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The human parahippocampal cortex subserves egocentric spatial learning during navigation in a virtual maze

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ABSTRACT

Background: Present evidence suggests that the hippocampus (HC) and the parahippocampal cortex (PHC) are involved in allocentric (world-centered) spatial memory. However, the putative role of the PHC in egocentric (body-centered) spatial learning has received only limited systematic investigation.
Methods: To examine the role of the PHC in egocentric learning, 19 healthy volunteers learned to find their way in a virtual maze during functional magnetic resonance imaging (fMRI). The virtual maze presented a first-person view, lacked any topographical landmarks and could be learned only using egocentric navigation strategies.
Results: During learning, increased medial temporal lobe activity was observed in the PHC bilaterally. Activity was also observed in cortical areas known to project to the PHC and proposed to contribute to egocentric spatial navigation and memory.
Conclusions: Our results point to a role of the PHC for the representation and storage of egocentric information. It seems possible that the PHC contributes to egocentric memory by its feedback projections to the posterior parietal cortex. Moreover, access to allocentric and egocentric streams of spatial information may enable the PHC to construct a global and comprehensive representation of spatial environments and to promote the construction of stable cognitive maps by translating between egocentric and allocentric frames of memory.

1. Introduction

Currently, spatial navigation and memory is modeled as a process supported by allocentric (i.e., world-centered) spatial representations, being independent of the observer, and egocentric (i.e., body-centered) spatial representations, which relate to the body axes (O'Keefe & Nadel, 1978). Allocentric spatial representations include prominent and salient environmental features ('places') that may serve as navigationally relevant locations for the purpose of spatial orientation and memory storage. On the other hand, egocentric spatial representations include the sensorimotor representation of whole-body, head and gaze motion, view-dependent place recognition, the mental representation of distance, time and number of routes that have been traveled, and the temporo-spatial relationship of all information. Typically, egocentric memory of large-scale space is induced by kinaesthetic sensory information as well as by eye- and head-centered representation of visual space (Andersen, Bracewell, Barash, Gnadt, & Fogassi, 1990; Andersen, Essick, & Siegel, 1985; Heide, Blankenburg, Zimmermann, & Kömpf, 1995; Quintana & Fuster, 1993).

The hippocampus (HC) is thought to play an important role in allocentric spatial representations. Neurons within the rat HC were shown to be place-sensitive (O'Keefe & Dostrovsky, 1971), and HC lesions were shown to impair place learning in the rat (Morris, Garrud, Rawlins, & O'Keefe, 1982). Human lesion studies have reported that individuals with HC or PHC damage are impaired in finding their way within their locomotor environment ('topographical disorientation and amnesia') (Abrahams, Pickering, Polkey, & Morris, 1997; De Renzi, Faglioni, & Villa, 1977; Habib & Sirigu, 1987; Landis, Cummings, Benson, & Palmer, 1986; Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001). Studies using complex real life surroundings (Barrash, Damasio, Adolphs, & Tranel, 2000; Bohbot et al., 1998; Epstein, DeYoe, Press, Rosen, & Kanwisher, 2001; Maguire, Burke, Phillips, & Staunton, 1996) or virtual reality large-scale environments (Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Spiers, Bergess, Maguire, et al., 2001) confirmed

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topographical memory deficits of subjects with medial temporal lesions.

In contrast to allocentric representation and memory formation, the neural representation of egocentric navigation and memory has received only limited systematic investigation. However, the development of virtual reality technology has brought a major progress to the study of spatial navigation and memory. Virtual realities have a major advantage for the assessment of spatial navigation and memory formation, as computer-simulated first-person environments can simulate navigation in a large-scale space. There are now a large number of studies investigating allocentric memory in healthy individuals using virtual reality environments and functional neuroimaging (e.g., Aguirre & D'Esposito, 1997; Aguirre, Detre, Alsop, & D'Esposito, 1996; Burgess, Becker, King, & O'Keefe, 2001; Burgess, Maguire, Spiers, & O'Keefe, 2001; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Janzen & van Turennout, 2004; Maguire, Frackowiak, & Frith, 1996; Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998). Studies on egocentric memory in virtual reality large-scale space are rare. However, three studies of our group demonstrated egocentric memory deficits of individuals with PHC (Weniger & Irle, 2006) or parietal cortex (Weniger, Ruhleder, Wolf, Lange, & Irle, 2009) lesions and spared egocentric memory in individuals with schizophrenia (Weniger & Irle, 2008).

In the present investigation, subjects were scanned with functional magnetic resonance imaging (fMRI) while navigating in a virtual maze. We used a computer-simulated first-person virtual reality environment in order to simulate navigation in a large-scale space. The virtual maze did not include any landmarks and all intersections appeared identical when approached from different directions, thus forcing subjects to use egocentric navigation strategies. The goals of the present study were to investigate whether the PHC of healthy volunteers is engaged during egocentric learning and retrieval in visual space, and to establish multi-method convergence for the novel finding of PHC involvement in egocentric navigation and memory formation (Weniger & Irle, 2006).

2. Methods

2.1. Participants

We studied 19 right-handed healthy volunteers (age range: 20–38 years, mean ± SD: 25 ± 5 years, 11 males) with normal or corrected to normal vision. After a complete description of the study was given to the subjects, written informed consent was obtained. The study was approved by the Ethical Committee of the Medical Faculty of the University of Göttingen and performed in accordance with the Declaration of Helsinki.

2.2. Virtual environment

The virtual reality environment was realized using previously described techniques (Weniger & Irle, 2006). The environment was three-dimensional, fully colored and textured and presented a first-person view. Subjects wore an MRI compatible head mounted display (Resonance Technology, Northridge, USA) and controlled their movements with a joystick (Current Designs, Inc., 3950 Haverford Avenue, PA 19104, USA).

An aerial view of the virtual maze is presented in Fig. 1b. The virtual maze comprised six points of two-way intersection and seven cul-de-sacs containing pots, from which only one contained money. The maze consisted of brick walls, a similarly colored floor and a blue sky. All intersections appeared identical when approached from different directions (see Fig. 1a). The maze did not include any landmarks and, therefore, could only be solved using egocentric navigation strategies.

Subjects were instructed to find the shortest way to the pot with money in it. Five trials were applied. The intertrial interval was about 1 min. Subjects were asked in this time whether they felt comfortable or had any questions. Thereafter, the next trial was announced. Trials were discontinued if the subject found the pot with money or after 5 min had expired, respectively. In each trial, subjects started at the same location and then had to find the target which remained in the same location across trials. Subjects were not able to see the target from the starting position or from other vantage points in the environment.

Prior to the task, subjects underwent a training session in a differently shaped virtual maze. Subjects were not scanned during the training session and communicated with the experimenter. They were told to walk through the maze and have a look at the pots within the various cul-de-sacs, and were encouraged to move actively by using the joystick. The goal of the training session was to familiarize subjects with the virtual environment and the task demands and to ensure that activity changes during the first trials of the task were related to learning the maze rather than learning to orientate and move within the maze.

Subjects learning performance was characterized by the number of errors (visiting cul-de-sacs or intersections not lying within the direct way to the goal) committed across the five trials. After finishing the task, subjects completed a questionnaire indicating what kind of navigation strategies they used. The questions described the specific navigation strategies and required a yes/no answer. Subjects were asked whether they tried to memorize their imagined head, body and gaze motion at different decision or time points of the virtual maze (storage of egocentric cues; e.g., "Did you try to remember the direction of turns within the maze"), or whether they tried to construct a kind of map of the virtual maze in their mind (survey perspective; e.g., "Did you try to get a sort of spatial survey of the maze"). Subjects were also given the opportunity to describe their navigation strategies in a free field response and were given oral support, since egocentric strategies are likely to be stored in an implicit manner (Weniger & Irle, 2008), requiring a free field format to translate them into verbal frames of memory.

2.3. Image acquisition

Data were acquired using a three Tesla Siemens Magnetom Trio (Siemens, Erlangen, Germany). Subjects were placed supine inside the magnet bore and wore headphones for noise protection. Initially, an anatomical T_1-weighted MR dataset covering the whole head at 1 mm^3 isotropic resolution was acquired (3D Turbo FLASH, repetition time (TR): 1950 ms, inversion time: 1100 ms, echo time (TE): 3.93 ms, flip angle: 12°). For functional imaging a T_2^*-sensitive gradient-echo EPI technique with an in-plane resolution of 2 mm^2 was used (TR: 2000 ms, TE: 36 ms, flip angle: 70°, acquisition matrix: 96 × 128, 22 sections, interleaved ascending scanning order, 4 mm thickness, lower bound of the acquisition field adjusted to fit the lower bound of the temporal lobe).

2.4. Image analysis

Functional data were analyzed and visualized using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). Preprocessing included 3D motion correction, slice scan time correction, linear trend removal and high pass filtering, and spatial smoothing with a Gaussian kernel (full width at half maximum 5 mm^3). Subsequently, functional datasets were co-registered to the anatomical dataset and transformed into Talairach space. Statistical analysis was restricted to standard Talairach space.

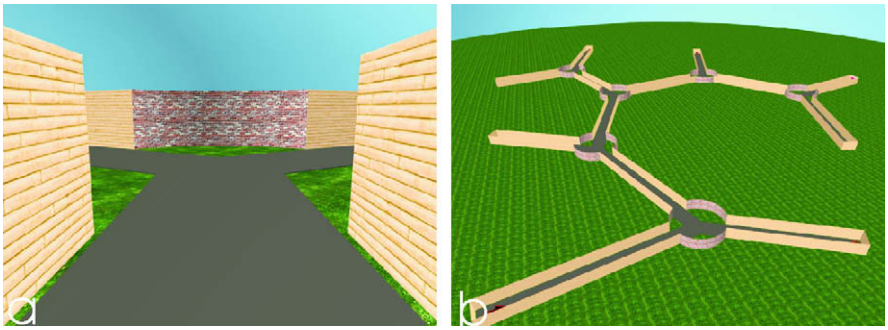

Fig. 1. Subject view (a) and aerial view (b) of the virtual maze. Actual stimuli were in full color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.4.1. DECIDE predictor

Pilot experiments indicated that subjects started deciding about directional choices and memorizing body and head position at that time point when the intersection and its openings became clearly visible. This time point preceded the arrival at intersections by 3 s (total time while moving along the corridors: 9 s). Furthermore, subjects reported ongoing spatial mnemonic activity during the beginning of the time spent at intersections (lasting approximately 1–1.5 s), as turning at intersections was modulated to a low speed. On the basis of this information, we defined our predictor DECIDE as activation arising during a time period 3 s before arriving at intersections and the onset (=first sixth) of time spent at intersections (total time spent at intersections: 7 ± 4 s). Fig. 2 illustrates the time course of the DECIDE predictor for trial 1 and the first trial performed without errors. As a validation of our DECIDE predictor, activation of a statistically defined cluster in the right-sided PHC was plotted (see Fig. 2), indicating that PHC activity changes were evident in that time period assumed to represent navigationally relevant cognition. To further ensure that subjects would restrict navigationally relevant cognition to this time period, we instructed subjects to internally recite the alphabet while moving along the corridors. Subjects reported having stopped reciting and concentrating on the intersections when these became clearly visible.

Group analyses were performed using the multi-subject random effects (RFX) approach of the general linear model (GLM). The time courses of the experimental condition – convolved with a model of the expected hemodynamic response function – were entered into the design matrix. Analyses of covariance (ANCOVA) were used to calculate *t*-tests of the DECIDE-predictor vs. the BASELINE. BASELINE is automatically calculated by the software and refers to the mean confound of the GLM (b0). The following analyses were performed:

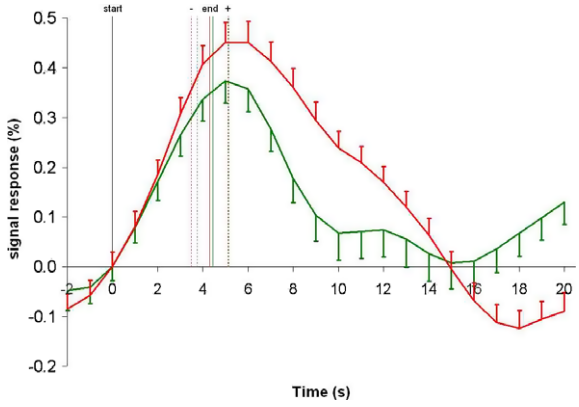

Fig. 2. Event-related averaging of DECIDE in trial 1 (red) and in the first trial performed without errors (green). 0.0 refers to the BASELINE, being automatically calculated by the software and referring to the mean confound of the GLM (b0). Plot of a statistically defined cluster in the right PHC with $t > 4.00$ in a multi subject ($n = 15$) analysis using RFX–ANCOVA *t*-test, degrees of freedom $t(14)$. 'start' refers to a time point 3 s prior to arrival at an intersection (beginning of DECIDE). Average duration of DECIDE: 4.3 s for trial 1 (red vertical line) and 4.4 s for the first trial performed without errors (green vertical line). '–' and '+' refer to the SD of DECIDE, error bars refer to SE of signal change.

(1) *DECIDE vs. BASELINE.* This analysis was done to elucidate activity changes during egocentric learning. Only the first two trials of the task were analyzed, as the majority of subjects ($n = 14$) succeeded to find the goal during trial 2. Furthermore, the exclusion of late trials from the analysis minimized the risk of confounding egocentric learning with potentially allocentric retrieval from survey perspective in late trials of the task. Effects were accepted as significant at a false discovery rate (FDR) of 0.001, which corresponds to a *t*-threshold of 5.58.

(2) *Activity changes (DECIDE) between trial 1 and the first trial performed without errors.* To assess the effects of egocentric learning vs. retrieval, we performed a group analysis comparing activity changes between the DECIDE condition in trial 1 and the DECIDE condition in the first trial performed without any errors. Three subjects performed first without errors on trial 2, one on trial 3, seven on trial 4, and four on trial 5. The respective first errorless trial of these subjects ($n = 15$) was entered into analysis. Effects were accepted as significant at $p < 0.005$, which corresponds to a *t*-threshold of 3.33.

(3) *ROI analyses.* To focus on the PHC and the HC, region-of-interest (ROI) analyses were performed. The region of the PHC and the HC were manually drawn upon an averaged T_1-weighted image, respectively. Borders were defined according to the protocols of Pruessner and coworkers (Pruessner et al., 2000, 2002). The anterior border of the HC was found on the coronal slice showing the alveus and/or the uncal recess of the inferior horn of the lateral ventricle, and the posterior border was found on the slice where an ovoid mass of gray matter appeared inferiomedially to the trigone of the lateral ventricle. The anterior border of the PHC was defined five millimeters posterior to the disappearance of the gyrus intralimbicus, and the posterior border was defined as the last slice in AC–PC orientation on which the HC could be identified.

Left and right PHC and HC were subjected to RFX–ANCOVA *t*-tests, testing the conditions "DECIDE vs. BASELINE (trials 1 and 2)", and "trial 1 vs. first trial performed without errors", respectively. We further added an analysis comparing "trial 1 vs. trial 5" in order to test whether PHC and HC are especially engaged in the retrieval of already stored egocentric information. Effects were accepted as significant at $p < 0.001$ (DECIDE vs. BASELINE) or $p < 0.005$ (trial 1 vs. first errorless trial or vs. trial 5).

(4) *Correlation analysis.* PHC-ROIs were drawn upon the individual T_1-weighted MRI according to the same protocol. The average beta-values (DECIDE vs. BASELINE) of left and right PHC of individual subjects were correlated with the amount of errors performed in trials 1, 2 and 3, respectively (Pearson correlation coefficients). Correlation analysis was restricted to trials 1–3, as the behavioral variability in late trials of the task was to low to allow for significant correlation coefficients (performance with 0 or 1 error: trial 4: $n = 12$; trial 5: $n = 18$; see also Fig. 3).

3. Results

3.1. Behavioral data

Fifteen subjects showed clear evidence of learning to find their way in the maze, indicated by one ($n = 3$) or more ($n = 12$) errorless trials (trials 2–5). The remaining four subjects performed in trial 4 and/or trial 5 with one error, respectively. The behavioral data (i.e., committed errors) of all subjects across the five trials of the virtual maze are outlined in Fig. 3. The number of visited intersections (means and SD) was 8.5 ± 1.5 (range: 5–10) in trial 1, 7.7 ± 2.4 (range: 5–12) in trial 2, 7.6 ± 2.2 (range: 5–11) in trial 3, 6.2 ± 1.9 (range: 5–12) in trial 4, and 5.8 ± 1.8 (range: 5–12) in trial 5.

Sixteen subjects reported to have memorized egocentric cues (i.e., virtual changes of head and whole-body direction, time and distances that had been traveled). For example, some subjects reported to have memorized that at the first intersection they should orientate to the left, and then keep right for a longer time. Other subjects tried to imagine at intersections a correct run performed in an earlier trial. Subjects reporting no specific strategy said that they moved through the maze "by chance" or "by intuition". Five subjects further reported to have tried to construct a survey perspective of the maze during learning. None of the subjects reported to have verbalized a sequence of left and right turns. Subjects reporting that they did not use a specific navigation strategy ($n = 3$) were among those who did not achieve one or more errorless trials.

3.2. Imaging results

3.2.1. Activity changes during trials 1 and 2 (DECIDE vs. BASELINE)

Results are shown in Table 1 and Figs. 4 and 5. Increased activity emerged in a cluster (size: 33,627 voxels) spreading across the posterior parts of the parahippocampal, fusiform and middle temporal gyri, and lingual and medial occipital gyri of both hemispheres. The right-sided and left-sided retrosplenial cortices showed increased activity as well. Increased activity within the right PHC was more pronounced than that within the left PHC (paired t-test using mean beta-values; trial 1: $t(18) = -4.84$, $p < 0.001$; trial 2: $t(18) = -2.60$, $p = 0.018$) (see also Fig. 4). Further areas with increased activity included the left postcentral gyrus and the left anterior insula. Local maxima of increased activity are summarized in Table 1. Two small clusters with significantly decreased activity emerged along the midline within the cingular (BA 24, 32; 1675 voxel) and medial frontal (BA 10; 504 voxel) gyrus.

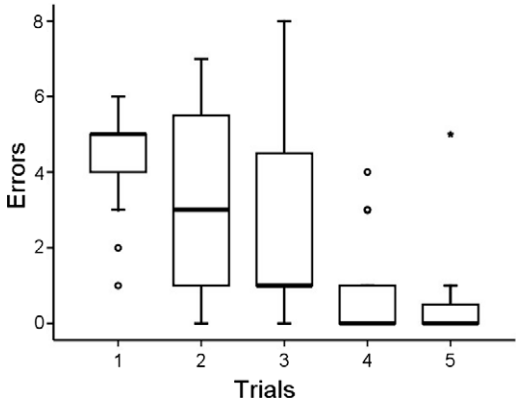

Fig. 3. Box plot of errors performed across the five trials administered in the virtual maze showing the five statistics: minimum, first quartile, median, third quartile, and maximum. The box length is the interquartile range. Outliers (cases with values between 1.5 and 3 box lengths from the upper or lower edge of the box) are marked with a circle. Extreme outliers (cases with values more than 3 box lengths from the upper or lower edge of the box) are marked with an asterisk.

3.2.2. Activity changes (DECIDE) between trial 1 and the first trial performed without errors

Significant activity changes between trial 1 and the first trial performed without errors emerged in the left- and right-sided PHC and in a small region of the right-sided medial frontal and precentral gyrus. These regions were more activated during trial 1 when compared with the first trial performed without errors (Table 2 and Fig. 6). There were no areas showing decreased activity.

3.2.3. ROI analyses

Activity changes (DECIDE vs. BASELINE) of both regions of interest, i.e. PHC and HC, are summarized across all trials in Fig. 7.

3.2.3.1. Activity changes during trials 1 and 2 (DECIDE vs. BASELINE). The ROI analysis of the left-sided PHC (RFX single-factor repeated measures ANCOVA; $n = 19$; $F(1;18) = 26.36$, $p < 0.001$) and right-sided PHC ($F(1;18) = 78.69$, $p < 0.001$) confirmed significantly increased activity during trials 1 and 2. Right-sided activity changes were significantly stronger than left-sided activity changes (paired t-test using mean beta-values; trial 1: $t(18) = -5.24$, $p < 0.001$; trial 2: $t(18) = -2.43$, $p = 0.026$). The analysis of the right-sided HC ($F(1;18) = 2.50$, $p > 0.05$) was not significant. The left-sided HC showed a trend towards less activation during DECIDE in trials 1 and 2 ($F(1;18) = 10.35$, $p < 0.01$).

3.2.3.2. Activity changes (DECIDE) between trial 1 and the first trial performed without errors. ROI analyses confirmed significantly stronger activity of the left-sided PHC (RFX single-factor repeated measures ANCOVA; $n = 15$; $F(1;14) = 13.27$, $p < 0.003$) and right-sided PHC ($F(1;14) = 11.42$, $p < 0.005$) in trial 1 when compared with the first trial performed without errors. The ROI analyses of the left-sided HC ($F(1;14) = 1.18$, $p > 0.05$) and the right-sided HC ($F(1;14) = 1.39$, $p > 0.05$) did not yield significant results.

3.2.3.3. Activity changes (DECIDE) between trial 1 and trial 5. ROI analyses showed stronger activity of the left-sided PHC (RFX single-factor repeated measures ANCOVA; $n = 15$; $F(1;14) = 11.46$, $p < 0.005$) and right-sided PHC ($F(1;14) = 8.73$, $p < 0.01$) in trial 1 when compared with trial 5. The analysis of the left-sided HC ($F(1;14) = 0.04$, $p > 0.05$) and the right-sided HC ($F(1;14) = 0.56$, $p > 0.05$) did not yield significant results.

3.2.4. Correlation analysis

Correlation analyses of average beta-values of the left and right PHC-ROIs of individual subjects with the amount of committed errors revealed significant results for the second (left PHC: $r = 0.536$, $p = 0.018$; right PHC: $r = 0.790$, $p < 0.001$) and third (left PHC: $r = 0.613$, $p = 0.005$; right PHC: $r = 0.470$, $p = 0.042$) trial. More errors were related to stronger activity increases (DECIDE vs. BASELINE) within the PHC. Fig. 8 summarizes the results for the first, second and third trial.

Table 1
Local maxima of increased activity during trials 1 and 2 (DECIDE vs. BASELINE).

Anatomic description	Talairach coordinates			Local maximum (*t*)
	X	*Y*	*Z*	
Posterior parahippocampal gyrus R	20	−38	−7	10.05
Posterior parahippocampal gyrus L	−18	−43	−5	11.13
Posterior fusiform gyrus R	24	−49	−8	9.67
Posterior fusiform gyrus L	−24	−49	−5	7.96
Retrosplenial cortex (Brodmann area 30) R	9	−46	4	7.33
Retrosplenial cortex (Brodmann area 30) L	−15	−52	4	6.83
Parieto-occipital sulcus R	27	−73	34	11.22
Parieto-occipital sulcus L	−21	−73	25	8.23
Lingual gyrus R	9	−67	1	12.19
Lingual gyrus L	−6	−79	−3	8.18
Middle temporal gyrus (V5) R	39	−58	7	8.98
Middle temporal gyrus (V5) L	−39	−61	7	8.98
Medial occipital gyrus R	29	−76	22	10.03
Medial occipital gyrus L	−21	−79	21	8.46
Postcentral gyrus L	−33	−31	49	7.71
Postcentral gyrus L	−42	−25	43	7.56
Anterior insula L	−30	23	4	9.51

Statistically significant clusters according to multi subject (n = 19) analysis using RFX–ANCOVA t-test (threshold $t > 5.58$, FDR < 0.001, degrees of freedom $t(18)$, voxel t-values interpolated to 1 mm^3, cluster threshold > 15).
R: right hemisphere, L: left hemisphere. *X*, *Y* and *Z* refer to three dimensions of Talairach coordinates.

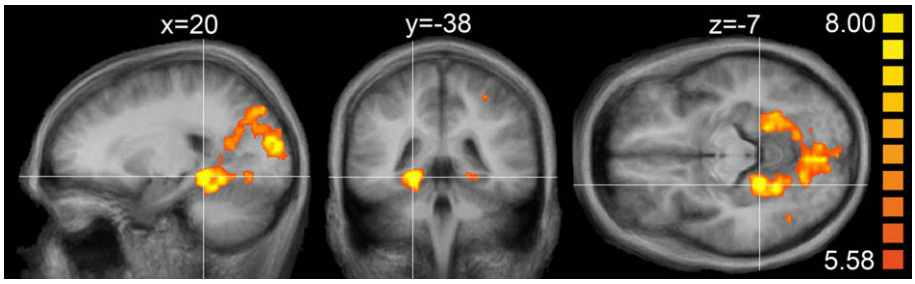

Fig. 4. Increased activity during egocentric learning in trial 1 and 2 (DECIDE vs. BASELINE). Multi subject (n = 19) analysis using RFX–ANCOVA t-test. Positive t-values (see color bar) overlaid on averaged T_1-weighted MRI. Threshold $t > 5.58$, FDR < 0.001, degrees of freedom $t(18)$, voxel t-values interpolated to 1 mm^3, cluster threshold > 15. *X*, *Y*, *Z*: Talairach coordinates. Centre of the cross hairs refers to local maximum t-value within the right PHC. Figures in radiological convention.

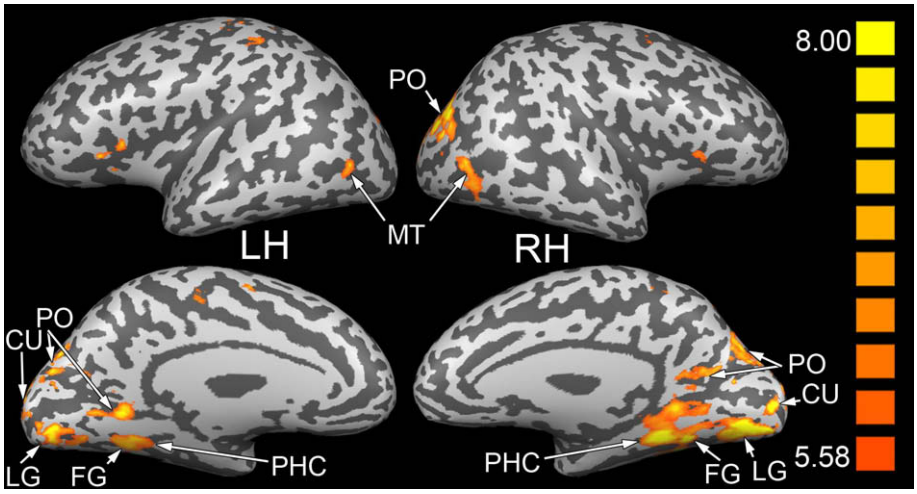

Fig. 5. Increased activity during egocentric learning in trial 1 and 2 (DECIDE vs. BASELINE). Multi subject (n = 19) analysis using RFX–ANCOVA t-test. Positive t-values (see color bar) overlaid onto inflated brain of one of the subjects. Lateral view (top) and medial view (bottom). Threshold $t > 5.58$, FDR < 0.001, degrees of freedom $t(18)$, voxel t-values interpolated to 1 mm^3. RH: right hemisphere; LH: left hemisphere; CU: Cuneus; FG: fusiform gyrus; LG: lingual gyrus; MT: medial temporal gyrus (V5); PHC: parahippocampal cortex; PO: gray matter along parieto-occipital sulcus.

Table 2
Local maxima of increased activity (trial 1 > first trial performed without errors).

Anatomic description	Cluster size	Talairach coordinates			Local maximum (t)
		X	Y	Z	
Posterior parahippocampal gyrus R	452	24	−31	−8	4.73
Posterior parahippocampal gyrus L	463	−24	−40	−5	5.63
Medial frontal and precentral gyrus R	530	21	4	41	4.14

Statistically significant clusters according to multi subject ($n = 15$) analysis using RFX–ANCOVA t-test (threshold $t > 3.33$, $p < 0.005$, degrees of freedom $t(14)$, voxel t-values interpolated to 1 mm^3, cluster threshold > 15). R: right hemisphere, L: left hemisphere. X, Y and Z refer to three dimensions of Talairach coordinates.

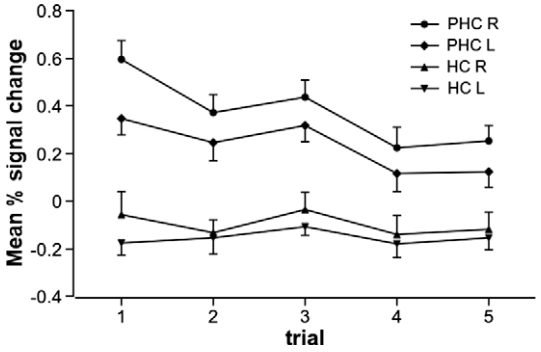

Fig. 7. Mean percent signal change across the five trials of the virtual maze. The bars represent standard errors. PHC: parahippocampal cortex; HC: hippocampus.

4. Discussion

To our knowledge, the present study is the first to investigate egocentric learning in a virtual maze using fMRI, and to investigate the role of the PHC during task performance. We found that during learning to find the way within the maze, medial temporal lobe activity of healthy volunteers was confined to the PHC. Accordingly, results of our previous investigation (Weniger & Irle, 2006), using the same virtual environment as that of the present study, revealed that subjects with PHC removals were completely unable to learn the maze and that HC damage did not contribute to the observed learning deficits. A recent fMRI study investigating path integration while traveling along two legs of a virtual triangle (Wolbers, Wiener, Mallot, & Büchel, 2007) found that better egocentric localization of the starting position was related to enhanced right HC but not PHC engagement. However, subjects of this study underwent extensive pre-fMRI learning, and thus HC activity during task performance within the scanner probably reflected high-level spatial aspects of the path integration process and not egocentric learning.

In the present study, increased activity within the PHC was bilaterally, but more pronounced in the right-sided PHC, whereas the previous lesion study found deficits in virtual maze learning only after right-sided PHC removals. It seems possible that fMRI is able to identify any brain region being necessary to support a given behavior, whereas lesion studies only detect brain regions being necessary and sufficient for the behavior in question. Thought in this way, the right-sided PHC may be capable to fully support spatial navigation and memory formation in the presence of left-sided PHC lesions, but not *vice versa*. Taken together, our previous (Weniger & Irle, 2006) and present study provide strong multi-method convergence for a role of the PHC in the representation and learning of spatial relationships between the body and its environment, i.e., egocentric spatial information.

4.1. A role for the PHC in egocentric navigation and memory

The PHC of the macaque brain was shown to be strongly connected with the posterior parietal cortex (Cavada & Goldman-Rakic, 1989; Lavenex, Suzuki, & Amaral, 2002; Suzuki & Amaral, 1994). Single unit recordings in monkeys and rats have demonstrated that egocentric representations of visual space are modulated by posterior parietal (Andersen et al., 1985; Andersen et al., 1990) and medial temporal, i.e. entorhinal (McNaughton, Battaglia, Jensen, Moser, & Moser, 2006; Sargolini et al., 2006) neurons. A recent study of our group (Weniger et al., 2009) demonstrated that individuals with parietal cortex lesions are severely impaired learning the same virtual maze as used in the present study. Thus, it may be speculated that the PHC contributes to the memory consolidation of egocentric spatial information by its feedback projections to the posterior parietal cortex. This assumption is supported by further lesion studies in humans, demonstrating that lesions of the PHC, but not lesions of the HC or perirhinal cortex, delay memory-guided saccades in a task assessing spatial memory in a retinotopic, egocentric frame of reference (Ploner et al., 1999; Ploner et al., 2000).

An additional role of the PHC for egocentric representation and navigation in visual space is also likely. Single unit recordings in monkeys suggest that information about whole-body motion as well as about where the monkey is looking at in its environment ('spatial view cells') are located in the HC and parahippocampal gyrus (O'Mara, Rolls, Berthoz, & Kesner, 1994; Rolls, 1999). Single unit recordings in humans with temporal lobe epilepsy have revealed that the majority of PHC neurons respond to views of landmarks within a virtual town, however, place-responsive cells within the PHC were also frequent, and 30% of the view-responsive cells within the PHC responded as a function of the subjects' location in the virtual environment (Ekstrom et al., 2003). Accordingly, a functional imaging study provided evidence that the human PHC

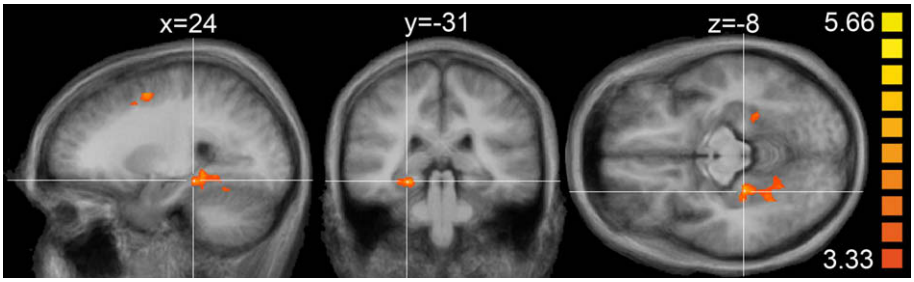

Fig. 6. Regions with increased activity (trial 1 > first trial performed without errors). Multi subject ($n = 15$) analysis using RFX–ANCOVA t-test. Positive t-values (see color bar) overlaid on averaged T_1-weighted MRI. Threshold $t > 3.33$, $p < 0.005$, degrees of freedom $t(14)$, voxel t-values interpolated to 1 mm^3, cluster threshold > 15. X, Y, Z: Talairach coordinates. Centre of the cross hairs refers to local maximum t-value within right PHC. Figures in radiological convention.

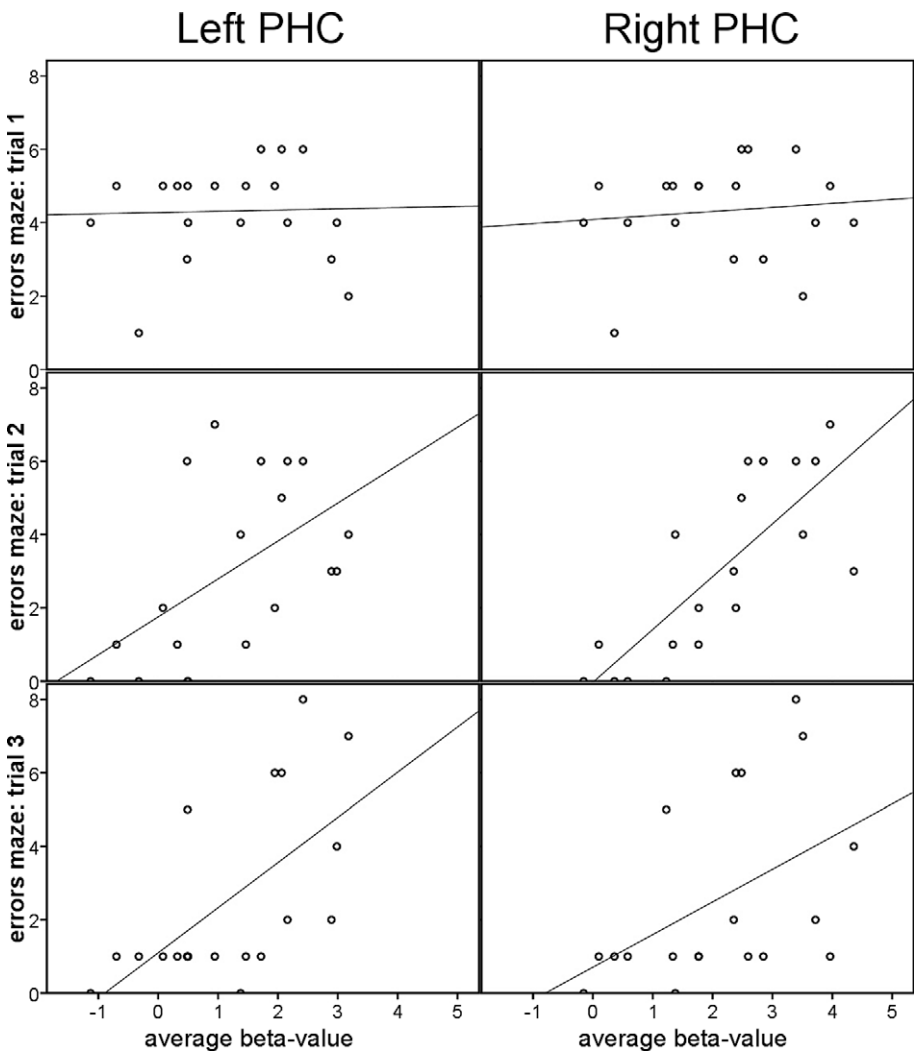

Fig. 8. Correlation analyses of average beta-values (DECIDE vs. BASELINE) of individual PHC-ROIs with the amount of errors performed in the first, second and third trial. The results of the second (left PHC: $r = 0.536$, $p = 0.018$; right PHC: $r = 0.790$, $p < 0.001$) and third (left PHC: $r = 0.613$, $p = 0.005$; right PHC: $r = 0.470$, $p = 0.042$) trial were significant. More errors were related to stronger activity increases (DECIDE) within the PHC.

responds equivalently to place changes and viewpoint changes (Epstein, Graham, & Downing, 2003), suggesting that the PHC is also involved in encoding the relationship between the observer and the scene.

Taken together, there is now evidence that the PHC is involved in allocentric representation and memory (e.g., Aguirre & D'Esposito, 1997; Aguirre, Detre, Alsop, & D'Esposito, 1996; Burgess, Becker et al., 2001; Burgess, Maguire et al., 2001; Ekstrom et al., 2003; Epstein et al., 2003; Maguire, Frith et al., 1998; Maguire, Frackowiak et al., 1996) as well as in the representation and memory of the spatial relationships between the body and its environment, i.e., egocentric spatial information (Ekstrom et al., 2003; Epstein et al., 2003; McNaughton et al., 2006; O'Mara et al., 1994; Sargolini et al., 2006; Weniger & Irle, 2006; results of the present study). Accordingly, both kinds of navigational strategies should recruit the PHC. Access to both streams of spatial information may enable the PHC to construct a global and comprehensive representation of spatial environments and to promote the construction of stable cognitive maps by translating between egocentric and allocentric frames of memory.

4.2. The PHC and egocentric learning vs. retrieval

Profound increase of PHC activity was seen during trials 1 and 2 (DECIDE vs. BASELINE). Comparisons of PHC activity in trial 1 with the first errorless trial or with the last trial (trial 5) demonstrated stronger PHC activity during trial 1. It may be justified to assume that performance during the early trials of the maze mainly reflected egocentric navigation and learning, whereas performance on (late) errorless trials mainly reflected egocentric memory retrieval or allocentric memory retrieval from survey perspective. Thus, it may be suggested that egocentric or allocentric memory retrieval recruit the PHC to a much lesser degree than egocentic learning during early trials of the task.

We found a correlation between errors committed in trial 2 and trial 3 of the virtual maze and activity increases within the PHC. Task performance across subjects in trial 1 showed a similar variability, but was not correlated with PHC activity changes (cf. Fig. 8), possibly due to statistical noise being included in the behavioral measures of trial 1. The difference between trial 1 and trials 2 and 3 may be seen in that trial 1 demands directional choices while few if any knowledge about the maze has been acquired, whereas trials 2 and 3 are characterized by the acquisition of profound knowledge about the maze. This seems to be the situation which most clearly recruits the PHC. Thus, we propose that PHC activity increase in trials 2 and 3 reflected learning of navigationally relevant egocentric cues. Errors in the virtual maze may be seen as an (inverse) indicator of the learning success, with few errors definitely indicating good task performance, and *vice versa*.

Again, our data suggest that good task performance, i.e. retrieval of already stored egocentric memories, demands the PHC to a lesser degree than bad task performance, which is characterized by the subjects' effort to increase their knowledge about the maze.

4.3. Partition of egocentric and allocentric navigation and memory

In everyday practice, conjoint usage of allocentric and egocentric information in spatial navigation and learning is likely, and it is evident that situational and interindividual differences exist in the usage of predominantly allocentric vs. predominantly egocentric strategies (Bohbot, Iaria, & Petrides, 2004; Burgess, 2006; Wang & Spelke, 2002). Accordingly, spatial learning may occur in some instances in an almost exclusively allocentric or an almost exclusively egocentric manner. This applies also to large-scale virtual environments being used for the investigation of spatial navigation and learning. Even if a virtual environment is specifically designed to assess allocentric processing, a person may learn to navigate within this environment by using egocentric information instead of the provided objects and landmarks. *Vice versa*, the virtual maze of the present study might be solved by constructing a survey perspective of the maze, which is an allocentric frame of memory. However, it should be noted that an allocentric spatial representation of the environment will require egocentric inputs, whereas an egocentric representation of the environment does not necessarily require allocentric information.

It must be kept in mind that most subjects of the present study explicitly reported to have memorized egocentric cues (i.e., virtual changes of head and whole-body direction), and none of the subjects agreed to have memorized a verbal sequence of left and right turns. Furthermore, our subjects were forced to learn the maze using egocentric navigation strategies, because the maze did not contain any landmarks and all intersections appeared identical when approached from different directions. Translation of egocentric memories of the maze into a survey perspective of the maze should be possible only in late trials of the task, when most or the entire maze had already been stored in an egocentric frame of memory. We tried to minimize confounding egocentric learning with potentially allocentric retrieval from survey perspective in later trials by analyzing trials 1 and 2 (DECIDE vs. BASELINE), and by analyzing PHC activity changes in trial 1 vs. the first errorless trial and vs. trial 5. Increased PHC activity turned out to be significantly stronger during trial 1, suggesting that potential retrieval from survey perspective in late trials recruit the PHC to a much lesser degree than egocentric learning during the early trials. Moreover, we could not find evidence for increased HC activity during retrieval in the late trials of the maze, suggesting that the maze was primarily stored in an egocentric frame of memory.

Previous studies have shown that the PHC is involved in scene recognition (Aguirre, Zarahn, & D'Esposito, 1998a; Epstein, Harris, Stanley, & Kanwisher, 1999; Epstein et al., 2003), even when a scene lacks any landmarks (Epstein & Kanwisher, 1998). This may leave open the possibility that PHC activation in our study emerged also in response to viewing intersections. However, all intersections appeared visually identical. Furthermore, a correlation between task performance and increased PHC activity emerged only for trials 2 and 3 but not for trial 1. Last not least, given the fact that the HC was not engaged during learning the maze, we consider it rather unlikely that increased PHC activity observed at intersections of our maze were solely induced by viewing identical scenes, whereas learning of the maze principally occurred outside the temporal lobe.

Recent studies on fMR-adaptation have found adaptation in the PHC due to repeated stimulation with identical spatial stimuli (Avidan, Hasson, Hendler, Zohary, & Malach, 2002; Ewbank, Schluppeck, & Andrews, 2005). However, in both studies adaptation of the MR signal was measured within stimulus blocks lasting 12 s, respectively. In contrast, our experiment afforded several minutes to proceed from trial 1 to the first trial performed without errors. Furthermore, our subjects approached the intersections from different positions, respectively. Adaptation of the PHC was reported not to occur when a scene is observed from different viewpoints (Epstein et al. 2003). Accordingly, we suggest that stronger PHC activity during early vs. late trials of our virtual maze reflected egocentric learning rather than continuing adaptation towards spatial scenes.

Nevertheless, future studies are needed to elucidate the specific role of the PHC in egocentric navigation and memory. Event-related fMRI should be used to assess whether specific actions within large-scale virtual environments, such as eye movements, velocity, distances that have been traveled, or reaction time changes at intersection points, are related to specific activity changes of the PHC. A further question is whether egocentric representation is restricted to shorter timescales of memory, and to small-sized and rather simple environments (Burgess, 2006; Burgess, Becker et al., 2001). Comparing subjects being prone to either allocentric or egocentric navigation strategies, and learning the same virtual environment during light and during darkness could further help to elucidate the neural substrates of egocentric vs. allocentric navigation and memory.

4.4. Differential contributions of PHC and HC to spatial memory

We could not observe increase of HC activity during learning (early trials) or retrieval (late trials) of the virtual maze, suggesting that the HC is not involved in egocentric memory formation. However, moving along the corridors and internally reciting the alphabet possibly may have recruited the HC to a similar degree as our predictor DECIDE. Accordingly, we cannot completely rule out that the HC may be significantly engaged during egocentric memory formation. Nevertheless, only our experimental condition DECIDE demanded egocentric memories. Although negative findings in functional imaging need to be considered with caution, together with our recent lesion study (Weniger & Irle, 2006) these results would be compatible with a predominant role of the PHC in egocentric memory.

Evidence from other human studies also points to differential contributions of the HC and PHC to visuo-spatial representation and memory formation. Single case studies investigating humans with relatively selective bilateral HC damage suggest that the HC has a greater involvement in allocentric than egocentric spatial memory (Holdstock et al., 2000; King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002; Spiers, Burgess, Hartley, et al., 2001). Accordingly, neuroimaging studies investigating healthy humans in virtual environments suggest that the HC is rather involved in route learning and recall from survey perspective (Burgess, Maguire, & O'Keefe, 2002; Burgess, Maguire, Spiers, & O'Keefe, 2001; Hartley, Maguire, Spiers, & Burgess, 2003; Maguire, Burgess et al., 1998; Maguire, Frackowiak, & Frith, 1997; Maguire, Frackowiak et al., 1996; Mellet et al., 2000; Shelton & Gabrieli, 2002; Wolbers & Büchel, 2005).

4.5. General pattern of cortical activity during virtual maze learning

Current models emphasize a network of posterior parietal and temporal, retrosplenial/cingular and premotor cortices for the spatial representation and memory of extrapersonal events. FMRI studies frequently reported parietal cortex activations in topographic tasks, although to a larger degree in tasks demanding position judgments when compared with tasks demanding landmark recognition (Aguirre & d'Esposito, 1997; Aguirre, Detre, Alsop, & D'Esposito, 1996; Aguirre, Zarahn, & D'Esposito, 1998b; Burgess,

Becker et al., 2001; Burgess, Maguire er al., 2001; Epstein et al., 2003; Maguire, Frackowiak, & Frith, 1997; Zaehle et al., 2007). Activation of the entire length of the parieto-occipital sulcus and the retrosplenial cortex may be indicative for episodic and autobiographical memory processes (Burgess, Becker et al., 2001; Maguire, 2001; Maguire et al., 1997). Activation of posterior temporal and temporo-occipital cortices is regularly observed in allocentric navigation tasks (Aguirre & D'Esposito, 1997; Aguirre et al., 1996; Burgess, Maguire, Spiers, & O'Keefe, 2001; Maguire et al., 1997) and interpreted as reflecting object memory. Our results fit well into the present knowledge and confirm the importance of the proposed cortical network for the generation of spatial representation and memory. However, our results also strongly indicate that the cortical networks processing allocentric and egocentric spatial information are highly overlapping. The PHC may be seen as a kind of bottle-neck structure, enabling the construction of a global and comprehensive representation of spatial environments and to promote the construction of stable cognitive maps by translating between egocentric and allocentric frames of memory.

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