R parietal, incl. angular gyrus	486	51	−75	30	6.01	<0.0001
	297	42	−72	54	6.32	<0.0001							
Subcortical													
L thalamus (pulvinar)	621	−9	−27	6	5.8	<0.0001							
L cerebellum (uvula)	1080	−3	−63	−39	6.56	<0.0001							

Brain networks are similar across sex, and appear to correspond to a “default” brain network (Raichle et al., 2001). Corrected P values are based on a search volume of 65,730 voxels in women, 61,595 voxels in men. [Brain regions *inversely* correlated with left MFG can be found in Supplementary Table 3 online].

correlated with left MFG activity in women and men are listed in Supplementary Table 2 online.

Left PIVC functional connectivity

Brain regions identified as correlating inversely with left PIVC in men and women are presented in Table 5. In contrast to similar MFG-correlated networks in men and women, PIVC-correlated networks differed markedly by sex, in particular for the inverse correlation, as shown in Fig. 5. In men, left PIVC inversely correlated activity was extensive and consisted of a large-scale network of visuospatial-related brain regions including most prominently bilateral parieto-occipital association cortex (precuneus, BA 7). Activity inversely correlated with PIVC was also present in men in left parahippocampal gyrus, bilateral post-central gyri, and anterior and posterior cingulate.

In women, inverse correlation with activity in left PIVC was relatively sparse and was most prominent in bilateral frontal regions, with scattered foci of inversely correlated activity also present in bilateral temporal and temporal–occipital association cortices and right precuneus. Brain regions *positively* correlated with left PIVC activity in women and men are listed in Supplementary Table 3 online.

Discussion

Behavioral findings

Behavioral results show the expected increasing reaction time and decreasing accuracy with increasing angle of rotation originally described by Shepard and Metzler (1971), confirming that subjects were appropriately engaged in the task. Despite slightly better mental rotation performance by men (men: average 83% correct; women: average 75% correct), there were no significant sex differences in accuracy or reaction time. Thus, the sex-specific neural profiles identified using fMRI were detected in a setting of no significant difference in performance. The absence of

Table 5
Brain regions in men and in women functionally connected (inverse correlation) to left posterior insula (corresponding to parieto-insular vestibular cortex [PIVC]; $x = -33$, $y = -3$, $z = 9$), the region most correlated with accurate mental rotation performance in men. Corrected P values are based on search volume = 61,595 voxels in men, 65,730 voxels in women

Brain region	Volume (mm^3)	x	y	z	z score	P_{corr}
Men						
Bilateral parieto-occipital (precuneus, BA7)	17,739	21	−75	51	<−8	<0.0001
R inferior occipital gyrus (BA 18)	1296	27	−84	12	−6.57	<0.0001
L parahippocampal gyrus	1269	−30	−45	−12	−6.54	<0.0001
	1161	−30	−27	−21	−6.52	<0.0001
L midbrain/diencephalon	540	−9	−6	−6	−6.11	<0.0001
L postcentral gyrus	1377	−36	−39	60	−5.96	<0.0001
R postcentral gyrus	162	30	−45	69	−5.77	<0.0001
R rostral anterior cingulate (BA 32)	648	9	42	15	−5.59	<0.0001
L posterior hippocampus	351	−27	−45	3	−5.54	0.001
R posterior cingulate	837	6	−54	9	−5.53	0.001
L inferior occipital gyrus	324	−30	−78	−6	−5.31	0.002
R occipital (lingual gyrus)	162	3	−69	−3	−5.21	0.003
Women						
R fusiform gyrus	999	24	−81	−21	−6.00	<0.0001
L inf. temporal gyrus	405	−54	−75	−6	−5.84	<0.0001
Bilateral superior medial frontal gyri	567	0	42	54	−5.53	0.001
R precuneus	297	15	−60	−45	−5.43	0.001
R periventricular (near post. corpus callosum)	648	15	−36	18	−5.32	0.002
R middle frontal gyrus	405	51	33	33	−5.25	0.002

Brain regions *positively* correlated with left PIVC can be found in Supplementary Table 2 online.

in-scanner behavioral sex differences may be due to low statistical power for the behavioral data, since prior extensive testing has shown the mental rotation task used in the present study to be a valid measure of mental rotation abilities which does in fact give rise to the expected male performance advantage when applied to a larger population (Voyer et al., 2006).

fMRI findings

Rotate versus compare

Although this report focuses on sex differences, it should be noted that mental rotation activated widespread, bilateral prefrontal, frontal, parietal, occipitotemporal, and occipital cortical regions in both men and women (see Supplementary Fig. 1 and Table 1 online), in agreement with multiple prior mental rotation studies (e.g., Carpenter et al., 1999; Cohen et al., 1996). Contrary to early electrophysiologic and behavioral studies, but in agreement with many fMRI studies of mental rotation (e.g., Cohen et al., 1996), we found no marked asymmetry of cortical activation during mental rotation.

Subcortical structures active in both men and women during mental rotation in the present study included thalamus and basal ganglia. Although subcortical activity during mental rotation has received little prior attention, possibly due to an original focus (theoretical or due to scanning limitations) on cortical regions and laterality issues, caudate activation during mental rotation has been reported previously (Alivisatos and Petrides, 1996). Patients with basal ganglia damage have been shown to have specific deficits in the ability to perform mental rotation (Harris et al., 2002; Lawrence et al., 2000). Discrete cortical–basal ganglia–thalamocortical circuits (Alexander et al., 1986) are known to mediate a variety of cognitive and emotional behaviors, including voluntary eye movements and visuospatial learning and memory (Packard and Knowlton, 2002) relevant to mental rotation.

Rotate, women versus men

Between-sex comparisons between men and women performing mental rotation (Table 2 and Fig. 2) revealed significantly greater activity in women in left greater than right dorsal medial prefrontal cortex—a region strongly implicated in top–down, effortful cognitive processing (Frith and Dolan, 1996) including decision making (Turk et al., 2004) and spatial working memory (McCarthy et al., 1994). Greater frontal activity in women is in broad accord with the majority of prior functional neuroimaging studies of mental rotation demonstrating sex differences (Seurinck et al., 2004; Thomsen et al., 2000; Weiss et al., 2003).

There was greater activity in women in a region of left temporal–occipital association cortex during mental rotation. This finding is in close agreement with two prior fMRI studies of sex differences in mental rotation, one of which found greater activity in women in a left temporal–occipital region overlapping the cluster detected in the present study (Jordan et al., 2002), while another reported greater temporal–occipital activity in women in the right hemisphere (Weiss et al., 2003). This temporal–occipital region appears to correspond anatomically to area LOC, a region that mediates object recognition (Grill-Spector et al., 1999). In the present study, both men and women activated LOC bilaterally during mental rotation. Based on the idea that the amount of neural activity that a given cognitive process engenders is dependent on the computational demand that the task imposes (Just et al., 1996), greater intensity of LOC activation in women can perhaps be considered indicative of more effortful, less automatic recognition of complex three-dimensional objects from two-dimensional line drawings. In support of this explanation, the traditional male performance advantage for mental rotation can be abolished when the task uses actual objects (constructed from wooden blocks) rather than line drawings (McWilliams et al., 1997, though also see Robert and Chevrier, 2003). Future functional neuroimaging studies could examine sex differences during mental rotation of

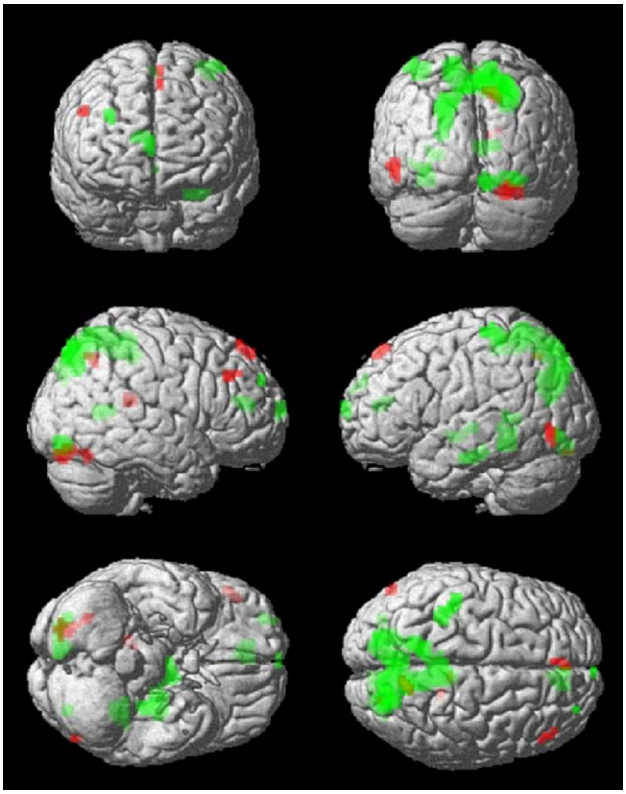

Fig. 5. Network of brain regions active in inverse correlation with activity in left parieto-insular vestibular cortex (PIVC; $x = -33$, $y = -3$, $z = 9$) during mental rotation in men (green) and women (red). Results are displayed at a threshold of $P < 0.05$, corrected for multiple comparisons over the whole brain. Note extensive activation of parietal–occipital cortices in men, but not women.

stimuli varying systematically in three-dimensional depth cues (e.g., shading, shadowing) to verify this speculation.

At a more liberal statistical threshold, women showed greater activity than men in posterior right middle temporal gyrus just inferior to angular gyrus ($x = 51$, $y = -72$, $z = 15$), a region of heteromodal association cortex considered essential for binding visual and other information into a coherent spatial representation necessary for the adaptive deployment of spatial attention (Mesulam, 2000). As with area LOC, greater activity in this region in women may relate to possible greater effort required to integrate complex visual information into a representation conducive to efficient image manipulation. It should be noted, however, that lack of effort quantification renders these explanations speculative.

In contrast to women's greater cortical activity in regions associated with conscious, effortful processing, men showed greater activity in basal ganglia, which has been implicated in automatic, effortless task performance (Rauch et al., 1997; Salmon and Butters, 1995).

Greater activation in men was also present in left precuneus, corresponding to Brodmann area (BA) 7. The precuneus has been called "the mind's eye" for its role in memory-related visual imagery (Fletcher et al., 1995). Specific precuneus activation was recently demonstrated in association with improved performance of a motor learning task (Oishi et al., 2005). Greater precuneus activity in men during mental rotation may indicate sex differences in the use of visual imagery to facilitate task performance. In addition, as further discussed below, the precuneus appears to play a key role in coordinating interactions between visuospatial cortical regions and cortical regions responsible for vestibular processing (Brandt and Dieterich, 1999), and in the present study was found via functional connectivity analysis to be a prominent node in a visual–vestibular network of brain regions active in men during accurate mental rotation performance.

Men showed greater activity than women in bilateral postcentral gyri. This finding is in accord with a previous report demonstrating greater sensorimotor activity in men during mental rotation (Jordan et al., 2002), in which it was suggested that men may take a more concrete, "hands on" approach to mental rotation. In addition, this region may be involved in vestibular processing (Guldin and Grusser, 1998).

Considered broadly, patterns of sex-specific activity obtained through standard between-sex group analysis suggest that women rely more upon frontal and other high-order heteromodal association cortices to perform mental rotation in an effortful, "top–down" fashion. In contrast, men appear to take a more "bottom–up" approach, with less dorsal prefrontal involvement, consistent with the notion of "flow" by which less frontal control of task performance allows primary/early sensory brain regions to interact most effectively with subcortical structures to facilitate accurate, effortless task performance (Dietrich, 2004).

Correlational and connectivity analyses

To integrate behavioral data into image analyses, correlational analyses were performed in which each subject's fMRI data from each Rotate condition (40°, 80°, 120°, 160°) was correlated with his or her level of performance in that condition. By incorporating precise, empiric information about a subject's actual performance at a given point during scanning (rather than information about what that subject should have been doing based on paradigm design), such correlational methods complement and extend traditional categorical analyses.

Brain regions correlated with accurate performance in men

By this correlational analysis, a key, novel finding of the present study is that accurate mental rotation performance in men, but not women, was associated with deactivation of a region of left posterior insula/claustrum which appears to correspond anatomically to parieto-insular vestibular cortex (PIVC), the cortical projections of the vestibular system. It should be emphasized that PIVC was less active during mental rotation as compared to the control condition or to rest, highlighting the increasingly acknowledged importance of considering task-related deactivations when interpreting functional imaging results (Greicius et al., 2003; McKiernan et al., 2003; Raichle et al., 2001). PIVC has been identified recently in humans via functional imaging performed during caloric or electrical stimulation of the peripheral vestibular apparatus in the ear (Bottini et al., 1994; Brandt and Dieterich, 1999; Lobel et al., 1998). In men, level of putative PIVC deactivation was exactly proportional to angle of rotation, strongly supporting the involvement of this region in the mental rotation process (see Fig. 4A). Based on this pattern of PIVC activity, as well as on results from functional connectivity analysis discussed below, we believe this stepwise deactivation of PIVC in correlation with stepwise increases in angular disparity reflects activity of a visual–vestibular reciprocally inhibitory brain network (Brandt et al., 1998; Brandt and Dieterich, 1999; Deutschlander et al., 2002) intimately involved (in men) in the neural process of mental rotation. Women also deactivated the left PIVC region during mental rotation, but unlike men, showed no clear pattern with respect to task difficulty or level of performance.

Analysis of PIVC functional connectivity (Table 5 and Fig. 5) indicated that, in men (much more so than in women), decreased PIVC activity was associated with increased activity in a network of visual regions composed most prominently of bilateral parietal–occipital visual association cortices (precuneus, BA 7). An interpretation for this mental rotation-associated pattern of activity in men comes from recent work demonstrating a relationship of reciprocal inhibition between cortical regions responsible for vestibular and visual processing: deactivation of visual regions occurs during vestibular stimulation (Deutschlander et al., 2002; Wenzel et al., 1996), while deactivation of PIVC has been demonstrated when visual regions are activated during visually induced perceived self movement in the absence of actual body movement, a phenomenon known as vection (Brandt et al., 1998; Brandt and Dieterich, 1999; Deutschlander et al., 2002; Kleinschmidt et al., 2002). By minimizing mismatch between visual and vestibular input, this reciprocally inhibitory relationship between visually responsive and vestibularly responsive cortex is considered to allow perception of motion to be based on the most reliable sensory source, perhaps serving to minimize such unpleasant consequences as motion sickness. Interestingly, susceptibility to motion sickness has been shown to vary inversely with spatial ability in men (Levine and Stern, 2002) and to be more common in women than in men (Turner and Griffin, 1999, though see Cheung and Hofer, 2002), perhaps suggesting sex differences in the nature of these visual–vestibular connections.

In the context of the present study, deactivation of vestibular cortex in proportion to angle of rotation suggests that, for men, mental rotation of three-dimensional visual stimuli may in a sense be neurally similar to visually induced perceived self-motion. Given that no subjects reported such a sensation or engaging in imagined self-rotation as a task strategy (based on a post-scan questionnaire), a plausible explanation for findings is that male subjects automatically and unconsciously activated brain regions involved in egocentric visuomotor transformations during mental rotation, and that activation of these regions was associated with accurate performance. Sex-based differences in utilization of this visual–vestibular network consisting of activated and deactivated cortical sensory processing nodes could reasonably contribute to sex-based differences in mental rotation performance.

This first demonstration of an apparent role for the cortical projections of the vestibular system in mental rotation sheds light on prior behavioral findings. Present results provide a mechanistic explanation for how actual movement (active or passive) around an array of objects can improve visuospatial performance (Wang and Simons, 1999), and why egocentric strategies (imagined self-movement around an object) are in general more effective than allocentric strategies (imagined object rotation) (Wraga et al., 1999). From an evolutionary perspective, egocentric transformations have been considered a more "natural" ability, since organisms have been walking around objects to inspect them for millions of years, while revolving objects remain rare (Wraga et al., 1999). It makes sense, then, that the vestibular system – a phylogenetically conserved neural system active during actual circumnavigation around objects – should play a role in accurately imagined object rotations. An explanation for why women appear not to recruit the vestibular system during performance of mental rotation will require additional study but may relate to prior findings of sex differences in the use of egocentric versus allocentric strategies for spatial memory (Burgess et al., 2001). Present results are also relevant to understanding how such factors as weightlessness (Leone, 1998; Matsakis et al., 1993) and head tilt (Corballis et al., 1978) affect visuospatial functioning. In strong support of a role for the vestibular system in mental rotation, direct vestibular stimulation has recently been shown to specifically disrupt performance of tasks requiring mental imagery, including mental rotation (Mast et al., 2005).

Brain regions correlated with accurate performance in women

In women, the region most associated with accurate performance was a portion of left MFG in the region of dorsolateral prefrontal cortex (DLPFC). Activity in this region was decreased (as compared to a resting baseline) in both men and women under all active experimental conditions. In women, it decreased further with decreasing accuracy (and increasing angle of rotation; see Fig. 4B). Based on the well-known role of DLPFC in working memory, *increased* activity in DLPFC during mental rotation – a task requiring mental maintenance and manipulation of complex images – might have been predicted. In accordance with this prediction, and in close agreement with prior studies of spatial working memory (e.g., D'Esposito et al., 1998), a more inferior portion of right MFG/DLPFC corresponding to BA 9 was in fact activated by both men and women during mental rotation (men Rotate versus rest: $x = 45$, $y = 12$, $z = 30$, z score = 3.68; women Rotate versus rest: $x = 48$, $y = 24$, $z = 33$, z score = 3.76). The region of left MFG deactivation during mental rotation in the present study was located dorsal/superior ($z = 45$) to this probable spatial working memory-related region of MFG activation and appears instead to overlap with MFG activity detected in studies of the brain's default network (Greicius et al., 2003; Raichle et al., 2001). As a node in this default network, this region of DLPFC has been shown to be more active at rest than during performance of any specific cognitive activation task, providing an explanation for the initially unexpected finding that this region was less active during the Rotate (and Compare) conditions than at baseline in the present study. In support of this explanation, functional connectivity analyses (Table 4 and Supplementary Fig. 2 online) showed that left MFG activity co-varied with almost the entire default network as described in prior studies (Greicius et al., 2003; Raichle et al., 2001) in both men and women (though more prominent in women). In this context, identification of left MFG as the region most associated with accuracy in women can perhaps be understood as reflecting effort and/or cognitive demands, with greater task demands associated with both suppression of default network activity and with poor performance, though further investigation would be needed to confirm this notion.

Conclusion

In sum, using a validated mental rotation task in association with fMRI, we have demonstrated distinct, sex-based patterns of neural activity during mental rotation. Between-sex group analysis revealed greater activity in females of heteromodal cortical regions involved in top–down, effortful maintenance in working memory of visuospatial transformations and calculations, including dorsal medial prefrontal cortex. In contrast, men appear to take a more bottom–up approach, demonstrating greater activity in brain regions such as precuneus and basal ganglia involved in more automatic processing. A mechanistic explanation for *why* men and women may take these different approaches was provided by functional connectivity analysis, which showed that men, but not women, engaged a large-scale network composed of reciprocally inhibitory visuospatial and vestibular brain regions when they performed mental rotation accurately. Accurate mental rotation performance in women was most associated with deactivation of a "default network" of brain regions, which may be a marker of task demands and effort rather than a specific processing mode. Automatic evocation by men to a greater extent than women of a visual–vestibular network during mental rotation may represent an unconscious, bottom–up neural strategy which could reasonably account for their traditional performance advantage, and help explain why women appear to rely upon brain regions implicated in more effortful, top–down processing. Future functional neuroimaging studies could utilize actual vestibular stimulation to confirm this new finding of vestibular cortex inhibition during mental rotation and further investigate sex differences in this network.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2006.03.030.

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