Gender-related differences in lateralization of hippocampal activation and cognitive strategy

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Gender-related differences in brain activation patterns and their lateralization associated with cognitive functions have been reported in the field of language, emotion, and working memory. Differences have been hypothesized to be due to different cognitive strategies. The aim of the present study was to test whether lateralization of brain activation in the hippocampi during memory processing differs between the sexes. We acquired functional magnetic resonance imaging data from healthy female and male study participants performing a spatial memory task and quantitatively assessed the lateralization of hippocampal activation in each participant. Hippocampal activation was significantly more left lateralized in women, and more right lateralized in men. Correspondingly, women rated their strategy as being more verbal than men did. *NeuroReport* 17:417–421 © 2006 Lippincott Williams & Wilkins.

Keywords: cognitive strategy, functional magnetic resonance imaging, gender, hippocampus, lateralization, object location, spatial memory

Introduction

Performance differences between women and men have been demonstrated in diverse cognitive tasks, most impressively in the domain of spatial functions, such as mental rotation [1,2]. Through the development of functional neuroimaging techniques, such as positron emission tomography and functional magnetic resonance imaging (fMRI), the scope has been broadened to gender-related differences in brain activation patterns putatively underlying performance differences.

Gender-specific brain activation was frequently reported in the language domain: several studies demonstrated brain activation patterns that were more lateralized in men than in women [3]. Canli *et al.* [4] and Cahill *et al.* [5] demonstrated sex-related hemispheric lateralization of amygdala function in recognition memory for previously learned emotionally arousing pictures: amygdala activation was more left lateralized in women and right lateralized in men. This pattern of asymmetrical amygdala activation was confirmed by Killgore and Yurgelun-Todd [6] who tested the perception of positive facial affect. Bell and colleagues [7] found significantly larger fMRI activation clusters in men than in women in the right parietal and occipital lobes associated with a working memory task. Using four different working memory tasks in one fMRI study, Speck *et al.* [8] detected activation of the prefrontal cortex to be differentially more left lateralized in female participants and more right lateralized in male participants. Jordan *et al.* [9] carried out an fMRI study using mental rotation tasks. Comparing female and male brain activation patterns revealed overlapping task-related activation mainly in the parietal and in the premotor cortex, but also differences in the temporal, parietal, and precentral areas.

In the latter two studies [8,9], the authors hypothesized gender-related differences in brain activation to be due to different cognitive strategies. Evidence for differences in the employment of cognitive strategies between the sexes was provided by McGlone and Kertesz [10], suggesting that female participants tend to make more use of verbal mediations even in a 'nonverbal' task. Similarly, Kimura [11] proposed that male participants prefer to employ right hemisphere, nonverbal systems whereas female participants prefer to employ left hemisphere, verbal systems. Sandstrom *et al.* [12], applying a virtual reality version of the Morris water maze, were able to show that women employed a different cognitive strategy than men as they relied predominantly on landmark information, whereas men used both landmark and geometric information.

Differential influences of cognitive strategies on brain activation patterns have been demonstrated by previous functional imaging studies [13,14]. Regarding cognitive strategies in the verbal vs. nonverbal dimension, Stephan *et al.* [15] used the same stimuli for two different tasks in an fMRI study: Either a lexical or a geometrical decision had to be made on pairs of letters. Correspondingly, the authors detected rather left-lateralized brain activation in the lexical task, and rather right-lateralized activation in the geometrical task. Investigating brain activation patterns in superior memorizers, Maguire *et al.* [16] detected increased activity in the right hippocampus associated with a memory task in the superior memorizers compared with controls, which the authors related to the employment of a spatial memorizing strategy.

Lateralization of memory-related medial temporal lobe activation in healthy participants is known to depend on material [17]. Yet it has not been systematically analysed how far this functional asymmetry is influenced by cognitive strategies (verbal vs. nonverbal).

The aim of the present study therefore was (1) to assess whether lateralization differences between the sexes also exist in the hippocampi, which are crucially involved in spatial memory [18], and (2) to examine the role of cognitive strategies in lateralized brain activation. We expected to find women using more verbal strategies and exhibiting more left-lateralized hippocampal activation patterns than men.

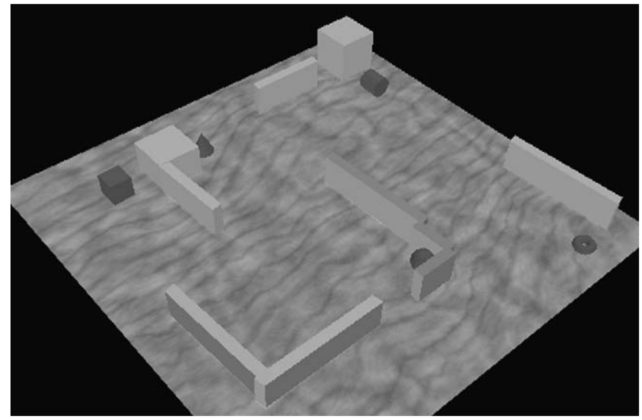

Fig. 1 Survey of the virtual environment containing all objects at target locations.

Methods

Study participants

Ten female and 10 male healthy volunteers participated in this study. Groups were matched for age ($M_{age} \pm$SE: 25 ± 2 years for women and 27 ± 2 years for men) and education ($M_{education\ time} \pm$SE: 17 ± 1 years for the female as for the male group). All participants were right handed ($M_{HQ} \pm$SE: 87 ± 3 for women and 81 ± 5 for men) according to the Edinburgh Handedness Questionnaire [19] and without a history of neurological or psychiatric illness. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee. All participants gave written informed consent.

Magnetic resonance imaging scanning

Scanning was carried out on a Siemens Vision Magnetom (Erlangen, Germany) at 1.5 T using an echo planar imaging-capable head coil. From each participant, 109 functional T2*-weighted images were acquired, of which the first five images were later discarded, leaving 104 images per participant for the analysis. Parameters of the interleaved echo planar imaging sequence were TR/TE=4000/64 ms, 64×64 matrix, 30 axial slices (3 mm plus a gap of 0.3 mm), and voxel size $4 \times 4 \times 3.3\,mm^3$. After instruction outside the scanner, the participant was positioned in the scanner with the head immobilized with foam cushions. A mirror was placed on the head coil to enable the participant to look at the screen at the top end of the scanner, on which the task pictures were projected with a video projector. Following the acquisition of fMRI data, an additional anatomical sequence was used to obtain a high-resolution image of each participant's brain (magnetization-prepared rapid gradient echo, TR/TE=9.7/4 ms, 256×256 matrix, 170 sagittal slices, $1 \times 1 \times 1\,mm^3$ voxel size).

Memory task

The spatial memory task was specially developed for this block-design fMRI study. It comprised encoding and recognition of object locations in an immersive virtual three-dimensional environment (Fig. 1).

During encoding (ENC) trials, participants were presented with a 28-s video sequence showing a walk through the environment, passing five coloured objects, each at a specific location, one at a time. Participants were instructed to later remember the object locations. During recognition (REC) trials, aerial views of the environment were displayed, each containing one of the objects, either as presented before or at a new location. Participants had to decide whether the object's location was correct or incorrect and press one of the corresponding two buttons. As a control condition (CON), pictures of two differently sized versions of one of the five objects were presented. Participants had to decide whether the larger one was on the left or the right side and again press the corresponding button. The whole experiment comprised four cycles of the sequence ENC–CON–REC–CON, whereas ENC trials were exactly repeated.

Strategy rating

We used a 4-point rating scale after scanning to assess to what degree the participants used verbal or pictorial memorizing strategies. Participants had to indicate whether they estimated their strategy as completely verbal (1), more verbal than pictorial (2), more pictorial than verbal (3), or completely pictorial (4).

Data analyses

Image analysis was performed using MATLAB 6.1 (www.mathworks.com). It comprised single-subject preprocessing and statistical analysis with SPM2 (www.fil.ion.ucl.ac.uk/spm).

Preprocessing

The acquired functional images were converted to ANALYZE format. To correct for head movement during functional magnetic resonance scanning, all images were realigned using six parameter rigid-body transformations. All volumes were unwarped to correct for echo planar imaging distortions. The resulting images were then normalized to match a template brain in standard space and resampled to $3 \times 3 \times 3\,mm^3$ voxel size. Afterwards, images were spatially smoothed with a Gaussian kernel of $9 \times 9 \times 9\,mm^3$ full width at half maximum.

Single-subject regression analyses

The preprocessed data were statistically analysed on a voxel-by-voxel basis according to a general linear model approach for time-series data. A design matrix was created with one regressor for the memory task blocks (box-car function convoluted with a canonical haemodynamic response function), the control condition being implicitly modelled. Before model estimation, the regressor was band-pass filtered to remove high and low-frequency noise from the data. To obtain a statistical parametric map of brain activation, the contrast 'memory task vs. control condition' (memory) was computed applying a threshold of $P<0.05$. The statistical analysis was performed on hippocampal voxels only, as determined by a predefined region of interest that included the fields of the cornu Ammonis, the dentate gyrus, and the subiculum along the full length of the hippocampus ($y=-8$ to -38). The region of interest was created on a normalized template brain.

Lateralization indices

On the basis of the resulting individual hippocampal activation maps, lateralization indices ($LI=[(R-L)/(R+L)]\times 100$) were computed for each participant. These represent the left–right distribution of activated voxels, weighted with their respective *t*-values. The LIs can range from -100, representing complete left-sided activation, to $+100$, representing complete right-sided activation.

Group level statistics

t-Tests for independent samples were applied on the variables LI (one-tailed), handedness, and performance (percentage of correct responses and reaction times) to compare the female groups with the male groups. A nonparametric Mann–Whitney *U*-test for two independent samples was performed on the variable strategy to test for group differences. Additionally, we carried out a χ^2 test with sex and dichotomized positive (right) and negative (left) LIs to assess gender-related differences in the direction of lateralization.

Results

Behavioural data

Female and male participants did not significantly differ either by performance or by handedness (independent samples *t*-test, $P<0.05$). Mean performance ($\pm$SE) levels were 94% ($\pm$2) and 93% ($\pm$2) correct responses, respectively. The mean reaction times for button presses during recognition were 1886 ms ($\pm$145 ms) for female participants and 1736 ms ($\pm$103 ms) for male participants.

Median strategy ratings were 2.5 for female participants and 4 for male participants; the Mann–Whitney *U*-test revealed a significant group difference ($P<0.05$; see Fig. 2). Five women had rather verbal or completely verbal strategies, five women reported rather pictorial or completely pictorial strategies. By contrast, one man reported more verbal than pictorial strategies, eight men reported rather pictorial or completely pictorial strategies. The strategy rating from one male participant could not be obtained.

Functional magnetic resonance imaging data

All participants except for one man showed hippocampal activation. Mean LI ($\pm$SE) were -45 ($\pm$19) for female participants and $+18$ ($\pm$24) for male participants. The group difference in LIs was significant ($P<0.05$, one-tailed *t*-test for independent samples).

Within the male group, seven participants displayed positive (right) LIs and two had negative (left) LIs. Within the female group, nine participants exhibited negative (left) LIs and one participant had a positive (right) LI (see Fig. 2). The χ^2 test revealed a significant difference in the frequency distribution with regard to dichotomized lateralization across sex ($P<0.05$).

Discussion

To test for a gender-related difference in hippocampal activation associated with spatial memory, we measured the blood oxygen-level-dependent response in healthy female and male participants performing an allocentric object location task in an immersive virtual environment. We focused on lateralization of activation patterns, which has been shown to be a considerably reliable measure [20]. Our

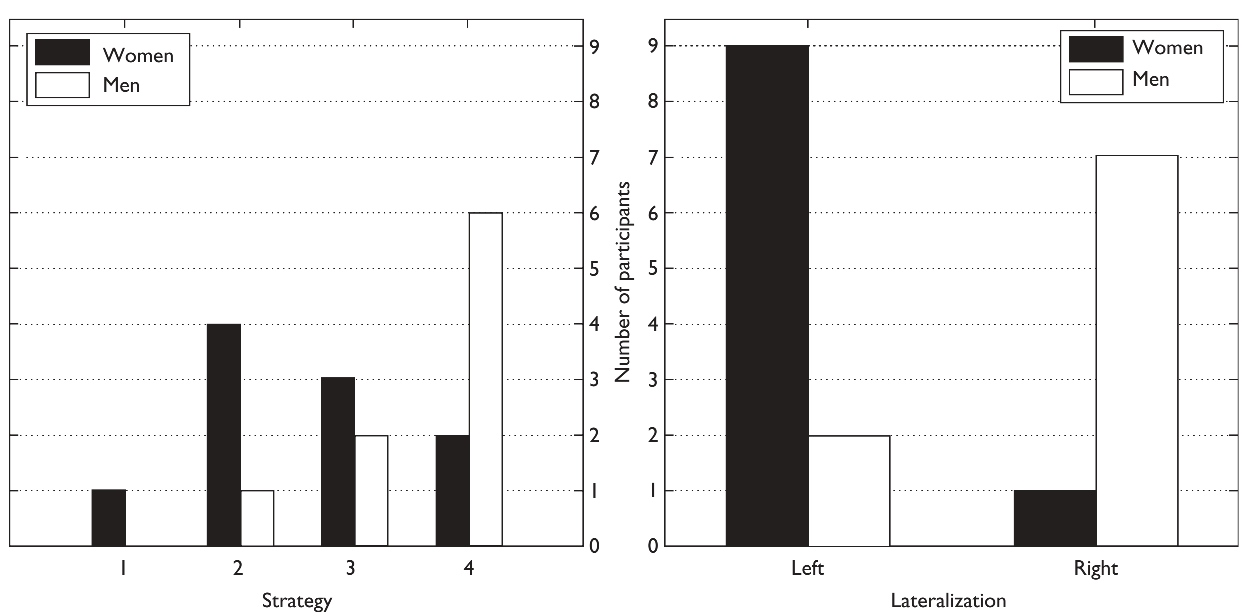

Fig. 2 Histograms of strategy ratings (left) and dichotomized lateralization of hippocampal activation (right) from female (black) and male participants (white).

analyses revealed significantly different lateralization between the sexes: women showed more left-lateralized activation and men showed more right-lateralized activation patterns, whereas both groups exhibited large intersubject variability. Thus, we were able to demonstrate that gender-related differences in brain activation patterns, as have been reported for other brain structures, also exist for the hippocampal region. Regarding cognitive strategy ratings, men estimated their strategy to be significantly more nonverbal (pictorial) than women. So far, on the group level, strategy ratings correspond to lateralization of hippocampal activation. We did not find a difference in performance between women and men. This suggests that a strategy that mixed spatial/pictorial and verbalized representations, as was used by the female participants, in this setting led to equally successful performance as predominantly pictorial representations. The high percentage of correct responses in both groups indicates a ceiling effect, that is, the task might have been too easy to detect a differential group effect.

Employment of different cognitive strategies in women and men has been previously demonstrated in a behavioural study [12]. The authors were able to show that women relied on landmark cues only, whereas men used both landmarks and geometric information in a computerized version of the Morris water maze. Neidhardt and Schmitz [21] demonstrated in a behavioural study that as early as at primary school age, girls and boys use different strategies for orienting in a new, unfamiliar environment. In their study, girls preferentially used landmark cues, whereas boys created a survey representation. Kimura [11] proposed that when a task can be performed by either left or right-hemisphere mechanisms, male participants tend to employ right-hemisphere, nonverbal systems whereas female participants tend to employ left-hemisphere, verbal systems. Stronger verbal processing in female than in male participants even in 'nonverbal' tasks was supported by McGlone and Kertesz [10], who investigated visuoconstructive and verbal performance in neurological patients with unilateral lesions.

Our finding that lateralization of brain activation corresponds to cognitive strategy is in line with a study by Stephan *et al.* [15], who let participants perform two different tasks on the same stimuli (letter strings): in the lexical decision task, participants displayed more left-lateralized activation, whereas in the geometrical decision task, activation was more right lateralized. These tasks can be interpreted as processing the same stimuli in two different ways or strategies. Our findings are in line with an fMRI study by Maguire *et al.* [16], who assessed brain activation patterns in superior memorizers and asked them to describe their strategy: in contrast to controls, they reported having employed a spatial strategy, which was reflected by right hippocampal activation.

Previous functional imaging studies in several cognitive domains reported differentially more left-lateralized activation in women and more right-lateralized activation in men [4,5,8]. So far, our results are in line with the literature. Other studies, however, reported less concordant findings. Piefke *et al.* [22] detected differential involvement of the right prefrontal cortex in female participants and the left parahippocampal gyrus in male participants in an autobiographical memory task. From two studies investigating sex differences in brain activation related to cognitive planning using fMRI and mental rotation using single-photon emission computed tomography, respectively, Unterrainer *et al.* [23,24] concluded that an individual's performance level rather than his or her sex largely determines the neuronal activation patterns during higher-level cognition. The lateralization differences between the sexes we observed, however, cannot be explained by performance differences, as both groups were equally successful in the task.

Conclusion

Using fMRI and a spatial memory paradigm, we were able to demonstrate gender-related differences in (1) lateralization of hippocampal activity and, correspondingly, (2) cognitive strategy: women displayed more left-lateralized activation patterns and reported having employed more verbal strategies than men. Differences in brain activation and cognitive strategy did not reflect differential performance levels.

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