



Egocentric spatial learning in schizophrenia investigated with functional magnetic resonance imaging [☆]



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ABSTRACT

Psychotic symptoms in schizophrenia are related to disturbed self-recognition and to disturbed experience of agency. Possibly, these impairments contribute to first-person large-scale egocentric learning deficits. Sixteen inpatients with schizophrenia and 16 matched healthy comparison subjects underwent functional magnetic resonance imaging (fMRI) while finding their way in a virtual maze. The virtual maze presented a first-person view, lacked any topographical landmarks and afforded egocentric navigation strategies. The participants with schizophrenia showed impaired performance in the virtual maze when compared with controls, and showed a similar but weaker pattern of activity changes during egocentric learning when compared with controls. Especially the activity of task-relevant brain regions (precuneus and posterior cingulate and retrosplenial cortex) differed from that of controls across all trials of the task. Activity increase within the right-sided precuneus was related to worse virtual maze performance and to stronger positive symptoms in participants with schizophrenia. We suggest that psychotic symptoms in schizophrenia are related to aberrant neural activity within the precuneus. Possibly, first-person large-scale egocentric navigation and learning designs may be a feasible tool for the assessment and treatment of cognitive deficits related to self-recognition in patients with schizophrenia.

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1. Introduction

Currently, human spatial navigation is modeled as depending on two different spatial processing modes. First, *allocentric spatial learning* is based on memorizing prominent and salient landmarks (“places”) within an environment and may be associated with episodic memory in the context of spatial navigation. Second, *egocentric spatial learning* integrates 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 (O’Keefe and Nadel, 1978). Typically, egocentric memory of a large-scale space is induced by kinesthetic sensory information as well as by eye- and head-centered representation of visual space (Andersen et al., 1985).

Allocentric representation of space is considered to depend mainly on medial temporal cortices (Burgess et al., 2001). On the other hand,

egocentric representation of space is mainly modulated by parietal association cortices and subcortical regions, especially the striatum (Burgess et al., 2001; Maguire et al., 1998; Iaria et al., 2003; Etchamendy and Bohbot, 2007). Studies of our group using the same virtual maze task as the present study demonstrated egocentric memory deficits in patients with parietal cortex abnormalities (Weniger et al., 2009, 2011, 2012). Specifically, the role of the precuneus may be seen in gathering an imaginable representation of the world around and within us, thus enabling a continuous perspective of the organism relative to its environment (Gusnard and Raichle, 2001). Accordingly, the precuneus was shown to be activated during tasks requiring visuospatial and motor imagery, episodic memory retrieval, and self-processing operations (Cavanna and Trimble, 2006). fMRI studies have further pointed out that activation of the parietooccipital sulcus, posterior cingulate and retrosplenial cortex (PCRS) and parahippocampal cortex is indicative of large-scale spatial memory (Maguire et al., 1998; Aguirre et al., 1996; Weniger et al., 2010).

Up to now there are only very few behavioral studies on spatial navigation and memory formation in first-person large-scale virtual reality environments in schizophrenia. Studies investigating the neural underlying of first-person large-scale egocentric spatial learning in schizophrenia are lacking. Four behavioral studies so far agree that individuals with schizophrenia are substantially impaired in allocentric spatial learning (Hanlon et al., 2006; Weniger and Irle,

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2008; Landgraf et al., 2010; Folley et al., 2010), being considered a form of hippocampus-dependent memory deficit. On the other hand, egocentric spatial learning in schizophrenia may be less impaired (Weniger and Irlle, 2008; Landgraf et al., 2010). A previous study of our group investigated a mixed sample of schizophrenia patients (paranoid, disorganized, and undifferentiated subtype) without extrapyramidal motor symptoms and rather mild positive symptoms in egocentric virtual maze learning (Weniger and Irlle, 2008). Many of these patients experienced their first episode. We observed mainly spared egocentric learning in these individuals, suggesting that egocentric strategy use is not impaired in schizophrenia patients with very short disorder duration and weak positive symptoms.

In our previous studies and the present one, we used a computer-simulated first-person virtual reality environment in order to simulate navigation in a large-scale space. The virtual maze does not include any landmarks and all intersections appear identical when approached from different directions. Accordingly, the maze forces subjects to use egocentric navigation strategies at the beginning of the task, until enough egocentric information has been gathered and stored to allow possible construction of an allocentric mental survey perspective. There is ample evidence that healthy persons have individual preferences for navigation strategy use, and that these preferences may shift with practice (Iaria et al., 2003; Etchamendy and Bohbot, 2007).

Individuals with schizophrenia were shown to be impaired in recognizing their own actions as being caused by themselves (Franck et al., 2001), and these deficits are associated with positive schizophrenia symptoms (Waters and Badcock, 2010). Functional imaging studies have shown that parietal cortices, being recruited during egocentric navigation and memory formation (Burgess et al., 2001; Maguire et al., 1998; Weniger et al., 2010), are also recruited during imagination of one's own actions or movements (Cavanna and Trimble, 2006; Ruby and Decety, 2001; Farrer and Frith, 2002). The rationale of the present study was to establish our virtual maze task as an experimental paradigm to investigate the neural underlying of both positive symptoms and related deficits in self-recognition and experience of agency in schizophrenia. Navigating in a virtual environment solely by use of egocentric processes (i.e., imagined head and whole body movements and gaze motion) demands self-representation and self-recognition and motor imagery and experience of agency, all being crucial

domains of positive psychopathology in schizophrenia (Waters and Badcock, 2010). Virtual environments have the advantage to simulate real life surroundings, and may be a feasible tool for the assessment and treatment of clinically relevant cognitive deficits in individuals with schizophrenia. Specifically, schizophrenia symptoms reflect difficulties in social interaction and are affected by the social context, and virtual environments may allow controlling variables representing the social environment and social interactions (Freeman, 2008).

In the present investigation, 16 inpatients with schizophrenia and prominent positive symptoms and 16 matched healthy comparison subjects were scanned with functional magnetic resonance imaging (fMRI) while navigating in a virtual maze. We hypothesized that participants with schizophrenia show impaired virtual maze learning and impaired recruitment of brain regions during egocentric learning, and that stronger positive symptoms would be related to worse task performance and aberrant activity changes during egocentric learning.

2. Methods

2.1. Participants

The sample comprised 16 inpatients (5 women) with schizophrenia consecutively admitted to the Psychiatric Hospital of the University of Göttingen (Table 1). Patients fully met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* for a lifetime diagnosis of schizophrenia on the basis of interviews with the *Structured Clinical Interview for DSM-IV (SCID)* (Wittchen et al., 1997). Patients with a history of neurological diseases or comorbid mental disorders (SCID) were excluded. Patients were assessed within 3 weeks after admission to the hospital when they were in a clinically stable phase. All patients were on antipsychotic medication.

The participants with schizophrenia were compared with 16 healthy controls (6 women) recruited for the study by public advertisement (Table 1). Only participants without a history of neurological or psychiatric disorder (as assessed by the SCID) were studied. Control subjects were paid for their participation and matched participants with schizophrenia in terms of age and years of education on a group-level basis. Data of control participants are included in a

Table 1
Clinical characteristics of all participants.

Characteristics ^a	Healthy controls (n = 16)	Participants with schizophrenia (n = 16)	Statistic	P
Age, year	26.3 ± 5.5	29.5 ± 6.8	$t(30) = -1.47$	0.153
Education, year	14.6 ± 3.2	13.3 ± 2.7	$t(30) = 1.30$	0.210
Handedness, right:left	16:0	14:2		0.484 ^b
Sex, female:male	6:10	5:11	$\chi^2 = 0.1$	0.710
Disorder duration, year		5.3 ± 5.7		
Previous hospitalizations, no.		2.6 ± 3.2		
First episode, no. (%)		4 (25%)		
DSM-IV subtype, no (%)				
Paranoid		15 (94%)		
Undifferentiated		1 (6%)		
SAPS/SANS: positive symptoms		2.4 ± 0.9		
SAPS/SANS: negative symptoms		2.1 ± 0.6		
SAPS/SANS: disorganized symptoms		1.9 ± 0.5		
Global assessment of functioning		50.6 ± 8.5		
Extrapyramidal motor symptoms ^c (none:mild:moderate:severe)		16:0:0:0		
Antipsychotic dosage, mg ^d		1038 ± 662		

DSM-IV = 4th edition of the Diagnostic and Statistical Manual of Mental Disorders; SAPS = Scale for the assessment of positive symptoms; SANS = Scale for the assessment of negative symptoms. Summary scores (means) were calculated according to Höschel and coworkers (Höschel et al., 1998); positive symptoms – hallucinations and delusions; negative symptoms – avolition, anhedonia, affective flattening and alogia; disorganized symptoms – bizarre behavior, positive thought disorder and attention.

^a Table values are given as mean ± SD unless indicated otherwise.

^b Fisher's exact test.

^c Symptoms included: akathisia, abnormal involuntary movements, wrist rigidity, tremor, dystonia, and tardive dyskinesia.

^d Chlorpromazine equivalent dose (Bezchlibnyk-Butler and Jeffries, 2001; Gardner et al., 2010; Jahn and Mussgay, 1989; Woods, 2003) at testing. Second generation antipsychotics were used throughout.

previous study on egocentric virtual maze learning (Weniger et al., 2010).

All participants were given a complete description of the study and 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. Clinical and neuropsychological investigation

Positive and negative symptoms were assessed by using the *Scale for the Assessment of Positive Symptoms (SAPS)* (Andreasen, 1984) and the *Scale for the Assessment of Negative Symptoms (SANS)* (Andreasen, 1983). Current psychosocial functioning was rated on the *SCID (DSM-IV) Global Assessment of Functioning Scale (GAF)*. Intellectual and mnemonic functions were assessed by use of subtests of the *Wechsler Adult Intelligence Scale-Revised (WAIS-R)* (Tewes, 1991) and the *Wechsler Memory Scale-Revised (WMS-R)* (Härting et al., 2000).

2.3. The virtual environment

The virtual environment was three-dimensional, fully colored and textured and presented a first-person view (Fig. 1). Subjects wore a head mounted display (Resonance Technology, Northridge, CA, USA) and controlled their movements with a joystick (Current Designs, Philadelphia, PA, USA).

The maze comprised six points of two-way intersections and seven cul-de-sacs containing pots. Only one of these pots contained money (goal). Subjects could move through the maze by pushing the joystick forward once to move to the next intersection or cul-de-sac, respectively. Once having arrived at an intersection or a cul-de-sac, subjects could freely turn around using left-right movements of the joystick. When subjects headed a corridor they could push the joystick forward once to move on. All intersections appeared identical when approached from different directions.

Five trials were applied. Trials were discontinued if the subject found the goal or after 5 min had expired, respectively. In each trial, the subjects started at the same location and then were instructed to find the goal which remained in the same location across trials. The subjects were not able to see the target or the survey perspective from the starting position or from other vantage points in the environment. To ensure that the subjects would restrict navigationally relevant cognition to the time periods spent at intersections, we instructed the subjects to internally recite the alphabet while moving along the corridors.

Errors were defined as visiting cul-de-sacs or intersections not lying within the direct way to the goal. Repetitive errors were counted when a participant repeated the same error in a given trial. Furthermore, the

time needed to find the goal and the number of unsuccessful trials (failure to find the goal in the required time of 5 min) were recorded. After finishing the task, the participants completed a questionnaire indicating what kind of navigation strategies they used. The participants were asked whether they tried to memorize their imagined head, body and gaze motion at different decision or time points of the virtual environment (egocentric cues) or whether they tried to construct a kind of map of the virtual environment in their mind (survey perspective).

2.4. Image acquisition

Data were acquired using a 3 Tesla Siemens Magnetom Trio (Siemens, Erlangen, Germany) and an 8 channel head coil. An anatomical T₁-weighted MR data set covering the whole head at 1 mm³ 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 T₂-sensitive gradient-echo EPI technique for the detection of blood oxygenation level dependent (BOLD) changes with an in-plane resolution of 2 mm² was used (TR: 2000 ms, TE: 36 ms, flip angle: 70°, slice plane = transversal, acquisition matrix: 96 × 128, 22 sections, interleaved ascending scanning order, 4 mm section thickness, lower bound of the acquisition field adjusted to fit the lower bound of the temporal lobe).

2.5. Image analysis

The acquired images were preprocessed and analyzed using BrainVoyager QX version 1.9× (Brain Innovation B.V.) and the *NeuroElf toolbox* Version 0.9c (copyright 2010, 2011 by J. Weber, <http://neuroelf.net>) run under *Matlab 7.8.0* (Mathworks, Natick, MA, USA). For VOI-analysis β -values were extracted and subjected to statistical analyses with *SPSS Statistics (Predictive Analysis Software PASW, Version 17)*.

The T₁-data sets were transformed to standard Talairach space. Pre-processing of T₂-data included 3D motion correction, slice scan time correction, linear trend removal, high pass filtering, interpolation to a resolution of 3 mm³, spatial smoothing with a Gaussian kernel (full width at half maximum) of 5 mm³, coregistration to the original T₁-data sets and transformation into Talairach space. Statistical analysis was restricted to the cerebrum in standard Talairach space.

2.5.1. Predictor

Pilot experiments indicated that subjects started thinking about directional choices when the intersection and its openings became visible and during the beginning of the time spent at intersections. Therefore, we defined the predictor “DECIDE” for the General Linear

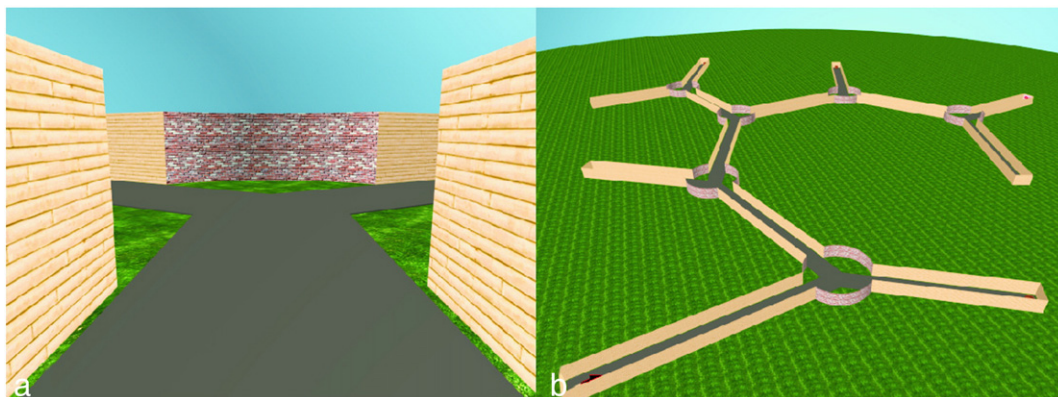


Fig. 1. Subject view (a) and aerial view (b) of the virtual maze. Actual stimuli were in full color.

Model (GLM) as the time period (3 s) before arriving at intersections and at the onset (= first sixth) of time spent at intersections. A detailed description of the predictor has been published previously (Weniger et al., 2010).

Using the multi-subject random effects approach of the GLM with the hemodynamic response function as suggested by Boynton et al. (1996) we calculated statistical maps of z-transformed β -values of DECIDE for trials 1 and 2. In the following “BASELINE” refers to the automatically calculated mean confound of the GLM (b_0). Trials 3–5 were not part of “BASELINE”.

The virtual maze did not contain any landmarks, i.e. allocentric cues. Accordingly, the maze could only be learned in an egocentric frame of memory. However, egocentric frames of memory may be transformed into an allocentric frame by mentally constructing a survey perspective. As the majority of healthy subjects succeed to find the goal during trials 1 or 2 we suggest that these trials may exclusively or at least predominantly represent egocentric learning (Weniger et al., 2010). Late trials of the task may be solved using egocentric or allocentric (survey) strategies, or both. In order to assess egocentric memory formation, the whole-brain analysis (Section 2.5.2) was restricted to trials 1 and 2. However, the volume-of-interest (VOI) analysis (Section 2.5.3) was computed for each trial separately in order to elucidate possible BOLD signal differences between participants with schizophrenia and controls in task-relevant regions across trials.

2.5.2. Whole-brain analysis

Due to different types of analyses and to account for adequate sensitivity of each test, we applied differing statistical thresholds given with $\alpha_{\text{uncor.}}$ (uncorrected). All maps were corrected for multiple comparisons with $\alpha_{\text{cor.}} = 0.05$ using cluster thresholding with k functional (3 mm^3) voxels. k was estimated using random field statistics (Forman et al., 1995).

ANOVAs were calculated with DECIDE > BASELINE ($\alpha_{\text{uncor.}} = 0.0001$, $k = 4$) for controls and participants with schizophrenia, respectively, and for the direct comparison of both groups (controls > participants with schizophrenia; $\alpha_{\text{uncor.}} = 0.001$, $k = 7$). The latter map was then masked with a combined map of the contrast DECIDE > BASELINE for each the control group and participants with schizophrenia ($\alpha_{\text{uncor.}} = 0.05$, $k = 57$), being used for further analysis. Using linear regression we calculated three maps with the β -values of DECIDE as dependent variable and the positive, negative and disorganized symptom score (SAPS and SANS) as covariate, respectively ($\alpha_{\text{uncor.}} = 0.001$, $k = 9$). The resulting t -maps were then transferred to a map of correlation coefficients (r). These were then masked with a map of the contrast DECIDE > BASELINE for participants with schizophrenia ($\alpha_{\text{uncor.}} = 0.05$, $k = 57$).

Analyses were restricted to positive t -values and masking procedures were performed to ensure only regions being task-positive are reported. For anatomically defined regions containing more than one local maximum only the maximum with the highest t -value is reported.

2.5.3. Volume-of-interest (VOI) analysis

For the VOI analysis we analyzed regions having been shown to be involved in spatial learning, i.e. precuneus, PCRS, hippocampus, parahippocampal cortex, caudate nucleus and putamen. Based on the statistical map of the control group during trials 1 and 2, local maxima within these regions defined the VOIs. We restricted the analysis to statistical significant voxels lying within a sphere of 6 mm around the local maximum. Regarding the hippocampus, VOIs were drawn upon an averaged T_1 -dataset of all subjects. The protocol of Pruessner et al. (2000) was used to guide tracing. For each VOI the mean z-transformed β -values of DECIDE for each subject and trial were extracted and a two-sided 2 (group) \times 5 (trial) repeated measures ANOVA ($\alpha = 0.05$) was calculated. Post hoc analyses included two-sided 5 (trial) repeated measures ANOVAs for each group and VOI, respectively.

2.6. Statistical analysis of behavioral data

T -tests and Fisher's exact tests were applied to compare differences between groups on virtual maze performance and clinical and demographic variables. Correlation and regression analyses were performed to examine the relationship between neural activity changes and virtual maze performance and clinical symptoms of participants with schizophrenia ($n = 16$). All analyses were two-tailed, and the alpha was defined as $P < 0.05$. Statistical computations were performed using SPSS Statistics (Predictive Analysis Software PASW, Version 17).

3. Results

3.1. Behavioral results

All study participants succeeded in navigating within the virtual maze, and none of them experienced side effects (i.e., simulator-sickness). Participants with schizophrenia committed significantly more errors and needed more time to solve the virtual maze compared with controls (Table 2). Accordingly, they performed significantly less successful trials (i.e. finding the goal in the allotted time of 5 min) compared with controls. However, participants with schizophrenia did not commit more errors in trials 1 and 2, being used for the whole-brain analysis (Table 2).

Participants with schizophrenia and controls did not differ with respect to navigation strategies. The most frequently reported navigation strategy was memorizing egocentric cues in controls (88%) and participants with schizophrenia (81%) (Table 2). Five controls and 8 participants with schizophrenia reported having tried to construct a survey perspective. However, none of these participants reported a complete shift from egocentric strategy use to the survey perspective in late trials of the task. Virtual maze performance parameters (as outlined in Table 2) did not differ significantly for participants reporting to have used ($n = 13$) or not used ($n = 19$) a survey perspective (t -tests; P -values > 0.20). The same is true when the errors performed in trials 3–5 were considered ($P = 0.355$).

Positive, negative and disorganized symptoms (SAPS and SANS; calculated according to Höschel et al. (1998) were entered into multiple regression analyses (method: stepwise; significance level for selecting variables: $\alpha = 0.05$). Considering participants with schizophrenia, positive symptoms significantly predicted performance on the virtual maze (total errors: $\beta = 0.51$; $t = 2.20$; $P = 0.045$; errors trials 1–2: $\beta = 0.58$; $t = 2.68$; $P = 0.018$), indicating worse performance of individuals with stronger symptoms. The other variables did not significantly improve the prediction, respectively.

3.2. Imaging results

3.2.1. Whole-brain analysis

Considering the control group, regions with significant BOLD-responses comprised bilateral superior parietal lobules, precuneus and left inferior parietal lobules, right postcentral gyrus and bilateral gray matter along the parietooccipital sulcus, right PCRS, left fusiform gyrus, and bilateral parahippocampal cortex (Table 3 and Figs. 2 and 3). Furthermore, the right superior and left inferior occipital gyri showed significant responses. The bilateral anterior insula, left anterior cingulate gyrus and right sided middle frontal gyrus showed clusters of voxels with significant values. Each right and left middle temporal gyri contained a significant cluster as well.

Both controls and participants with schizophrenia showed an overlap of regions involved in egocentric spatial learning, namely significant results within the bilateral precuneus, medial occipital regions and gray matter along the parietooccipital sulcus. However, a number of regions involved in the control group did not show significant signal increase in participants with schizophrenia, namely bilateral superior parietal

Table 2
Behavioral results.

Variable ^a	Healthy controls (n = 16) ^b	Participants with schizophrenia (n = 16)	Statistic	P
WAIS-R, Similarities	23 ± 5	24 ± 5	t(25) = -0.23	0.812
WAIS-R, Block Design	38 ± 7	28 ± 9	t(25) = 1.52	0.141
WMS-R, Logical Memory I	32 ± 7	28 ± 9	t(25) = 1.31	0.202
WMS-R, Logical Memory II	28 ± 8	23 ± 9	t(25) = 1.50	0.147
WMS-R, Visual Reproduction I	36 ± 3	35 ± 4	t(25) = 0.25	0.808
WMS-R, Visual Reproduction II	34 ± 5	31 ± 8	t(25) = 0.89	0.384
WMS-R, Verbal Span forward	9 ± 2	8 ± 2	t(25) = 0.78	0.444
WMS-R, Verbal Span backward	8 ± 2	7 ± 3	t(25) = 0.52	0.605
WMS-R, Visual Span forward	10 ± 3	9 ± 2	t(25) = 0.61	0.547
WMS-R, Visual Span backward	10 ± 1	9 ± 2	t(25) = 2.34	0.027
Virtual maze				
Total errors	11.4 ± 6.0	17.0 ± 7.6	t(30) = -2.30	0.030
Total time, s	1090 ± 163	1237 ± 229	t(30) = -2.10	0.044
Successful trials, no. ^c	3.6 ± 1.0	2.6 ± 1.4	t(30) = 2.20	0.036
Errors, trials 1–2	7.4 ± 3.2	9.2 ± 3.1	t(30) = -1.56	0.128
Repetitive errors, trials 1–2 ^d	2.9 ± 2.8	3.9 ± 2.9	t(30) = -1.10	0.323
Navigation strategy, no. (%)				
Egocentric cues	14 (88)	13 (81)		1.000 ^e
Survey perspective	5 (31)	8 (50)		0.473 ^e
None	1 (6)	1 (6)		1.000 ^e

Significant differences are given in boldface type. WAIS-R: Wechsler Adult Intelligence Scale-Revised; WMS-R: Wechsler Memory Scale-Revised.

^a Table values are given as mean ± SD unless indicated otherwise.

^b Eleven controls completed the WAIS-R and the WMS-R.

^c The five trials were discontinued if the subject found the target or after 300 s had expired, respectively.

^d Repetitive errors were counted as repeatedly committed false decisions at the same intersection, which led away from the direct way to the goal.

^e Fisher's exact test.

lobules, right postcentral gyrus, right superior occipital gyrus, right PCRS, left posterior cingulate gyrus, bilateral middle temporal gyri, right inferior temporal gyrus, right middle frontal gyrus and left anterior cingulate gyrus. Altered lateralization was also present in participants with schizophrenia, i.e. left-sided involvement of the PCRS, and right-sided involvement of the cuneus, inferior parietal lobule and inferior occipital gyrus. The right-left ratio of the precuneus as found in control subjects was altered in participants with schizophrenia in favor of the right hemisphere (Table 3 and Figs. 2 and 3).

Regarding the comparison of controls and participants with schizophrenia, there were no regions with significantly stronger BOLD-response in participants with schizophrenia. Mainly right-sided regions

contained significant clusters with stronger BOLD-signal increase in the control group, including the inferior parietal lobule, middle frontal gyrus, superior and middle occipital gyrus, precuneus, and caudate nucleus (Table 4). A further cluster was located in the region of the left parahippocampal cortex. PCRS and middle temporal gyri contained clusters bilaterally.

3.2.1.1. Correlation and regression analyses. One cluster located within the right-sided precuneus (Talairach coordinates of maximum: 18 -61 40 (X Y Z), 13 functional voxels) correlated significantly ($r = 0.84$) with the positive symptom score (SAPS) of participants with schizophrenia, indicating stronger activation in individuals with stronger

Table 3
Local maxima of increased activity during egocentric learning.

Anatomical description	Healthy controls (n = 16)		Participants with schizophrenia (n = 16)	
	X Y Z (t-value/cluster size)		X Y Z (t-value/cluster size)	
	Right	Left	Right	Left
Anterior insula	27 23 7 (9.34/28)	-30 23 4 (13.80/40)	27 20 7 (7.36/9)	
Anterior cingulate gyrus		-9 -1 46 (9.04/52)		
Middle frontal gyrus	36 -7 43 (8.38/45)			
Precentral gyrus	27 -10 49 (8.13/19)	-33 -16 49 (8.52/35)		-30 -10 52 (5.78/5)
Postcentral gyrus	51 -22 40 (5.70/4)			
Posterior cingulate gyrus		-12 -22 43 (7.56/19)		
Inferior parietal lobule		-30 -37 49 (8.73/43)	36 -40 46 (7.59/13)	
Parahippocampal cortex	21 -46 -8 (12.89/124)	-18 -43 -5 (10.82/68)		-18 -49 -2 (7.37/16)
Superior parietal lobule	21 -52 43 (10.63/50)	-24 -58 37 (6.29/5)		
Posterior cingulate and retrosplenial cortex	24 -58 19 (12.46/75)			-18 -58 7 (6.91/4)
Middle temporal gyrus	39 -58 10 (9.81/9)	-36 -58 4 (10.22/47)		
Fusiform gyrus		-18 -61 -8 (11.92/117)	24 -55 -8 (10.91/139)	-27 -61 -11 (9.78/52)
Inferior temporal gyrus	45 -64 -2 (9.27/7)			
Precuneus	18 -79 40 (10.38/10)	-18 -58 22 (10.01/15)	24 -73 28 (10.29/108)	-27 -70 22 (6.76/10)
Cuneus		-18 -76 25 ^a (13.77/435)	12 -67 7 ^b (8.89/5)	
Inferior occipital gyrus		-39 -70 -8 (11.66/46)	33 -82 -5 (7.11/8)	
Superior occipital gyrus	24 -82 22 (16.42/17)			
Middle occipital gyrus	15 -88 16 (21.68/1882)	-30 -76 19 (10.32/7)	12 -91 13 (10.77/160)	-9 -94 13 (8.76/67)

X Y Z correspond to the three dimensions of Talairach coordinates. t-values refer to the peak voxel. Cluster sizes are given as numbers of functional voxels (3 mm³). For statistical thresholds see Methods, 2.4.1.

^a Local maximum is located within the parietooccipital sulcus.

^b Local maximum is located within the calcarine sulcus.

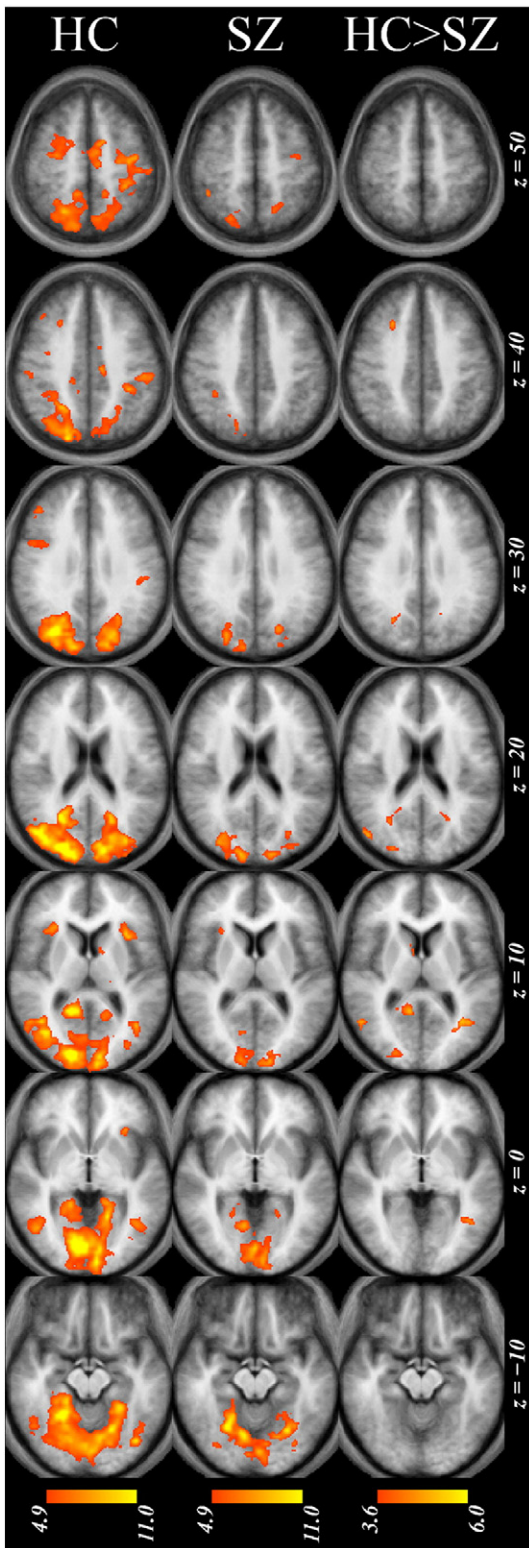


Fig. 2. Statistical maps of healthy controls (HC) (left), participants with schizophrenia (SZ) (middle) and HC > SZ (right), overlaid on transversal slices of an averaged T₁-dataset of all participants. Color bars and figures refer to the range of *t*-values. *z* corresponds to the Talairach coordinate. The left hemisphere is represented on the right.

positive symptoms (Fig. 4). Correlation analyses using the mean β -values of DECIDE revealed a positive relation between right-sided precuneus activation and errors committed in trials 1 and 2 ($r = 0.61$; $P = 0.012$). However, the correlation between right-sided precuneus activation and positive symptom score remained significant ($r = 0.77$;

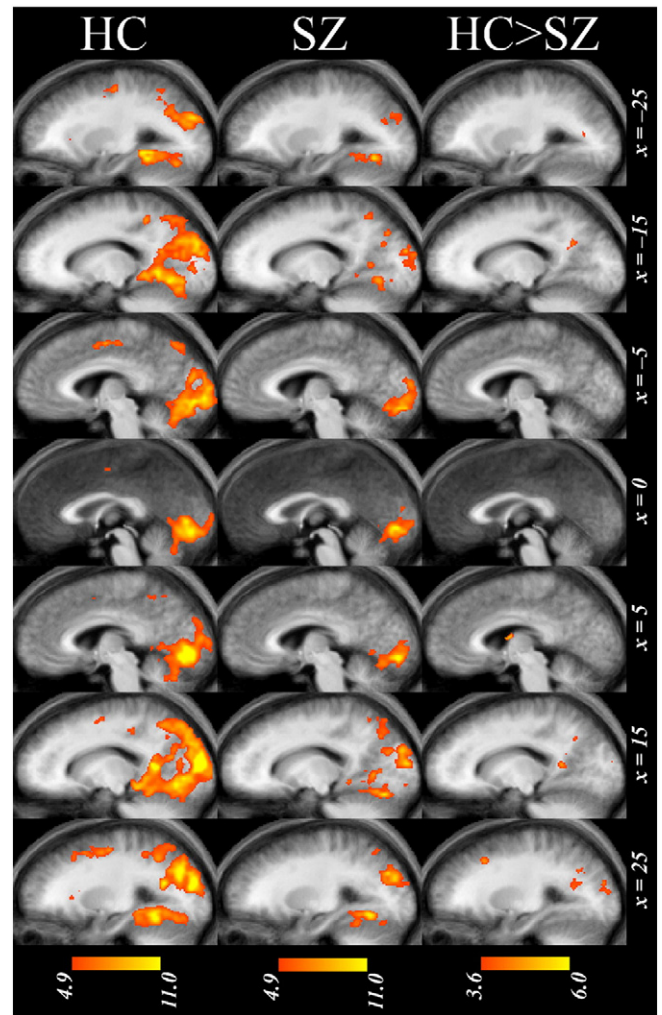


Fig. 3. Statistical maps of healthy controls (HC) (left), participants with schizophrenia (SZ) (middle) and HC > SZ (right), overlaid on sagittal slices of an averaged T₁-dataset of all participants. Color bars and figures refer to the range of *t*-values. *x* corresponds to the Talairach coordinate. Slices proceed from the left hemisphere (top) to the right hemisphere (bottom).

$P = 0.001$) in a partial correlation controlling for the errors, underlining an independent relation between right precuneus activation and positive symptoms. Furthermore, the relation between positive symptoms and errors (see Section 3.1) did not survive a partial correlation controlling for right precuneus activation ($r = -0.04$; $P = 0.896$), again

Table 4

Local maxima of activity change differences: controls > participants with schizophrenia.

Anatomical description	X Y Z (<i>t</i> -value/cluster size)	
	Right	Left
Middle frontal gyrus	24 20 40 (4.64/7)	
Caudate nucleus	3 -1 13 (5.13/12)	
Parahippocampal cortex		-36 -40 -5 (4.45/8)
Posterior cingulate and retrosplenial cortex	9 -49 10 (4.97/24)	-18 -55 22 (4.66/11)
Precuneus	24 -61 31 (4.60/9)	
Middle temporal gyrus	48 -58 10 (4.71/20)	-39 -58 7 (5.94/49)
Inferior parietal lobule	45 -70 19 (4.69/9)	
Superior occipital gyrus	36 -76 25 (4.32/10)	
Middle occipital gyrus	21 -85 10 (4.38/27)	

X Y Z correspond to the three dimensions of Talairach coordinates. *t*-values refer to the peak voxel. Cluster sizes are given as numbers of functional voxels (3 mm³). For statistical thresholds see Methods, 2.4.1.

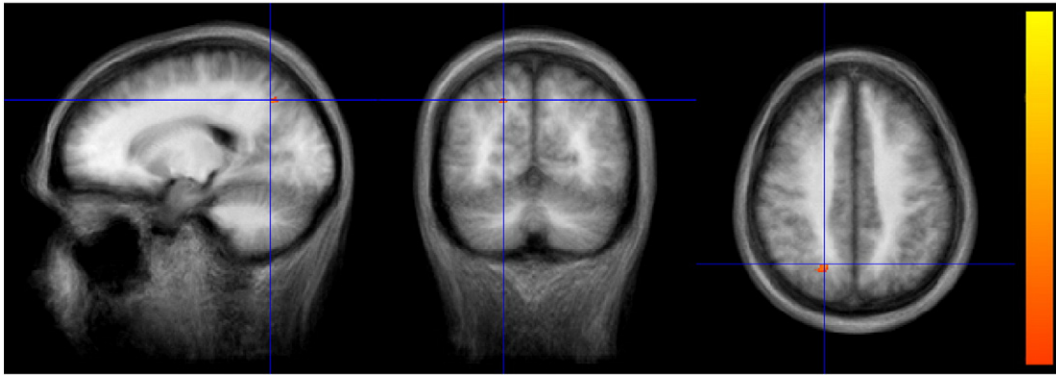


Fig. 4. Correlation of activity increase within the right precuneus with positive symptom strength (SAPS) of participants with schizophrenia ($\alpha_{\text{uncor.}} = 0.001$, $k = 9$, $\alpha_{\text{cor.}} = 0.05$). Sagittal (left), coronal (middle) and transversal (right) view. The color bar refers to a statistical range of $r = 0.74$ (orange) and $r = 0.95$ (yellow). Higher positive symptom strength was related to stronger activity within the right precuneus. The left hemisphere is represented on the right.

indicating an independent relation between right precuneus activation and positive symptoms and virtual maze errors.

Positive, negative and disorganized symptoms (SAPS and SANS) were entered into multiple regression analyses (method: stepwise; significance level for selecting variables: $\alpha = 0.05$). The positive symptom score significantly predicted the mean β -values of DECIDE of the cluster within the right-sided precuneus ($\beta = 0.86$; $t = 6.20$; $P < 0.001$), indicating stronger activation in participants with schizophrenia with stronger positive symptoms. The negative and disorganized symptom score did not significantly improve the prediction.

No clusters with significant activity change were found for the negative and disorganized symptom scores.

3.2.2. Volume-of-interest (VOI) analysis

Based upon the results in the control group, we could define the following VOIs (with the number of functional voxels): right-sided (31) and left-sided (22) parahippocampal cortex, right-sided PCRS (16), and right-sided (10) and left-sided (15) precuneus.

3.2.2.1. Comparison of participants with schizophrenia and controls. A significant effect of *group* could be found for the extracted mean β -values across trials for the left parahippocampal cortex ($F(1;30) = 6.23$, $P = 0.01$), the right PCRS ($F(1;30) = 11.01$, $P = 0.002$) and for the left precuneus ($F(1;30) = 9.16$, $P < 0.001$), indicating higher signals in control subjects, respectively.

A significant effect of *trial* could only be found for the right hippocampus ($F(4;120) = 3.27$, $P = 0.01$). Post hoc analyses (repeated measures ANOVAs for each of the groups) revealed a significant effect for the control group ($F(4;60) = 3.53$, $P = 0.012$), indicating a decrease of β -values across trials. Comparisons of consecutive trials revealed a significant decrease ($P = 0.003$) from trial 3 (mean β -value: 0.10 ± 0.48) to trial 4 (mean β -value: -0.21 ± 0.64).

Significant *group* \times *trial* interactions (Fig. 5) could be found for the right PCRS ($F(4;120) = 3.39$, $P = 0.01$) and for the right ($F(4;120) = 3.58$, $P = 0.009$) and left ($F(4;120) = 2.91$, $P = 0.02$) precuneus. Post hoc analyses revealed higher mean β -values in controls when compared with participants with schizophrenia for trials 1–3 and 5 (right PCRS and left precuneus) or trial 3 (right precuneus), indicating stronger activity of control subjects, respectively.

3.2.2.2. Relationship with clinical symptoms. Positive, negative and disorganized symptoms (SAPS and SANS) were entered into multiple regression analyses (method: stepwise; significance level for selecting variables: $\alpha = 0.05$). The positive symptom score significantly predicted the mean β -values of the VOI within the right-sided precuneus ($\beta = 0.67$; $t = 3.33$; $P = 0.005$), indicating stronger activation in participants

with schizophrenia with stronger positive symptoms. The negative and disorganized symptom score did not significantly improve the prediction.

Regression models regarding all other VOI's were not significant.

3.3. Effects of medication

3.3.1. Antipsychotic medication

All multiple regression analyses (behavioral data, whole brain and VOI analysis; see Sections 3.1, 3.2.1.1, and 3.2.2.2) using positive, negative and disorganized symptom scores as predictors were repeated with antipsychotic dosage (chlorpromazine equivalents) as further predictor. The results remained unchanged. Antipsychotic dosage did not significantly predict the amount of errors in the virtual maze, and did not significantly predict activity changes within the right-sided precuneus during virtual maze learning (whole brain and VOI analysis).

3.3.2. Sedatives

Seven participants with schizophrenia received small doses of benzodiazepines or zolpidem. These patients did not differ from those receiving no sedatives ($n = 9$) with respect to virtual maze performance or neuropsychological performance (P -values > 0.30).

3.4. Influence of cognitive performance

Participants with schizophrenia showed deficits in visual working memory (WMS-R; Visual span backward) when compared with controls (Table 2). All multiple regression analyses (behavioral data, whole brain and VOI analysis; see Sections 3.1, 3.2.1.1, and 3.2.2.2) using positive, negative and disorganized symptom scores as predictors were repeated with Visual span backward scores as further predictor, respectively. Visual span backward scores did not significantly predict the amount of errors in the virtual maze, and did not significantly predict activity changes within the right-sided precuneus during virtual maze learning (whole brain and VOI analysis). The same results were obtained when the GAF score (see Table 1) was added as further predictor.

4. Discussion

4.1. Decreased activation during egocentric learning in schizophrenia

Though the pattern of brain regions recruited during virtual learning was similar for controls and participants with schizophrenia (precuneus, cuneus, parietooccipital sulcus, PCRS and parahippocampal cortex), some essential differences emerged. Comparing controls and participants with

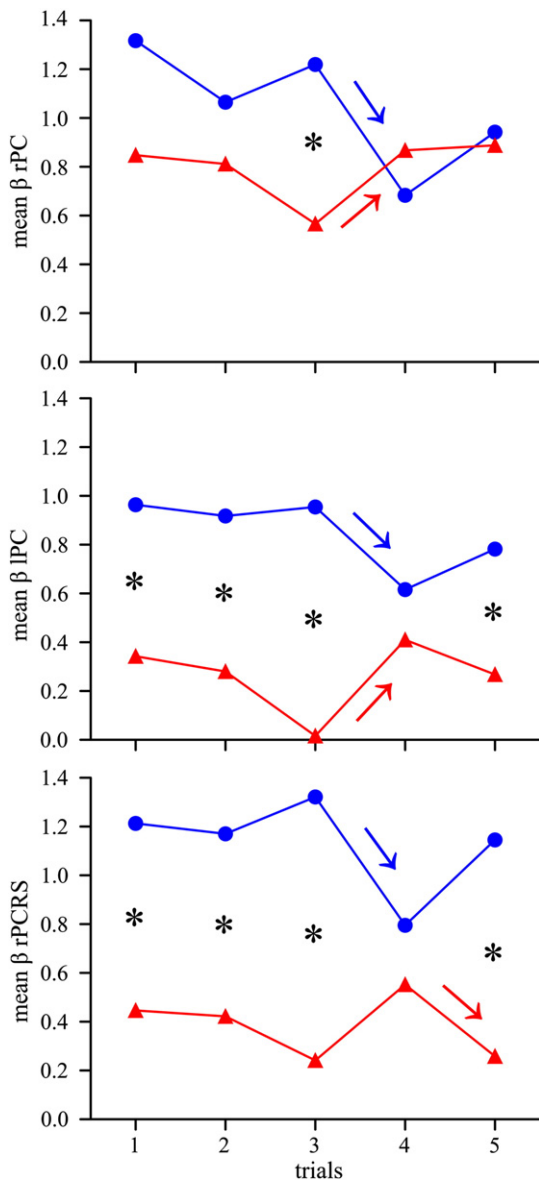


Fig. 5. z-transformed mean β -values of the right precuneus (rPC, top), the left precuneus (IPC, middle) and the right posterior cingulate and retrosplenial cortex (PCRS, bottom) for each of the five trials of the virtual maze. \blacktriangle = participants with schizophrenia; \bullet = control subjects. * = significant difference (*t*-test; $P < 0.05$) between participants with schizophrenia and controls. \downarrow , \uparrow = significant difference (paired *t*-test; $P < 0.05$) between subsequent trials. Trials 3 and 4 of participants with schizophrenia (rPC) differed marginally significant ($P = 0.053$).

schizophrenia, controls yielded significantly stronger activation of task-relevant regions mainly in the right hemisphere, i.e. precuneus, inferior parietal lobule, caudate nucleus and middle frontal gyrus. The PCRS of controls was significantly stronger activated in both hemispheres. Previous research has indicated that activity increases during virtual maze learning in the precuneus, postcentral gyrus and retrosplenial cortex are bilateral, but more pronounced on the right side (Weniger et al., 2010).

Functional imaging studies investigating spatial navigation and memory by using virtual environments have confirmed the importance of parietal cortices for egocentric navigation and memory formation (Burgess et al., 2001; Maguire et al., 1998; Weniger et al., 2010). Functional imaging studies have further pointed out that activation across the entire length of the parietooccipital sulcus, the parahippocampal cortex and the retrosplenial and posterior cingulate cortex is indicative for large-scale spatial memory (Burgess et al.,

2001; Maguire et al., 1998; Aguirre et al., 1996; Weniger et al., 2010; Maguire, 2001).

4.2. Precuneus activity, psychotic symptoms and egocentric learning in schizophrenia

Right-sided precuneus activity of participants with schizophrenia was significantly related to psychotic symptoms and to errors committed in trials 1 and 2, indicating stronger symptoms and more errors in individuals with stronger precuneus activation. Partial correlation analyses revealed an independent relation between precuneus activity and both psychotic symptoms and virtual maze errors.

Studies using voxel-based morphometry have shown that positive symptom strength of individuals with schizophrenia is related to insight impairments and gray matter deficits in the precuneus (Cooke et al., 2008; Morgan et al., 2010). Studies investigating the resting state activity in schizophrenia found aberrant functional connectivity correlations between the precuneus and positive symptom strength (Garrity et al., 2007; Lui et al., 2009). Tasks affording emotion discrimination and self-reflection have yielded hyperactivity of the region of the precuneus and PCRS in schizophrenia patients when compared with controls (Reske et al., 2009; Holt et al., 2011). Abnormally high metabolic rates and blood flow of these regions in schizophrenia patients have been reported as well (Andreasen et al., 1997; Haaznedar et al., 1997).

The link between hyperactivity of posterior cortico-limbic regions in schizophrenia and psychotic symptoms may be found in an altered glutamatergic neurotransmission. Deakin and co-workers (Deakin et al., 2008) found a ketamine-induced activity increase in the precuneus and PCRS of healthy volunteers, which was related to the amount of evoked psychotic and dissociative symptoms. Ketamine is long known to produce psychotic as well as dissociative states (Corlett et al., 2011), and recent studies underline the potential of ketamine to modulate the experience of illusory body ownership and the sense of agency (Morgan et al., 2011; Moore et al., 2012). Animal studies have demonstrated that ketamine application may cause excitotoxic damage of PCRS neurons (Olney and Farber, 1995). All these findings point to the possibility that aberrant structure and function of the precuneus/PCRS in schizophrenia, as well as psychotic symptoms and behavioral deficits related to these regions, may be partly influenced by a chronically pathological glutamatergic neurotransmission.

In a current study of our group (submitted for publication), we found that trauma-exposed patients with strong dissociation showed stronger activity within the precuneus while learning the virtual maze compared to patients with less dissociation. Inspection of individual data revealed that the mean β -values of participants with strong dissociation fell within the average range of control values, but not those of participants with less dissociation. Thus, participants with stronger dissociation showed a more normal precuneus activity during egocentric learning, in contrast to participants with less dissociation. These results are paralleled by the results of participants with schizophrenia: participants with strong psychotic symptoms showed increased precuneus activity within the range of controls, and participants with less psychotic symptoms fell below the range of controls.

Previous research has already indicated that trauma-related dissociative states are related to increased activity of the precuneus (Lanius et al., 2002). We have earlier suggested (Irle et al., 2007) that dissociation may be considered a pathological conscious state, and that both the resting state (default mode state) and the dissociative state may similarly recruit parietal cortices. Diverse structural abnormalities of parietal cortices (e.g., volumes larger or smaller compared to healthy controls) may be more prone to high levels of pathological dissociation and increased precuneus activity (Irle et al., 2007). The same may apply to psychotic symptoms in schizophrenia. Schizophrenia has been repeatedly related to various structural parietal cortex abnormalities (Shenton et al., 2001).

4.3. Mechanism of altered activity pattern during virtual maze learning in schizophrenia

Participants with schizophrenia did not only show weaker activity changes during virtual maze learning when compared with controls, but also showed a differing course of activation across trials. In contrast to control subjects, the activation of the precuneus and PCRS of participants with schizophrenia did not consistently decrease across trials.

First, it might be speculated that the abnormal activity pattern of precuneus and PCRS of participants with schizophrenia across trials emerged because they did not learn the maze completely during the first trials, i.e. committed more errors than controls during late trials of the task. In contrast, control subjects successfully learned the task within the first trials, resulting in no or very few errors during late trials. Thus, it seems possible that control subjects retrieved task memory during late trials of the task, whereas participants with schizophrenia still tried to learn the task. Both processes, egocentric learning and egocentric memory retrieval, may recruit different brain regions (Weniger et al., 2010; Wolbers and Büchel, 2005). However, an fMRI study investigating allocentric memory in a virtual environment found the precuneus being similarly activated during encoding and retrieval of spatial locations (Frings et al., 2006).

Second, the virtual maze performance of controls and participants with schizophrenia may have differed in late trials of the task with respect to egocentric and allocentric task representation. Basically, it is assumed that egocentric representation is restricted to shorter timescales of memory (Burgess, 2006), suggesting a translation of egocentric into allocentric frames of memory in late trials of the task. Healthy persons were shown to have individual preferences for navigation strategy use, and these preferences may shift with practice (Iaria et al., 2003; Etchamendy and Bohbot, 2007). However, there is also evidence that increasing practice may strengthen an egocentric strategy use, i.e. a habitual approach to the task (Iaria et al., 2003). Nevertheless, both egocentric and allocentric representation of space recruits a similar network of brain regions, i.e. the precuneus, PCRS, inferior parietal cortices and parahippocampal cortex (Maguire et al., 1998; Aguirre et al., 1996; Weniger et al., 2010; Neggers et al., 2006; Spiers and Maguire, 2007). The PCRS (Maguire, 2001) as well as the parahippocampal cortex (Weniger et al., 2010; Weniger and Irlé, 2006), having been proposed as pivotal structures for the translation between egocentric and allocentric frames of memory, showed relative hypoactivation in the schizophrenia patients of the present study.

Converging evidence has shown that the hippocampus is a key structure for allocentric navigation and memory formation (O'Keefe and Nadel, 1978; Iaria et al., 2003; Holdstock et al., 2000; King et al., 2002; Bohbot et al., 2004; Barry et al., 2006; Bohbot et al., 2007; Etchamendy et al., 2012). The whole-brain analysis of the present study did not reveal a significant cluster within the hippocampus, suggesting that allocentric processes were not prevalent during trials 1 and 2. However, control subjects showed activation of the right hippocampus during trial 3 and a significant right hippocampal signal decrease from trial 3 to trial 4, suggesting that they may have had successfully translated egocentric information into an allocentric survey perspective during trial 3.

In contrast to control subjects, participants with schizophrenia showed a flat signal course of the right hippocampus across trials (mean β -values for all trials < 0). Schizophrenia has been repeatedly associated with hippocampal volume loss (Wright et al., 2000; Honea et al., 2005), and previous studies have found impairments of individuals with schizophrenia in allocentric virtual reality tasks (Hanlon et al., 2006; Weniger and Irlé, 2008; Landgraf et al., 2010; Folley et al., 2010). Accordingly, we suggest that the schizophrenia patients of the present study may not have been able to apply allocentric strategies in late trials of the task because of an inability to recruit their (possibly anatomically damaged) hippocampus. We suggest that a disturbed translation of egocentric to allocentric

frames of memory in participants with schizophrenia may have caused a compensatory signal increase of other task-relevant regions, i.e. the precuneus and PCRS during trial 4 (cp. Fig. 5). However, we want to emphasize that we are not in the position to empirically test these assumptions, as we did not obtain information on participant's possible use of specific navigation strategies in specific trials.

4.4. Egocentric learning and the default mode network in schizophrenia

Activity patterns during egocentric virtual maze learning as used in the present and a previous study of our group (Weniger et al., 2010) share some similarities with the default mode network of the brain. Key regions implicated in this network are the precuneus, medial parietal cortices and the posterior cingulate and retrosplenial cortex (PCRS). Gusnard and Raichle (2001) proposed this network as tonically active and continuously gathering information about the world around and within us, thus enabling a continuous, stable and unified perspective of the organism relative to its environment. Specifically, the precuneus was suggested to be activated during imagination of one's own actions or movements and during tasks requiring introspection, self-evaluation and reflection upon one's own personality and mental state (Cavanna and Trimble, 2006; Ruby and Decety, 2001; Farrer and Frith, 2002). Ongoing research indicates the possibility that a core network, being highly similar to the default mode network, is engaged in diverse forms of self-projection, including episodic memory, prospection, theory of mind, and spatial navigation (Buckner and Carroll, 2007). Scene construction, being a crucial process in spatial navigation, has further been conceptualized as a core process underlying the diverse cognitive functions associated with the default mode network (Hassabis and Maguire, 2007).

Recent research indicates abnormal resting state activity of regions associated with the brain's default mode network in individuals with schizophrenia (Garrity et al., 2007; Bluhm et al., 2007, 2009; Huang et al., 2010; Lui et al., 2010; Jang et al., 2011). The results of the present study showed that activity of a core region of the default mode network, the precuneus, was related to psychotic symptom strength and virtual maze performance in schizophrenia patients. Our results are paralleled by recent investigations demonstrating that schizophrenia patients show stronger activity increase in the region of the posterior cingulate and precuneus during self-reflection (Holt et al., 2011) or emotion discrimination (Reske et al., 2009) when compared with controls. Individuals with schizophrenia were shown to be impaired in the domain of self-recognition and experience of agency, and these deficits are associated with the spectrum of positive schizophrenia symptoms (Franck et al., 2001; Waters and Badcock, 2010). It seems likely that a disturbed experience of agency as well as disturbed self-recognition in schizophrenia may contribute to first-person large-scale egocentric learning deficits, and relate to the observed aberrant activity of the precuneus and PCRS in the participants with schizophrenia of the present study.

4.5. Methodological considerations

Our study used a learning paradigm assessing spatial navigation and memory formation in a first-person large-scale virtual environment. The paradigm has proven its suitability for the investigation of spatial memory in various populations with neurological or mental disorders. The fact that our participants with schizophrenia were not impaired during trials 1 and 2 underlines our conclusion that their altered patterns of activity changes during egocentric learning were indicative for the presence of schizophrenia and not for egocentric learning impairments per se.

To our knowledge this study is the first to analyze cerebral activation during a virtual reality egocentric spatial learning task in schizophrenia. The results of the present study and previous studies of our

group (Weniger et al., 2010; Weniger and Irlé, 2008) suggest that virtual reality egocentric maze learning may be a suitable tool to investigate clinical aspects of schizophrenia: egocentric navigation demands self-representation and self-recognition, motor imagery and experience of agency, all being crucial domains of positive psychopathology in schizophrenia (Waters and Badcock, 2010).

Some recent studies found an increased resting state activity in schizophrenia (Garrity et al., 2007; Bluhm et al., 2009; Jang et al., 2011). It may be assumed that the observed relative hypoactivation during egocentric learning in schizophrenia may possibly also reflect higher resting state activity in schizophrenia. Future studies are undertaken in our departments to investigate egocentric virtual maze learning in schizophrenia while controlling for resting state activity of participants.

A limitation of our study is that we were not in the position to investigate medication-free schizophrenia patients. Two recent prospective studies found an influence of antipsychotic treatment on resting state activity in schizophrenia, being characterized by an increase in connectivity strength of resting state-related regions and an increase of low-frequency fluctuations (Lui et al., 2010; Sambataro et al., 2010). However, we could not find an effect of antipsychotic medication on virtual maze performance and brain activation during virtual maze performance. Nevertheless, future studies should make any effort to investigate egocentric learning in drug-naive first-episode patients before and after onset of antipsychotic medication.

The schizophrenia patients of the present study were well educated and presented with short disorder duration and only moderate psychosocial dysfunction. Accordingly, their neuropsychological deficits were rather mild, and did not contribute to virtual maze performance or BOLD signal changes. However, it should be kept in mind that generalized cognitive deficits in chronic schizophrenia (Chapman and Chapman, 1973) may prevent assessment of specific spatial egocentric learning and associated BOLD signal changes.

Our results were obtained in a schizophrenia sample with the paranoid subtype, and thus may not hold for other schizophrenia subtypes. In our previous study (Weniger and Irlé, 2008) using a schizophrenia sample including disorganized patients we found a positive correlation between disorganized symptoms and egocentric maze errors. Future studies comparing the neural activity changes during egocentric maze learning in diverse schizophrenia subtypes are warranted.

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