Brain activation during human navigation: gender-different neural networks as substrate of performance

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Visuospatial navigation in animals and human subjects is generally studied using maze exploration. We used functional MRI to observe brain activation in male and female subjects as they searched for the way out of a complex, three-dimensional, virtual-reality maze. Navigation activated the medial occipital gyri, lateral and medial parietal regions, posterior cingulate and parahippocampal gyri as well as the right hippocampus proper. Gender-specific group analysis revealed distinct activation of the left hippocampus in males, whereas females consistently recruited right parietal and right prefrontal cortex. Thus we demonstrate a neural substrate of well established human gender differences in spatial-cognition performance.

Continuous visuospatial navigation in familiar and unfamiliar environments is a requirement of daily life. It is also one of the few cognitive functions for which a reliable gender-specific performance difference is well known^{1,2}.

Several neuronal structures are involved in visuospatial cognition. Studies of human patients with brain lesions as well as animal research demonstrate the importance of the right mediotemporal lobe, including the hippocampus and the hippocampal formation, for the representation of space³⁻⁹. Specific place cells in the hippocampus are active whenever the animal is in a particular location in its environment^{10,11}. Other hippocampal neurons respond differentially to spatial stimuli, irrespective of the spatial location of the animal^{12,13}. These findings were integrated into the cognitive-mapping hypothesis¹⁴, suggesting a single allocentric (world-centered) representation of the environment residing mainly in the hippocampus.

The posterior parietal cortex is involved in egocentric (bodycentered) spatial cognition. Lesions of this structure significantly impair the formation of spatial representations of body locations with respect to the subject's environment¹⁵. Strong neural connections between the posterior parietal cortex and the hippocampal formation as well as the parahippocampal region^{16,17} suggest functional interactions of these structures during spatial-cognition tasks such as orienting, navigating and forming visuospatial-memory traces.

In addition to the hippocampus/parahippocampal areas and the parietal lobes, right prefrontal areas (Brodmann's areas 9 and 46) are also activated by visuospatial working memory tasks^{18–20} and are implicated in complex navigation.

Navigation through mazes, studied in humans since the beginning of the century^{21,22}, can now be combined with functional neuroimaging^{23–28}. Activition in the parahippocampus, medial parietal region and the posterior cingulate occurs during encoding of a maze, whereas no differences in brain activation are observed between encoding and retrieval²⁹. When objects can be

used as specific landmarks for navigation, there is significant activity of the right parahippocampal gyrus, but no activity of the hippocampus proper³⁰. Using a computer-simulated environment, successful retrieval of previously well learned routes to specific predefined goals activates the right hippocampal area³¹. It was found that the more accurate the route taken to the target place, the greater the activity in right hippocampus. These studies delineated relevant regions for visuospatial cognition which parallel and extend findings from previous animal and human studies.

However, gender-related aspects have not yet been addressed. Studies on lesioned animals demonstrate that spatial cognition is differently organized in male and female rats. Performance of female rats in the Morris water maze is disrupted by frontal lesions to a significantly greater extent than in male rats³², whereas lesions of the entorhinal cortex cause greater impairment in males than in females³³.

To investigate the neural basis of gender differences in maneuvering through unfamiliar environments, we used functional magnetic resonance imaging while male and female subjects navigated through totally unknown three-dimensional mazes. Subjects were instructed only to find a way out of the maze (Fig. 1a). In the navigation condition, subjects could move through the mazes by three buttons of a fiber optic-equipped keyboard that allowed turns to the left or right as well as forward movement. The control condition consisted of a reaction task with perceptual and motor components comparable to the activation condition (Fig. 1a). Three experimental sessions with three different mazes of comparable difficulty were scanned.

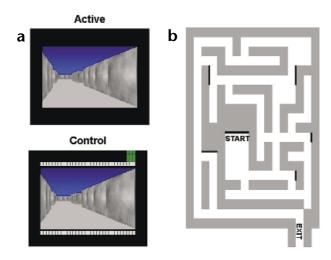
RESULTS

To validate our protocol, we first analyzed the neural activity of the whole group to determine consistency of our results with previous reports of functional brain imaging during navigation. Analysis revealed significant bilateral activity of the medial occipital gyri,

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the lingual gyri, the parahippocampal gyri, the posterior cingulate and the superior colliculi, as well as medial and lateral superior parietal lobules (Table 1). In addition, we found significant activation of the right hippocampus proper during maze navigation (Fig. 2).

To analyze gender differences in brain activation, we computed neural activity for each group of male and female subjects separately (Table 2). As expected from the group analysis, there was great overlap between men and women in brain regions that were significantly activated. However, we also observed brain regions that were activated exclusively by the male or by the female group (Table 2, anatomical regions in bold type). Most notably with respect to the brain-lesion studies in rats mentioned above, men showed activation in the left parahippocampal gyrus as well as the left hippocampus proper. In contrast, women showed activity of the left superior frontal gyrus and of the right medial frontal gyrus.

To statistically confirm this observation, we contrasted the neural activity of the male and female group against each other. With

Fig. 1. The maze protocol. (a) Typical view from inside the virtual maze. During the control condition, the screen was frozen at the last position of the active condition. Two white bars above and below indicated the control phase, during which green, flickering rectangles randomly appeared at the left, middle or right position above the upper bar. Subjects had to press the respective response buttons as quickly as possible. Rectangles appeared four to seven times at random intervals. (b) Aerial view of the virtual environment of one maze demonstrating the possible intersections and paths (not shown to subjects). Landmarks with distinct patterns are indicated by solid black lines.

this analysis women showed increased activity of the right prefrontal cortex at Brodmann's areas 46/9 (Fig. 3a). Additionally, the right inferior parietal lobule (Fig. 3a) and the right superior parietal lobule (BA 7; 36, -60, 62; Z=3.01) were significantly activated in women, in contrast with men. Men showed significantly increased activity in the left hippocampus proper (Fig. 3b). Additionally, an increased activity of the right parahippocampal gyrus (BA 27; 8, -34, 2; Z=3.50) and the left posterior cingulate (BA 29; -10, -44, 10; Z=3.20) was observed. On the behavioral level, men were significantly faster than women at finding the way out of the maze (mean runtime of the male group, 141.8 ± 31.9 s; mean runtime of the female group, 196.1 ± 26.6 s; $t_{22} = -4.97$; p < 0.001).

Discussion

Activity of the network of brain regions we observed during navigation of subjects in an unfamiliar, complex, virtual environment is consistent with previous findings³⁴ and demonstrates neural activity for allocentric and egocentric spatial-information processing. In this context, the parahippocampal activation as well as the activity of the right hippocampus proper reflect a neural circuit directly related to the allocentric aspects of navigation and route finding. At present, we agree with the view that the hippocampus is involved in the processing of spatial arrangements to serve navigation *per se*,

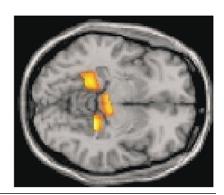
Table I. Group data: anatomical regions, Brodmann's areas (BA) and stereotactic coordinates of the voxels of peak activation

	Talairach coordinates								
Anatomical region	ВА	x	у	z	Z -value				
Left									
Cuneus	19	-20	-88	26	5.36				
Lingual gyrus	19	-6	–76	-2	5.95				
Medial occipital gyrus	19	-40	-74	-4	4.97				
Superior parietal lobule	7	-16	-74	38	4.94				
Precuneus	7	-20	-60	60	5.43				
Posterior cingulate	23/30	-16	-54	18	5.89				
Parahippocampal gyrus	30	-22	-44	-4	6.19				
Superior colliculus	-4	-24	-4	5.81					
Right									
Medial occipital gyrus	19	40	-80	20	5.10				
Precuneus	7	22	-74	42	6.02				
Posterior cingulate	30	18	-52	16	6.00				
Fusiform gyrus	37	22	-44	-6	5.66				
Parahippocampal gyrus	36	22	-36	-8	4.45				
Lingual gyrus	18	16	-66	0	4.29				
Superior parietal lobule	7	30	-44	60	4.89				
Hippocampus		28	-32	-8	4.05				
Superior colliculus		6	-24	-4	4.53				
Medial frontal gyrus	6	28	6	52	4.82				

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Fig. 2. Activity of the right hippocampal region in sagittal and transverse planes. Functional imaging data are superimposed on a T1-weighted image of a single subject in standardized space. Other brain regions shown on the sagittal plane are the right medial occipital gyrus and two foci in the right parietal lobule. The superior colliculi as well as the left parahippocampal gyrus are shown on the transverse plane.





whereas the parahippocampal region is involved in processing of specific places and routes, and probably reflects the encoding of new places and topographic constellations³⁵.

In line with previous reports, right parietal (BA 7) activity reflected the egocentric space-representation frame that subjects constructed during navigation³⁶. Because of the first-person view of the maze, parietal activity was generated during the translation of retinal coordinates to head-centered, or even body-centered, coordinates.

Activiation of the midparietal precuneus is commonly found in studies of episodic memory for either verbal or visual stimuli^{37–40} and is related to temporal-order retrieval⁴¹. Here we assume that activation of medial parietal regions reflects function of implicit (working) memory, recording data to keep track of an internal protocol of navigation.

The bilateral lingual gyri are part of the occipitotemporal pathway that is engaged in object discrimination and recogni-

tion⁴². Given the multiple perseverations, especially at the beginning of maze exploration, it is obvious that activity of the lingual gyri reflected the recognition of landmarks or specific intersections that were coded in an object-like manner.

Behavioral gender differences in navigation performance can be accounted for within the framework of different neural substrates for spatial cognition: women cope with the task by engaging a right parietal and a right prefrontal area, whereas men recruit the left hippocampal region. This distinct functional anatomy of spatial cognition in women versus men may be related to differences in the processing of spatial information.

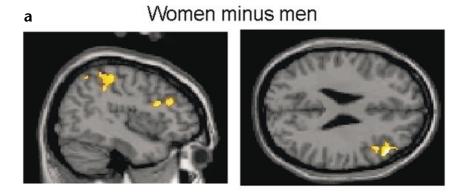
A behavioral study demonstrates that women rely predominantly on landmark cues, whereas men use both geometric and landmark cues⁴³. Accordingly, activity of the prefrontal area (Brodmann's area 9/46) in the female group reflected the working-memory demand to hold the landmark cues 'on-line', keeping track of

Table 2. Significantly activated brain regions for both groups of men and women

Men (n = 12)						Women (n = 12)					
Talairach coordinates							Talairach coordinates				
Anatomical region	BA				Z -value	Anatomical region	BA				Z- value
Left		X	у	z		Left		X	у	z	
Medial occipital gyrus	19	-18	90	30	4.27	Medial occipital gyrus	19	-46	-68	4	4.00
Lingual gyrus	18	-6	76	2	4.85	Lingual gyrus	30	-24	-46	-4	5.39
Precuneus	7	-10	74	52	3.96	Precuneus	7	-10	-58	60	4.36
Posterior cingulate	29	-8	48	10	3.92	Posterior cingulate	23	-18	-52	18	4.08
Superior colliculus		-4	24	-4	3.78	Superior colliculus		-4	-26	-4	4.44
Cuneus	19	-12	86	34	4.05	Superior parietal lobul	le 7	-20	-60	64	4.74
Parahippocampal gyrus	30	-16	48	2	4.57	Superior frontal gyrus	6	-18	0	54	3.94
Hippocampus		-18	32	-4	3.85						
Right						Right					
Medial occipital gyrus	19	32	86	26	4.15	Medial occipital gyrus	19/40	40	-76	36	5.30
Lingual gyrus	18	14	74	0	4.26	Lingual gyrus	19	14	-60	-4	4.38
Superior parietal lobule	7	20	74	42	4.70	Superior parietal lobule	7	26	-76	54	4.50
Posterior cingulate	23	20	56	18	4.74	Posterior cingulate	30	18	-48	14	4.42
Parahippocampal gyrus	35	22	38	8	3.64	Parahippocampal gyrus	37	22	-44	-8	4.55
Hippocampus		24	28	6	2.88	Hippocampus		26	-32	-6	2.79
Superior colliculus		4	-24	-4	3.82	Superior colliculus		10	-24	-6	4.41
Precuneus	7	8	-60	66	4.16	Fusiform gyrus	19	24	-58	-12	5.47
						Medial frontal gyrus	8	30	18	56	4.59
						Medial frontal gyrus	9	48	32	26	3.92
						Medial frontal gyrus	46	44	44	22	3.99

BA, Brodmann's area; non-consistent anatomical regions are in bold type

Fig. 3. Results of group comparisons superimposed on sagittal and transverse planes. (a) Activation of the right middle frontal gyrus (BA 46/9; 50, 30, 26; Z = 4.02) and the right inferior parietal lobule (BA 40; 44, -32, 54; Z = 3.03) when comparing the female with. the male group. The sagittal and transverse plane were sliced at the peaks of activation. Data are superimposed on a TI-weighted image of a single subject in standardized space. (b) Activation of the left hippocampus (-18, -26, -4; Z = 3.90) when comparing the male group with the female group. The coronal and sagittal planes are shown at the peak of hippocampal activation.



their navigational efforts. The left hippocampal activity in the male group represented the neural substrate that enables men to process multiple geometric cues. Alternatively, the hippocampal formation functions in episodic memory^{44–46}; thus, assuming a broader role of this area, male-specific hippocampal activity may reflect the males' reliance of on the use of episodic memory information in navigation.

In summary, regardless of the specif-

ic underlying neuropsychological interpretation, left hippocampal activity in men and right frontoparietal activity in women reflect the gender-specific recruitments that differentiate male from female subjects in navigation.

b

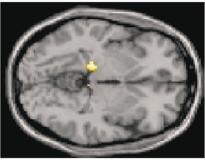
METHODS

Subjects. 24 healthy normal subjects (12 females) gave informed consent before the study. Mean age of the female group was 25.8 \pm 2.3 years; mean age of the male group was 26.3 \pm 1.8 years. All subjects were right-handed according to the Oldfield handedness quotients⁴⁷ (range between: +75 and +100). None had a history of neurological or psychiatric disorders or any sign of color blindness or visual field defects.

fMRI data acquisition. Data were acquired with a 1.5 Tesla Magnetom VISION (Siemens, Erlangen, Germany) whole-body MRI system equipped with a head volume coil. T2*-weighted functional MR images were obtained using echo-planar imaging in an axial orientation (TE = 66 ms; 121.9 ms per image). Image size was 64×64 pixels (3.6 \times 3.6 mm pixels). The volume consisted of 32 slices (TR = 4300 ms). Slice thickness was 3 mm with a gap of 0.6 mm. Thus, voxel size was isotropic. For anatomical reference, we obtained T2 weighted Turbo-Spin-Echo-images (256 × 256; 32 slices; voxel size, $0.9 \times 0.9 \times 3.6$ mm³). The fMRI protocol was a block design with alternating epochs of navigation and resting. Each epoch lasted 21.5 s (equivalent to 5 whole-brain fMRI volume acquisitions). The first six volumes in each session were discarded to allow for T1 equilibration effects. There were 3 different sessions for each subject, 36 sessions in total. Two sessions (one for each subject) were excluded from analysis because the subjects' early arrival at a solution limited the on-off cycles to fewer than five. Statistical analysis were carried out with Statistical Parametric Mapping (SPM99b, Wellcome Department of Cognitive Neurology, London, UK; www.fil.ion.ucl.ac.uk) executed in MATLAB 5.3 (MathWorks, Natick, Massachusetts). All individual functional images were corrected for motion artifacts (range of estimated individual head motion, 0.2-2.8 mm) by realignment to the first volume of the first session. A sinc interpolation was used to reslice the realigned volumes. A T2-weighted structural MRI was

Men minus women





coregistered to the mean image of the realigned volumes. All images were spatially normalized to a standard template of $2 \times 2 \times 2$ mm³ voxels. Images were then spatially smoothed with an 8-mm full width at half maximum (FWHM) isotropic Gaussian kernel. For each session, the variance of each voxel was estimated according to the general linear model using a box-car model convoluted with the hemodynamic-response function as the predictor. Images were adjusted for global effects and low-frequency drifts were removed via a high pass filter using low-frequency cosine functions with a cutoff of 95 s. Individual regionally specific effects between the active and resting phases were compared using linear contrasts. Because pairwise comparisons of the individual neural activity during navigation did not reveal any significant differences between the various mazes, data were pooled across the three sessions. The appropriate contrast image across the three sessions was calculated for each subject, producing a t statistic for each voxel. To account for interindividual variance, all group analyses were computed using a random-effects model. Group analysis across subjects involved a one-sample t-test on the images generated by pooling over the session the individual contrasts of activation versus rest for each subject. For analysis of the whole group, voxels and clusters of significant voxels were given a threshold of p < 0.05, corrected for multiple comparisons. For single group analysis, voxels were thresholded at an uncorrected level of p < 0.001. At the cluster level, significance was set to an uncorrected level of p < 0.05. Between subjects, effects were analyzed by two one-tailed, two-sample ttests for statistical significance of regionally specific group effects. Here the threshold at the voxel level was set to p < 0.01. The cluster level was thresholded at p < 0.05. Both p levels were not corrected for multiple comparisons. Areas were labeled using the nomenclature of Talairach and Tournoux⁴⁸ and Brodmann⁴⁹.

Navigation tasks. Three different three-dimensional mazes were programmed with Turbo Pascal 6.0 (Borland International, Scotts Valley, California) on a 90-MHz Pentium-based personal computer with 512 MB of conventional RAM and standard VGA-Chipset (640×480 ; 16 colors). Above the mottled gray walls, the screen was a flat blue with no additional spatial information. Possible floor crossings were indicated by black edges of the wall elements. To contrast with the wall elements, the floor

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color was of a gray brighter than the color of the walls and lacking the walls' mottled texture. Within each three-dimensional maze, six of the wall elements were in different colors and textures to serve as landmarks. Landmarks for each maze were positioned to give unambiguous hints at crossing points where turning to the left or right was crucial for successful navigation. When 'walking' through the maze, subjects had a first-person view. Moving was realized by means of a specifically designed keyboard with three buttons. The middle button allowed forward movement and the left and right buttons allowed turning in those respective directions. Turning was possible within the full range of 360° degrees, but moving was not possible while turning. During the control condition, the screen was frozen at the last position at which the subject had arrived during navigation, and two white horizontal bars were presented above and below the maze (Fig. 1). Green, flickering rectangles appeared randomly four to seven times at a left, middle or right position above the upper bar. Subjects had to respond with the respective button as quickly as possible. Responses were registered on the PC by means of a fiber-optic system and an opto-coupler. Before scanning, subjects were instructed and trained to become familiar with the specially designed response system. For that reason, a fourth, unbranched training maze was constructed. Within the scanner, mazes were presented by means of LCD video goggles (Resonance Technologies, Northridge, California) with two prism tubes placed over each eye to convert the digital input to an analog PAL-standard mono image. Onset of the PC-stimulation epochs was controlled by the fMRI scanner emitting a TTL pulse before each volume acquisition. The length of the signal was set

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