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Gender-specific cerebral activation during cognitive tasks using functional MRI: comparison of women in mid-luteal phase and men

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Abstract Previous studies of gender-specific differences in functional imaging during spatial and language tasks have been inconclusive. Furthermore, among women, such differences may occur during mid-luteal phase compared to the rest of the menstrual cycle. In order to examine further gender differences, functional MRI was performed in 12 male volunteers and 12 female volunteers (in the mid-luteal phase) during mental rotation and verb-generation tests. Two-sample *t*-tests with uncorrected *P* values of <0.001 for the specific regions of interest (ROIs) revealed cerebral activation differences in both stimuli. During mental rotation tests, higher levels of activation were noted in the right medial frontal, precentral, and bilateral inferior parietal cortex, while in women this occurred in the right inferior and medial temporal, right superior frontal cortex, and left fusiform gyrus. During verb-generation tests, higher levels of activation in men was found in the left medial temporal and precentral cortex. Our results indicate that differences in cerebral activity during cognitive tasks can be shown between men and women in the mid-luteal phase. Gender differences while performing a mental rotation task were more prominent than during a verb-generation task.

Keywords Gender · Cognition · fMR

Introduction

Gender differences in cognitive tasks have been investigated for many years and are thought to involve social factors influencing gender-specific behaviours, as well as genetic and hormonal influences [1, 2]. Differences in brain hormonal state and gene expression have led to the hypothesis that gender differences in behaviour and cognition may be related to structural differences in the brain [3, 4].

Gender, the feeling of being male or female, is considered to be dependent on prenatal hormones and compounds changing the level of these hormones, whereas postnatal social factors are considered to have less influence on gender identification. Swaab et al. found that genetic factors and prenatal hormone levels, rather than postnatal social factors, are the most important factors in determining sexual orientation, namely, heterosexuality, bisexuality or homosexuality [5]. Therefore, gender-specific cortical activation patterns are of great scientific and clinical interest.

Gender differences in cerebral activation patterns may occur during mental rotation tasks even when performances in this task are similar. Such differences suggest that the sexes use different strategies in solving mental rotation tasks [6]. In a previous study women exhibited significant bilateral activation in the superior and inferior parietal lobule, as well as in the inferior temporal gyrus and the premotor areas. Men showed significant activation in the right parieto-occipital area and the left superior parietal lobule [7]. Both men and women showed activation in the premotor areas, but men showed significantly higher levels of activation in the left motor cortex.

The verb-generation test is another task that may reveal gender-specific differences in performance, as well as specific activation and differences in lateralization during the female menstrual cycle [8, 9]. However, fMRI studies have not conclusively demonstrated gender differences in verbal tasks [10]. Results of such studies have not revealed gender differences in cortical activation during spatial tasks compared to verbal reasoning tasks. In general, a stronger lateralization has been found in men than in women [11]. Moreover, the phase of the menstrual cycle was not considered in these studies, despite evidence that hormonal changes over the cycle may result in different patterns of lateralization during cognitive tasks [12–14]. Analyses of lexical decision, figure recognition and face discrimination tasks have shown that an increase in progesterone is related to a reduction in asymmetries in a figure recognition task by increasing the performance of the left hemisphere, which is less specialized for this task [14]. Cerebral lateralization in females is probably modulated by the menstrual cycle such that some hemispheric asymmetries are diminished during the follicular and luteal phase and enhanced during the menstrual phase [8].

The purpose of this study was to compare the gender specificity of two different cognitive tasks: verb generation and mental rotation. Furthermore, evaluation of gender differences in cortical activation during these stimuli were evaluated in women in the mid-luteal phases and also compared to differences seen in a previous study where women were at various stages of the menstrual cycle.

Subjects and methods

Subjects

The study groups comprised 12 healthy male and 14 healthy female volunteers (mean age 29 years, range 17 to 55 years). All subjects were right-handed. No subject revealed any brain tissue abnormality on structural MRI, and none had a history of neurological or psychiatric

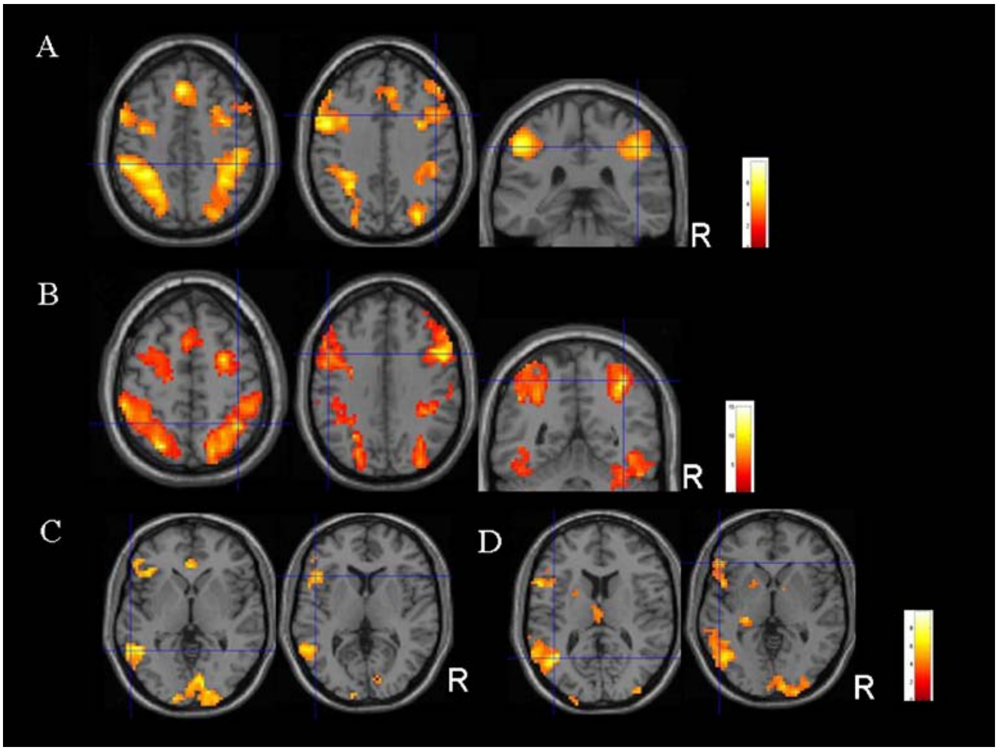

Fig. 1 Statistical parametric maps of activation in subjects performing mental rotation and verb-generation tasks compared with activation during the rest period. Task-related increases in MR signal are superimposed on three orthogonal sections of 3D T1-weighted standard brain images. SPM uses the neurological side convention: *R* right side. The corrected statistical threshold is $P<0.05$. **a** Female subjects; mental rotation task. The main activation is seen in the inferior parietal, superior parietal, medial prefrontal pre- and postcentral, and inferior prefrontal cortex. **b** Male subjects; mental rotation task. The main activation is seen in the inferior parietal, superior parietal, medial prefrontal pre- and postcentral, and inferior prefrontal and temporal cortex. **c** Male subjects; verb-generation task. The expected activation is seen in the left inferior frontal, medial temporal, and fusiform cortex. **d** Female subjects; verb-generation task. The expected activation is seen in the left inferior frontal, medial temporal and fusiform cortex, and left thalamus, and there are no differences in lateralization compared with male subjects

disease. Only female subjects in their ovulatory phase (day 11 to 18) and not receiving any hormonal therapy were chosen for this study. A follow-up evaluation was carried out at the start of the next menstrual period and subjects outside the ovulatory phase were discharged from the study. Two subjects had to be discharged. None of the women used hormonal contraception.

Informed written consent was obtained prior to scanning. The study was accepted by the local ethics committee.

Experimental design

All MR images were acquired using a 1.5 T MR (Sonata, Siemens, Erlangen, Germany) with a standard headcoil. A 3D FLASH sequence (TR 10 ms, TE 4.5 ms, flip angle 30°, FOV 240 mm, matrix 512, slice-thickness 1.5 mm) was acquired for individual coregistration of functional and structural images. BOLD contrast images were acquired using an echo-planar technique (TR 3100 ms, TE 50 ms, flip angle 90°, FOV 240 mm, matrix 64) with 34 transverse slices with a thickness of 3 mm and 0.3-mm slice gap. Three “dummy” scans were eliminated prior to data analysis.

Each subject underwent two functional sessions. The stimuli were presented in a block design and alternated with rest periods every 33 s. Each run was divided into six epochs.

During stimulation subjects were asked to lie relaxed inside the scanner and try to get involved in the presented stimuli. The first stimulus was the mental rotation task. The geometric figures presented every second scan were two-dimensional and rotated, flipped or both. The volunteers had to judge silently which operation of figures was presented. In the resting condition, two identical figures related to those in the active condition were presented every second scan. The resting condition was chosen as similar as the active condition differing only in the task-specific part.

The second stimulus was the verb-generation task. In the active condition, nouns were presented every second scan and the subjects were asked to find familiar verbs without speaking aloud. In the resting condition, numbers were presented and the subjects had to count backwards in their mind. All stimuli were presented using a screen inside the scanner room and beamed projection from outside.

At the end of scanning the subject had to rate her or his level of general alertness on a scale ranging from 0 to 10. The performance in the mental rotation task was measured in a further task before scanning.

Data analysis

For data analysis, SPM 99 software (Welcome Department of Cognitive Neurology, London, UK) was used. Prior to statistical analysis images were realigned utilizing the sinc interpolation and normalized to the standard stereotactic

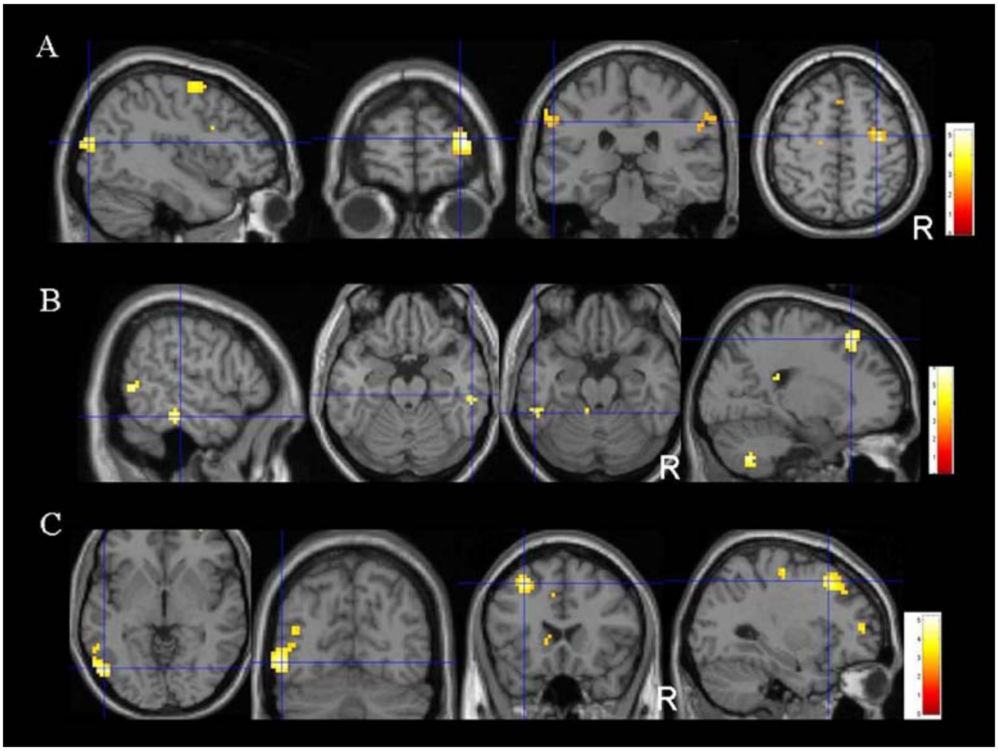

Fig. 2 Statistical parametric maps of areas showing more prominent gender-specific activation in a two-sample *t*-test during mental rotation and verb-generation tasks. The uncorrected statistical threshold is $P<0.001$. **a** Areas more prominently activated in men than in women; mental rotation task. Activation is seen in the right medial frontal, precentral, and bilateral inferior parietal cortex. **b** Areas more prominently activated in women than in men; mental rotation task. Activation is seen in the right inferior and medial temporal, right superior frontal cortex and left fusiform gyrus. **c** Areas more prominently activated in men than in women; verb-generation task. Activation is seen in the medial temporal and precentral cortex

Table 1 Gender-specific activated regions in relation to the performed tasks. The *t* values are also given. Only statistically reliable areas (uncorrected $P<0.001$) are included. Talairach coordinates are given in the x, y and z directions

Task	Gender	Talairach coordinates (mm)	Region (cortex)	Side	z score
Mental rotation	Male	−56; −27; 35	Inferior parietal	L, R	2.8
		33; 63; 12	Medial frontal	R	4.2
		33; −9; 54	Precentral	R	3.2
	Female	54; −63; 3	Fusiform	R	2.7
		18; 32; 54	Superior frontal	R	3.1
		57; −63; 3	Medial temporal	R	3.1
		57; −30; −21	Inferior temporal	R	2.9
Verb generation	Male	−30;−21;48	Precentral	L	3.8
		−62; −1; 33	Frontal	L	4.2
		−51; −69; −3	Medial temporal	L	4.2

space corresponding to the template from the Montreal Neurological Institute (http://www.mrccbu.cam.ac.uk/Imaging/mnispace.html). Bilinear interpolation was applied for normalization. The images were smoothed with an isotropic gaussian kernel of 9 mm. A voxel-by-voxel comparison according to the general linear model was used to calculate differences in activation between active and resting conditions. The model consisted of a box-car function convolved with the haemodynamic response function (hrf) and the corresponding temporal derivative. High-pass filtering with cut-off frequencies of 128 s and low-pass filtering with the hrf were applied.

For group analysis single subject contrast images were entered into a random effects model. Significant signal changes for each contrast were assessed by means of a *t* statistic on a voxel-by-voxel basis [15]. The resulting set of voxel values for each contrast constituted a statistical parametric mapping (SPM) of the *t* statistics. The threshold was set to $P<0.05$ (corrected for multiple comparisons).

Additionally, for analysis of gender-specific activation during each task, two-sample *t*-tests were performed using the individual contrast images for every task and subject. The resulting contrast images were taken to the second level analysis and entered into a two-sample *t*-test. The threshold of the *t* statistic was set to $P<0.001$ uncorrected for multiple comparisons assuming the following a priori regions of interest (ROIs):

(a) For the mental rotation task, gender differences have been described for the inferior and medial frontal, superior parietal, precentral, temporal cortex and fusiform gyrus [6, 7, 16–18].
(b) For verbal and mental rotation tasks, a stronger lateralization in men than in women has been described for the angular gyrus, frontal and temporal cortex as well as parietal cortex [10, 11, 19, 20].

Results

During the mental rotation task, the expected task-related cortical activations occurred in both sexes. Activation was noted in the inferior parietal and temporal, superior parietal, medial prefrontal pre- and postcentral and inferior prefrontal cortex (Fig. 1; part A shows the activated areas for female volunteers, and part B for male volunteers). During the verb-generation task, activation was found in the left inferior frontal, medial temporal, fusiform cortex, thalamus, and lentiform nucleus for both genders (Fig. 1c, d). No significant differences in lateralization were found for either task between men and women. Both groups revealed a non-specific activation in the visual cortex due to the mode of task presentation.

The two-sample *t*-test revealed gender differences in the specific ROIs as follows:

1. During mental rotation tests, men showed higher levels of activation in the right medial frontal, precentral and bilateral inferior parietal cortex (Fig. 2a). Women showed higher levels of activation in the right inferior and medial temporal, right superior frontal cortex and left fusiform gyrus (Fig. 2b). Cerebellar activation was not within the predefined ROIs, and therefore not significant using the uncorrected *P* value.
2. During verb-generation tests, men showed higher levels of activation in the left medial temporal and precentral cortex (Fig. 2c). Caudate nucleus activation was not within the predefined ROIs, and therefore not significant using the uncorrected *P* value. Women had only a small cluster in the left inferior parietal cortex as specific activation but only using uncorrected $P<0.001$. The results of both group comparisons and both tasks were confirmed in a factorial design using a corrected $P<0.05$.

A summary of gender-specific activated areas as well as the voxel extends and *t*-values are given in Table 1.

Discussion

Cortical activation during mental rotation task in men and women occurred in the known cortical areas within the inferior parietal and temporal, superior parietal, medial prefrontal pre- and postcentral and inferior prefrontal cortex [6, 7].

There is some evidence to suggest that fMRI is helpful in revealing differences between male and female cortical activation patterns and lateralization [6, 7, 10, 19, 21, 22]. Previous studies have indicated the following ROIs: (a) for the mental rotation task, gender differences have been described for the inferior and medial frontal, superior parietal, precentral, temporal cortex, and fusiform gyrus [6, 7, 16–18], and (b) for verbal and mental rotation tasks, a stronger lateralization in men than in women has been described for the angular gyrus, frontal and temporal cortex, and parietal cortex [10, 11, 19, 20].

The results of our study showed gender differences in distinct cortical areas: men showed higher levels of activation in the right medial frontal, precentral and bilateral inferior parietal cortex. This is not completely concordant with the findings of previous studies which indicate a predominant parietal activation in men [6, 7]. A higher level of inferior frontal activation in men has also been described by Weiss et al. [16]. Women showed a higher level of activation in the right inferior and medial temporal, right superior frontal cortex and left fusiform gyrus. In contrast, women in previous studies predominantly showed inferior frontal activation [6]. Only the inferior temporal cortex activation appears to be similar to the findings of previous studies [6].

One explanation of different results in mental rotation task may be the use of 2D instead of 3D geometrical figures [18]. Using 3D figures in mental rotation tasks leads to similar cerebral activation in parietooccipital and central areas compared with a task using 2D figures. Temporal and premotor areas are activated in both tasks but with different extension. However, the results revealed gender differences using 3D geometrical figures in cortical activation. However, the results of the mentioned studies are sometimes contradictory, revealing different activation patterns. Hormonal influences on mental rotation task activation patterns are controversial, but may offer one explanation for the reported specific activation patterns in women in the mid-luteal phase in contrast to former studies which have not addressed this factor. Blood oestrogen levels seem to influence the degree of activation more than the activation pattern itself. Additionally, no differences in cognitive performance have been revealed between men and women in low oestrogen states [23].

One deficit of our study is that we only evaluated the performance of the two genders in the mental rotation task outside the scanner before the fMRI measurements, but there is evidence that gender differences can be found apart from the specific performances in the mental rotation task [6]. Furthermore, in no other study has the female group been differentiated according to the stage of the female hormonal cycle. This may explain different activation patterns and should be addressed in a future study. Furthermore, this could be an explanation for the lack of significant differences in lateralization in our study, as lateralization in women during the mid-luteal phase is similar to that in men.

Our study design revealed gender differences in the mental rotation task. Interpretation of the gender-specific activation patterns is not straightforward, but the patterns may have several explanations. Women show activation particularly in the right inferior and medial temporal, right superior frontal cortex and left fusiform gyrus. These areas are known to be partially involved in memory processing (e.g. recall strategies) [24]. Object recognition seems to be superior in female volunteers.

Men show activation particularly in the right medial frontal cortex, precentral and bilateral inferior parietal cortex. These cortical areas are more or less involved in sensory motor function and voluntary movement. Results of former studies suggested that participants imagined moving their hands in the experimental condition [17, 25]. The action of motor imagery is known to mimic the "natural way" in which a person would manipulate the object in reality, and this action seems to be used particularly in male subjects. The parietal cortex is known to be involved in object perception and spatial cognition [18, 25, 26]. Furthermore, parietal areas are involved in attention processes [27].

Concerning the lexical task, we could not confirm the reported gender differences with females engaging more diffuse neural systems that involve both the left and right inferior frontal gyrus [11]. During verb-generation tests we found a higher level of activation in the left medial temporal and precentral cortex in men representing left-sided lateralization, but not a higher level of parietal activation. A higher level of activation in the left temporal cortex is concordant with the findings of the study reported by Gur et al. [10]. Women did reveal only a small cluster in the inferior parietal cortex as specific activation, but not the previously described frontal or bilateral activation patterns. In contrast to former studies, we used a verb-generation task and not orthographic (letter recognition), phonological (rhyme) or semantic (semantic category) tasks. Therefore, the activation pattern results are not directly comparable, but we decided to use this special test because of the known superior reliability [28, 29].

Phillips et al. found that women demonstrate a higher degree of bilateral language representation in temporal lobe regions than do men during passive listening [22]. There is also evidence that men and women showed very similar, strongly left lateralized activation patterns during a language comprehension task [21]. A previous study revealed no differences in lateralization in women in relation to the oestrogen blood level. This result implies that scanning women outside the mid-luteal phase should not lead to gender-specific activation patterns in this task [23]. Therefore, the revealed minimal gender differences in the verb-generation task is within the expected range of results.

According to previous studies, women should have reduced performance in verb-generation and in mental rotation tasks during the mid-luteal phase of the menstrual cycle [13]. In our study, only women during this phase were entered into the experimental group, in contrast to a previous study revealing activation differences between the genders during cognitive tasks with the women not in defined stages of the menstrual cycle. A further study applying both tests to women outside the mid-luteal phase should provide additional evidence for the importance of the influence of hormones on gender-specific activation patterns. Some studies have shown modulation of lateralization in relation to the stage of the menstrual cycle, but the asymmetry shift was not under the direct influence of oestrogen or progesterone. This provides further empirical support for cycle-dependent alterations in lateralization but makes it unlikely that this effect is directly caused by oestrogen or progesterone plasma level variations [8]. Therefore, we did not measure the blood hormone level, but evaluated the exact day of menses by checking the first day of the next menstrual bleed.

In conclusion, the functional cortical activation patterns presented in this study indicate that a mental rotation task is suitable to reveal gender differences in cerebral activity comparing women in the mid-luteal phase with men, while a verb-generation task revealed only a higher level of activation in men. The results of mental rotation tasks may indicate that women use predominantly a recall and recognition strategy for mental rotation while men use object orientation in space and assumed haptic manipulation.

Further studies are needed to clarify differences outside the mid-luteal phase in women and correlate these cortical activation patterns with the performance of the two genders.

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