Psychiatry Research: Neuroimaging 211 (2013) 47–56

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Decreased fMRI activity in the hippocampus of patients with schizophrenia compared to healthy control participants, tested on a wayfinding task in a virtual town

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ARTICLE INFO

Article history:
Received 6 February 2012
Received in revised form
17 September 2012
Accepted 23 October 2012

Keywords:
Navigation
Cognitive map
Episodic memory
Contextual binding
Neuroimaging
Healthy participants

ABSTRACT

Intact episodic memory requires the ability to make associations between the contextual features of an event, referred to as contextual binding. Binding processes combine different contextual elements into a complete memory representation. It has been proposed that binding errors during the encoding process are responsible for the episodic memory impairments reported in schizophrenia. Since the hippocampus is critical for contextual binding and episodic memory, it was hypothesized that patients with schizophrenia would show a deficit in information processing in the hippocampus, measured with functional magnetic resonance imaging (fMRI). In the current experiment, 21 patients with schizophrenia and 22 healthy control participants were scanned while being tested on navigating in a virtual town (i.e. find the grocery store from the school), a task that was shown to be critically dependent on the hippocampus. Between-group comparisons revealed significantly less activation among patients relative to controls in the left middle frontal gyrus, and right and left hippocampi. We propose that the context and the content are not appropriately linked, therefore affecting the formation of a cognitive map representation in the patient group and eliciting a contextual binding deficit.

1. Introduction

Episodic memory can be defined as memory for personal events in a spatial and temporal context (Tulving, 1983). Intact episodic memory requires the ability to make associations between the contextual features of an event, referred to as contextual binding. In binding processes, contextual elements are combined into a complete memory representation, providing the knowledge that the content and context have co-occurred (Chalfonte and Johnson, 1996). In order to form a complete episodic or autobiographical memory, the information (content; the "what") gets bound with the spatial and temporal information of the event (context; the "where" and "when") during a 'deeper level' of encoding (deeper semantic analyses of the stimuli involving meaning and implication compared with shallower sensory analyses of the stimuli, such as form or color; Craik and Lockhart, 1972). These binding abilities are dependent not only on the encoding processes but also on the capability to reactivate similar information (common context; Chalfonte and Johnson, 1996).

It has been proposed that binding errors during the 'deeper level' of the encoding process are responsible for the episodic memory impairments reported in schizophrenia (Boyer et al., 2007). The literature suggests that schizophrenia patients have difficulty binding the memory for an event with its contextual information to form an intact memory representation (Boyer et al., 2007; Danion et al., 1999; Gold et al., 2004; Rizzo et al., 1996a,b; Waters et al., 2004). The context memory deficit theory proposes that schizophrenia patients encode and store selected information normally but are unable to link it with the contextual features (spatial or temporal) to form an intact memory representation (Rizzo et al., 1996a). Contextual binding is mediated by the hippocampus, which suggests that this brain area may be impaired in patients with schizophrenia.

One of the most robust findings in schizophrenia is the abnormal hippocampal structure (Weiss et al., 2005). Evidence from postmortem evaluations (Bogerts et al., 1990) and *in vivo*

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http://dx.doi.org/10.1016/j.pscychresns.2012.10.005

magnetic resonance imaging (MRI) studies has demonstrated volume reductions (Nelson et al., 1998; Wright et al., 2000) and abnormal hippocampal shape (Shenton et al., 2002). Postmortem studies have demonstrated differences in the neuronal anatomy of the hippocampus. Reduced neuronal size (Arnold et al., 1995; Benes et al., 1991; Zaidel et al., 1997) and pyramidal cell disarray (Luts et al., 1998) in the hippocampus CA1 (Arnold et al., 1995), CA2, and CA3 subfields (Zaidel et al., 1997), as well as the subiculum (Arnold et al., 1995; Kovelman and Scheibel, 1984), have been reported. It can be hypothesized that episodic memory impairment is a direct consequence of the structural and molecular abnormalities found in the hippocampal formation.

Visuospatial navigation has been shown to be critically dependent on the hippocampus. According to cognitive map theory, the hippocampus is critical to construct and maintain spatial maps of the environment (Bohbot et al., 2004; Kumaran and Maguire, 2005; O'Keefe and Nadel, 1978). The recollection of the spatio-temporal context of an event has been said to be the distinguishing factor between episodic memory and other types of memory such as semantic memory and the simple recollection of object familiarity (Burgess et al., 2002). Spatial knowledge of an environment has been proposed as a good model of the acquisition of internal representations and is necessary for the storage and retrieval of events (Burgess et al., 2002; Kumaran and Maguire, 2005; Maguire et al., 1998a,b). Visuo spatial navigation tasks involving the construction of a cognitive map have been shown to require the hippocampus (Pigott and Milner, 1993). These tasks test the capacity to bind an event (e.g. change of orientation) with its spatial context (e.g. at the landmark). Neuroimaging studies have greatly enriched the literature by providing confirmatory evidence that the hippocampus, together with the parahippocampal cortex, posterior parietal cortices, medial prefrontal cortex, and striatum (or caudate nucleus in humans), are engaged in visuospatial navigation (Shelton and Gabrieli, 2002; Burgess et al., 2002; Iaria et al., 2003; Kumaran and Maguire, 2005). It is also commonly accepted that the human hippocampus is involved in episodic memory (Burgess et al., 2002; Maguire and Frith, 2004).

The current research investigated hippocampal function in patients with schizophrenia and healthy control participants with functional MRI (fMRI) and a virtual visuospatial navigation task called the wayfinding task, identical to the one used in Etchamendy and Bohbot (2007), modeled after Hartley et al. (2003). To our knowledge, no neuroimaging studies have yet explored the hippocampal deficit in schizophrenia with an ecological task that specifically targets the hippocampus. The first step of this study was to demonstrate an episodic memory deficit in schizophrenia with the Wechsler memory tests (WMS-III; Wechsler, 1987), it was hypothesized that there would be a significant difference between groups for memory assessment. The second step was to correlate WMS-III Family picture (FP) scores, a measure that assesses visual context-content binding (considered as a component of episodic memory; Gold et al., 2004), with behavioral navigation variables to determine whether the virtual navigation task relates to the FP assessment within our sample. The third step was to test participants' ability to navigate within a virtual town while using fMRI. It was hypothesized that during the navigation task, participants with schizophrenia would take longer routes to reach the goal locations in the virtual town and would have less hippocampal activity when navigating compared to controls.

2. Methods

2.1. Participants

A total of 54 study participants (28 patients with schizophrenia and 26 control participants) were recruited for this study. Participants included right-handed (determined by the Edinburgh Handedness Inventory; Oldfield, 1971) men and women between 18 and 40 years old. Patients with a primary diagnosis of schizophrenia were recruited from the Outpatient Schizophrenia Clinic at the Royal Ottawa Mental Health Centre, Ottawa, Ontario. Controls were recruited via newspaper and advertisement. Controls were matched to schizophrenia patients in terms of age, sex, and education level. Current diagnoses of abuse or dependence during the preceding 12 months with alcohol (Alcohol Use Disorders Identification Test (AUDIT), score ≥ 8 in men or ≥ 7 in women; Saunders et al., 1993) or drugs (Drug and Abuse Screening Test (DAST), score ≥ 6; Skinner, 1982) were exclusion criteria for all participants. Participants with a history of neurological disease, head injury, cardiovascular disease, stroke, or contraindications to MRI (determined by Medical Questionnaire) were also excluded.

Participants were paid a sum of $75 to take part in the study. The Research Ethics Board of the Royal Ottawa Mental Health Centre approved this project. All participants provided written informed consent.

2.1.1. Inclusion and exclusion criteria specific to the patient group

Patients were clinically diagnosed with schizophrenia by a psychiatrist and met the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV-TR; American Psychiatric Association, 2000) criteria for schizophrenia determined by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient Edition (SCID-P) interview (First et al., 2002a). Patients were clinically stabilized and had had no significant change in symptom severity, medication, or therapeutic methods following a three-month retrospective chart review.

For feasibility purposes patients with an acute psychotic episode on the total Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) or two or more of the following four PANSS items having a score 4 (conceptual disorganization, P2; hallucinatory behavior, P3; suspiciousness, P6; unusual thought content, G9) were excluded. Further, patients exhibiting comorbid depressive symptoms (Calgary Depression Scale (CDS), score ≥ 7; Addington et al., 1990) were also excluded because depression has been linked to hippocampal atrophy. Participants taking typical antipsychotics, benzodiazepines, or receiving electroconvulsive therapy were excluded from this study. These medications are excluded due to their side effect profile, which may contribute to the worsening of cognitive performance. Finally, extrapyramidal symptoms or overt signs of tremor or movement disorder (confirmed by clinician) were exclusion criteria.

2.1.2. Exclusion criteria specific to the control group

Exclusion criteria for controls included presentation of an Axis 1 DSM-IV TR diagnosis (using SCID Non-Patient interview; First et al., 2002b), report of a psychiatric history concerning participants' first-degree relatives (elicited by inquiry), or the presence of depressive symptoms (Hamilton Scale for Depression (HAMD), score ≥ 10; Hamilton, 1960).

2.2. Procedures

2.2.1. Clinical assessment

Participants underwent clinical interview during which the following assessments were administered: SCID, CDS or HAMD and the PANSS (for patients only) and the self-report AUDIT and DAST questionnaires.

2.2.2. Neurocognitive assessment

The following memory assessments of the Wechsler Memory Scale, 3rd edition (WMS III; Wechsler, 1987) were administrated to participants: logical memory (LM), verbal paired associates (VPA), and FP immediate and delayed components. Participants were also administered the National Adult Reading Test (NART; Nelson and Willison, 1991) to provide an estimate of premorbid intelligence.

2.2.3. MRI session

The behavioral and fMRI data for this study were generated during the performance of a virtual visuospatial navigation task called the wayfinding task. Briefly, this task required participants to navigate between specific landmarks in a previously encountered computer-generated virtual town. For the fMRI portion of the study, the contrast of interest was a comparison of brain activation in patients and controls during active navigation in the virtual town.

The MRI portion of this project occurred in two phases performed on the same day: the pre-scan training phase followed within 1 h by the scan phase. Since familiarity with first-person videogames may help in the virtual reality task performance, before the pre-scan training, participants were asked about their video game habits (e.g. what type of video game played). During the pre-scan training, participants were first familiarized with the keyboard to ensure their ability to maneuver through the environment. This was done in a virtual environment different from the virtual town used for the fMRI experiment. They then navigated in the virtual town created with the game editor of a commercially available computer game (Unreal Tournament 2003; Epic Games, Raleigh, NC). The virtual town was a visually complex computer-based environment which included several roads, intersections, and buildings, in addition to distinct landmarks (easily recognizable, labeled locations such as a school or a hospital). Participants engaged in a free exploration of the town for 20–30 min. During exploration,

participants were required to encounter every landmark twice and to travel along all roads. The path taken and the amount of time participants visited each landmark were recorded. The free exploration provided an opportunity for participants to encode and construct a cognitive map of the environment by building relationships between landmarks in the town. Participants were not permitted sufficient exploration time to form habitual routes between landmarks. Creating the paradigm using a modified video-game framework provided participants with a first-person perspective while navigating. Following the training outside the MRI, participants were scanned while performing tasks based on the navigation paradigm.

MRI scans were acquired using a 1.5 T Siemens Magnetom Symphony. An MRI-compatible virtual reality system, Silent Vision™ Model SV-7021 Fibre Optic Visual System with In Control Software (Avotec, Inc.), was acquired for this study, as well as a four-button fiber optic touch pad. Cerebral activation was measured with fMRI using blood oxygen level-dependant (BOLD) contrast. The International Consortium for Brain Mapping (ICBM) T1 protocol was used to acquire weighted structural images for coregistration with the echoplanar images (EPI). BOLD signals were obtained using the following T2* weighted EPI image parameters: 32 contiguous 4-mm axial slices, positioned parallel to the hippocampus, 64×64 matrix, repetition time = 3000 ms, echo time = 50 ms, field of view = 256, flip angle = 90°. A total of 160 volumes per run was used for the analysis.

Following a 12-min T1 structural scan, participants underwent an fMRI scanning session where they were required to complete the wayfinding (visuo-spatial navigation) task, which consisted of an alternating series of eight navigation trials and eight control conditions. In the task, participants were required to navigate between two landmarks in the previously explored town, taking the shortest possible route. For each navigation trial, participants were placed in front of one of the landmarks (e.g. school) and were required to navigate from there to another landmark (e.g. movie theater). For each trial, there were many different routes that could be taken to get to the target landmarks. Successful completion of this task required taking the shortest route by deriving it from a cognitive map, a task that critically requires the hippocampus. Once participants reached the target landmark, they initiated an automatic transition to the control task. If participants failed to find the target landmark during a predetermined time frame (determined by a pilot study), they were manually transported into the control town by the investigator. Since participants had not been previously exposed to the control town, it represented a novel, unfamiliar environment. The control task involved the completion of eight navigation routes during which participants followed different paths that were clearly indicated by arrows on the ground. This was thought to be an appropriate task to control for the visuo-motor components of the experimental task.

Participants navigated using their right hand to control an MRI-compatible touchpad. During completion of the navigation trials, participants were timed and their precise paths were recorded on a 2D aerial view of the town. This study used an fMRI block design with four fMRI BOLD scanning sessions of 8:06 min each, separated by 1-min rest periods. Each scan alternated between experimental and control tasks to control for scanner drift, and a 6-s transition period between experimental conditions was used to allow the hemodynamic response function to normalize. Software was used to detect transition between experimental and control tasks, as well as frame times. The entire MRI and fMRI scan time was 60 min per participant.

2.3. Data analyses

Participants were matched according to their age, sex, and education level for all analyses in this study. Behavioral data (demographics, cognitive assessment results, and navigation performance) were analyzed using Statistical Package for Social Sciences version 18 software (SPSS, 2008). Neuroimaging data were analyzed with Statistical Parametric Mapping software (SPM8, 2008).

2.3.1. Behavioral data

We hypothesized that there would be a significant difference between patient and control groups within the memory assessment and navigation performance. This hypothesis was tested using a multivariate analysis of variance (MANOVA). The memory variables considered for the analysis were (LM, VPA and FP) immediate and delayed scores. The navigation performance variables were accuracy (i.e. percentage of target locations reached) and percent error, time, distance traveled and sum of traveled and remaining distance.

$$\text{Percent error} : ((x+z)-y)/(x+z) \times 100$$

(i.e. x = total distance traveled, z = distance remaining to reach the goal, y = shortest distance to goal). The z variable was included to account for incomplete trials where the target landmark was not reached. Since incomplete trials by definition are missing part of the way to the goal location, the z variable was made to include this missing distance, whereby the shortest distance from the end point at which the trial was interrupted to the goal location is added to the distance traveled.

Time, distance traveled (measured by the length in centimeters of the route drawn on the 2D aerial view of the town), sum of traveled and remaining distance (they include the same variables as the $x+z$ used in the percent error calculation) are additional variables used to quantify behavior.

2.3.2. fMRI data

The second hypothesis, which predicts a significant difference in hippocampal BOLD activity between patient and control groups, was tested with the steps mentioned below.

Data quality assessment and preprocessing. DICOM images were converted to NIFTI format using SPM MRICONVERT. Data were preprocessed and analyzed with SPM8. Scans were realigned, co-registered, and spatially normalized to the ICBM EPI template. To improve the signal-to-noise ratio, data were spatially filtered with a Gaussian filter equal to twice the size of EPI voxels (full width at half maximum = $8 \times 8 \times 8$). The time series were high-pass-filtered (minimum cutoff frequency of 1/128 Hz) to remove low-frequency artifacts.

Artifact detection. Preprocessed data were visually inspected and reviewed for artifacts and motion using custom software from the Massachusetts Institute of Technology (http://web.mit.edu/swg/software.htm; Mozes and Whitfield-Gabrieli, 2009). Functional data were sub-jected to artifact detection if motion exceeded 2 mm in any direction (absolute maximum). Unphysiological global signal changes were identified using a cutoff for global image mean of ≥ 2.5 standard deviations. Nuisance regressors (identifying movement and unphysiological global signal changes) were included as a covariate of no interest in the first level design matrix. No group differences on the measures related to artifact detection were found. Motion parameters were included in the single-subject General Linear Model to reduce residual motion-related variance after realignment.

Statistical analysis of functional images. The first level subject-specific design matrices contained the following regressors: (1) two regressors encoding the average BOLD response at each of the two states (experimental task, following arrows); (2) a nuisance partition containing regressors modeling the individual scans that were identified as contaminated by movement and unphysiological global signal change (see Image Processing subsection above); and (3) a nuisance partition containing six regressors that encoded the movement displacement as estimated from the affine part of the image-realignment procedure.

These subject-specific design matrices were estimated and, for the purpose of this study, only images related to the experimental task were entered in a flexible factorial design (2×4 analysis of variance, ANOVA). Experimental images were not contrasted with the control task, as the control task produced equal amounts of hippocampal activity. This did not affect between-group analyses as both groups had the same level of variance. This experiment was a 4 (runs) by 2 (groups) factorial design.

The statistical threshold was set to $p < 0.05$ family-wise error (FWE)-corrected for the entire brain volume, with no cluster limit. Predetermined regions of interest (bilateral hippocampi) were defined with a structural mask of Pick Atlas extension (Maldjian et al., 2003) using the aal atlas (Tzourio-Mazoyer et al., 2002) and the statistical threshold was set to $p < 0.001$ uncorrected with a cluster-wise correction at pFWE = 0.05, for the reduced search volume. In order to verify if the ROIs used a more liberal region than participants' hippocampi, a visual inspection of the active hippocampal region was performed on the whole brain analysis at a $p < 0.001$. Plots of percent signal change (PSC) were created using the rfxplot toolbox for SPM8 (Gläscher, 2009).

3. Results

3.1. Demographics

Twenty-eight schizophrenia patients and 26 healthy control participants were enrolled in the study. Complete datasets were available for 21 patients and 22 controls. Altogether, 20 pairs were successfully age-, sex- and education-matched. Only one patient (male, age 30) and three controls (one female, age 22; two males, age 19 and 37) were matched with respect to the overall group. Altogether, there were no statistical differences between the two groups in terms of age, education or IQ, and experience with first person video games in the mean number of times participants visited the landmarks during the learning phase (visited landmarks), $p \geq 0.05$ (Table 1).

3.2. Episodic memory

Episodic memory was measured with the WMS-III LM, FP, and VPA subtests. Comparison of groups on these assessments revealed significantly lower mean scores among schizophrenia

Table 1
Participant demographics.

	Controls (n=22; SD)	Patients (n=21; SD)
Sex (F/M)	6/16	5/16
Age (years)	30.45 (1.25)	32.05 (1.08)
Education (years)	16.68 (2.64)	15.10 (2.09)
IQ (NART)	111.32 (1.67)	109.09 (1.47)
Played first person video game (Yes/No)	13/9	13/8
Visited landmarks	20.64 (4.76)	21.38 (5.36)
Age of onset (years)		20.52 (4.81)
Duration of illness (years)		11.38 (4.93)
PANSS total		64 (13.0)
PANSS positive		15.14 (4.33)
PANSS negative		18.14 (5.68)
PANSS general score		30.71 (6.93)

Note: $p \geq 0.05$ on all measures.

Table 2
WMS-III episodic memory subtests.

	Mean		Degrees of freedom	F-test
	Controls (SD)	Patients (SD)		
Logical memory immediate	46.91(10.74)	32.43(9.38)	1	22.08***
Verbal paired associates immediate	25.50(5.59)	17.38(8.10)	1	14.73***
Family pictures immediate	48.73(5.68)	41.95(10.86)	1	6.66**
Logical memory delayed	28.50(6.91)	19.19(7.72)	1	17.41***
Verbal paired associates delayed	7.36(1.00)	5.76(2.36)	1	8.50**
Family pictures delayed	48.59(5.51)	41.19(10.65)	1	8.31**

Note:
** $p < 0.01$.
*** $p < 0.001$.

patients relative to controls for the immediate and delayed component of these subtests (Table 2).

3.3. Behavioral navigation scores

Each group's accuracy, percent error, distance traveled, sum of traveled and remaining distances, and time are shown in Table 3. Each of the above-listed variables was significantly different between groups with controls outperforming patients. Since the percent error variable takes into consideration the error and the distance remaining to reach the goal for each participant, an ANOVA (2 groups × 8 trials) was computed for this variable. After applying a Bonferroni correction, only trial 4 remained significantly different between groups, $F_{(1,41)}=12.07$, $p < 0.005$. Overall, as demonstrated in Fig. 2, controls performed better than patients.

Pearson's correlations were calculated between FP (immediate and delayed) score and accuracy, time, and percent error. A significant positive relation was found between FP (immediate and delayed) memory scores and accuracy in the navigation task, and significant negative associations were found between FP (immediate and delayed) memory scores and time and percent error scores (Fig. 1). When the groups were separated and the same correlations were performed, patient scores of FP immediate still correlated significantly with the variables time, accuracy and performance ($r=-0.400$, $r=0.470$; $r=-0.431$; at $p < 0.05$). Patient's FP delayed score fell just short of correlating significantly with the navigation variables. Control FP immediate and delayed scores still correlated with the variable time ($r=-0.470$; $r=-0.519$; $p < 0.05$). The control group's FP delayed score came close to correlating significantly with percent error, though falling just below the statistical cutoff. For exploratory purposes, an investigation of discriminant validity was performed by correlating navigation performance scores with LM, VPA assessments, education and the NART. Since WMS-III assessments were significantly different between the two groups, correlations were performed separately for both groups. Immediate and delayed scores of VPA and delayed scores of LM correlated significantly with time, accuracy and percent error in the patient group. LM and VPA assessment did not correlate with navigation performance variables in the control group. NART and education did not correlate with navigation performance scores.

3.4. fMRI analyses

In order to determine between-group brain activity differences, a 2 × 4 flexible factorial analysis was performed. Results for the within-group analysis are shown in Tables 4 and 5. Both groups had similar regional activations, including the parietal lobe, precuneus, middle frontal gyrus, fusiform gyrus, insula, and hippocampus. All of these regions have been reported in previous visuospatial navigation studies with fMRI (Hartley et al., 2003; Iaria, et al., 2003; Maguire et al., 1997; Maguire et al., 1998a, 1998b; Maguire et al., 2000).

3.4.1. Between-group analysis

The between-group analysis (Controls ≥ Patients) revealed significant differences in the left middle frontal gyrus when comparing controls to patients. A small volume correction shows a between-group difference in the right caudate. A region of interest in the bilateral hippocampi demonstrated significant between-group differences in the right and left posterior hippocampus (Table 6; Fig. 1B). The analysis of the main effect of condition revealed an average linear effect in both groups at the level of the right hippocampus ($F_{(1,121)}=15.44$, FWE-corrected at $p < 0.05$). Furthermore, results of a between-group analysis (interaction group × condition) revealed differences in the linear effect of the left hippocampus across condition (time) ($F_{(1,121)}=$ 13,87, FWE-corrected $p < 0.05$). The PSC graph revealed significant positive signal change in the controls' posterior hippocampus, and the signal decreased over time. However, this was not the case in patients, where there seemed to be different activity patterns in the posterior hippocampus (Fig. 3). In fact, there was a significant positive signal change in the patient group only in Run 1.

Since there were significant differences in the overall behavioral navigation performance between groups, to control for the behavioral aspect of the task, a between-group analysis of only the successful trials was performed (Fig. 4). Behavioral analysis revealed no significant differences between groups for accuracy, time and percent error. The FWE-corrected fMRI analysis demonstrated no significant whole brain differences between groups. However, a significant difference between controls and patients (controls ≥ patients) in the right hippocampus was found at an uncorrected threshold of $p < 0.001$. Observation of the PSC graph (Fig. 5) demonstrates that the evolution of the task over time was the same in both groups. However, the PSC graph clearly shows that the pattern of hippocampal involvement differed between groups, with controls having an increase in right hippocampal BOLD signal compared to patients. In fact, in the patient group, there was only one trial where the BOLD signal was significantly

Table 3
Behavioral navigation performances.

	Mean		Degrees of freedom	*F*-test
	Controls (SD)	Patients (SD)		
Accuracy (%)	82.95(22.01)	53.57(26.85)	1	15.47**
Percent error	33.16(15.79)	48.34(16.26)	1	9.64**
Additional variables				
Time (s)	57.82(15.06)	73.94(15.09)	1	12.28**
Total distance traveled (cm)	12.88(3.65)	15.06(3.49)	1	3.98*
Sum of traveled and remaining distance (cm)	14.26(5.18)	18.85(5.05)	1	8.65**

Note:
* $p < 0.05$.
** $p < 0.01$.

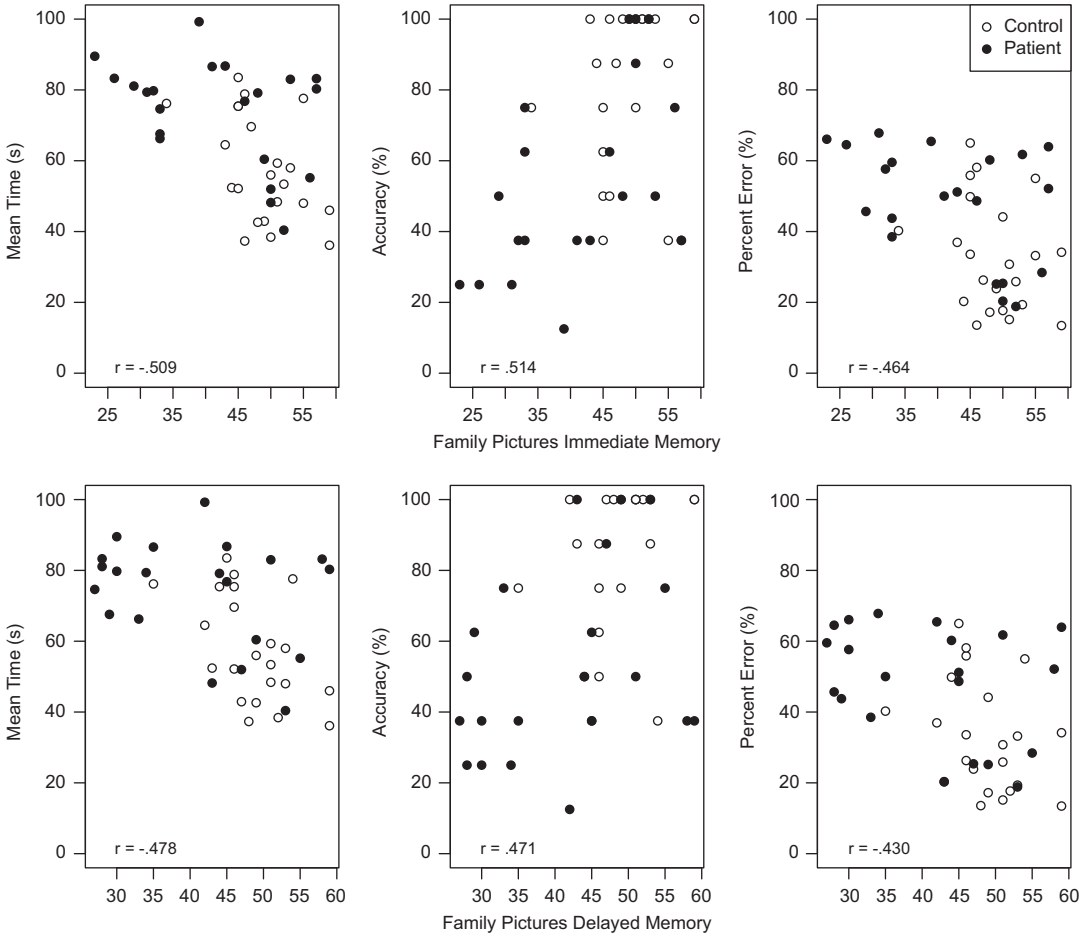

Fig. 1. Group correlations between FP (immediate and delayed) scores and Time, Accuracy and Percent Error, $p < 0.005$.

different from zero compared to controls where all trials were significantly different from zero.

4. Discussion

The goal of the current research was to investigate the hippocampal deficit in schizophrenia. In order to test our hypotheses, it was necessary to use a task that is critically dependent on the hippocampus. The wayfinding task in the virtual town is a visuospatial navigation task previously shown to involve the hippocampus (Hartley et al., 2003). Visuospatial navigation tasks explore the capacity to bind an event with its spatial context, using similar mechanisms as in contextual binding in episodic memory; thus, it can be considered as a valid assessment for contextual binding and a good method to activate the hippocampus. The task was most efficiently solved by using an allocentric strategy. Allocentric representations are frameworks that are independent of the observer, and thus fixed to the environment so that the locations of objects can be found irrespective of the starting position of an individual in the environment. This mental representation forms the basis of flexible navigation (being able to take shortcuts) and permits long-term storage of complex spatial relationships.

Episodic memory was tested with the auditory LM and VPA, and visual FP assessments. Immediate and delayed scores of these assessments were significantly different between groups. These results are consistent with the contextual binding hypothesis

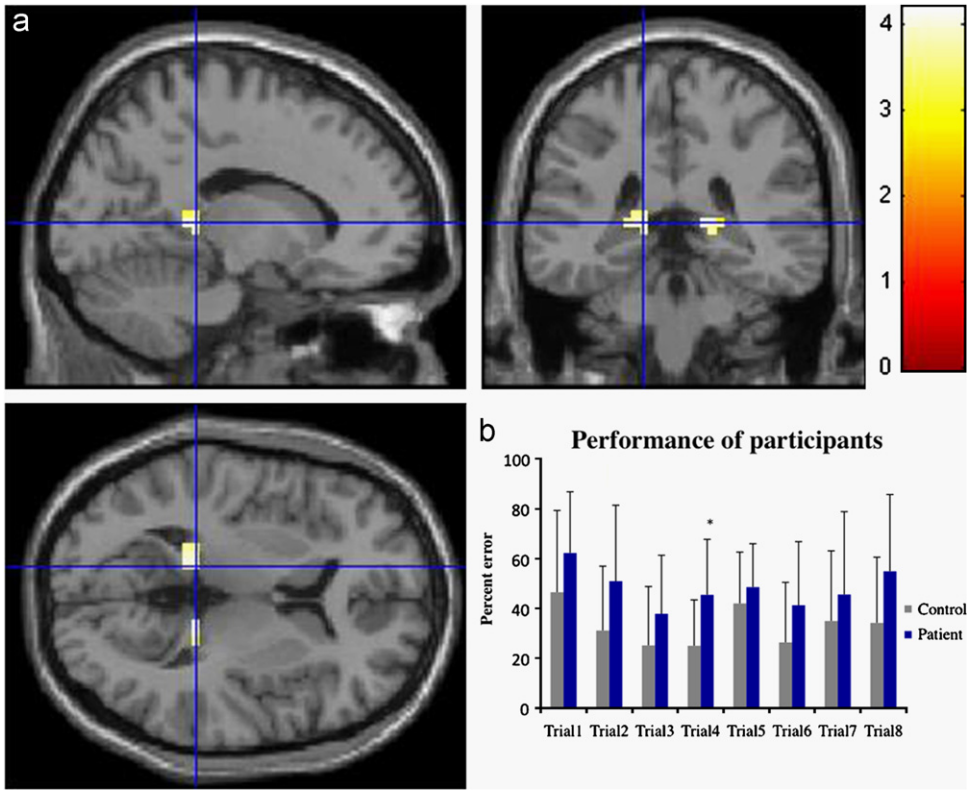

Fig. 2. Between-group analysis. (a) Differences (healthy controls > patients) in BOLD activity in the hippocampus. (b) Difference between controls and patients for the percent error variable (i.e. total distance traveled + distance remaining to reach the goal compared to shortest distance needed to reach goal location), Bonferroni corrected, $p < 0.005$.

Table 4
Healthy control within analysis.

[x,y,z]	Anatomical location of peak	Cluster size	Z equivalent
10, −68,58	R Precuneus	1621	Inf
−14, −72,54	L Superior parietal lobule		Inf
18, −76,54	R Superior parietal lobule		Inf
−26,0,62	L Middle frontal gyrus	95	7.54
−38, −28,54	L Postcentral gyrus		5.06
26,4,62	R Superior frontal gyrus	66	7.26
30,24, −2	R Insula	27	6.95
6,20,46	R Superior motor area	54	6.78
6,32,34	R Middle cingulum	54	5.73
−26,24,2	L Insula	18	6.16
42,44,22	R Middle frontal gyrus	16	5.95
−50, −24,38	L Inferior parietal lobule	7	5.28
6, −72, −2	R Lingual	4	5.05
ROI Hippocampus			
30, −36, −6	R Hippocampus	37	5.65
−14, −40,6	L Hippocampus	28	5.29

Significant FWE corrected $p < 0.05$.

Table 5
Patient within analysis.

[x,y,z]	Anatomical location of peak	Cluster size	Z equivalent
14, −68,54	R Superior Parietal lobule	258	Inf
−14 −76 50	L Superior Parietal lobule		Inf
−10, −60,66	L Precuneus		6.51
18, −56,18	R Calcarine	205	Inf
34, −84,26	R Middle occipital gyrus		7.10
26,0,54	R Superior frontal gyrus	70	7.25
26, −36, −14	R Fusiform	96	6.06
−22, −24,2	L Thalamus	59	6.37
−22,0,58	L Superior frontal gyrus	47	6.03
−30,20, −6	L Insula	11	5.84
10,28,34	R Middle cingulum	10	5.76
18, −16,10	R Thalamus	47	5.62
−50, −24,42	L Supramarginal gyrus	54	5.63
−38, −32,50	L Postcentral gyrus		5.56
−30,44,10	L Middle frontal gyrus	13	5.35
−14, −28,46	L Middle cingulum	8	5.16
−26, −84,30	L Middle occipital gyrus	7	5.22
ROI Hippocampus			
−26, −32, −2	L Hippocampus	31	5.25
30, −32, −10	R Hippocampus	12	4.97

Significant FWE corrected $p < 0.05$.

(Danion et al., 1999; Gold et al., 2004; Rizzo et al., 1996a,b; Waters et al., 2004), indicating a binding deficit in schizophrenia. FP assessment, which measures more adequately contextual binding, was significantly related to the wayfinding scores, indicating that participants who did poorest with respect to time and errors on the navigation task also performed poorly on the FP test. LM and VPA assessments are two measures of auditory memory, measuring the ability to associate context and content. These assessments were not related to the wayfinding task in the control group; however, VPA and LM delayed scores were related to the navigation performance in the patient group. This result is not surprising as these assessments also measure the ability to associate information together. On the contrary, the NART and education were not related to the navigation variables, indicating that the behavioral navigation variables do not measure a general cognitive factor.

The main purpose of this study was to evaluate hippocampal function in schizophrenia patients with fMRI and the wayfinding visuospatial navigation task. It was hypothesized that due to a contextual binding deficit, patients would have less hippocampal activity while navigating compared to controls. Behavioral navigation results demonstrated that controls did successfully

Table 6
Between-group analysis Control > Patient.

[x,y,z]	Anatomical location of peak	Cluster size	T-value
−38,40,30	L Middle frontal gyrus	3	4.98*
14,16,10	R Caudate	4	3.91*
14,−36,6	R Hippocampus	4	4.22*
−14,−36,6	L Hippocampus	10	4.07*

Note:
* FWE corr. $p < 0.05$.

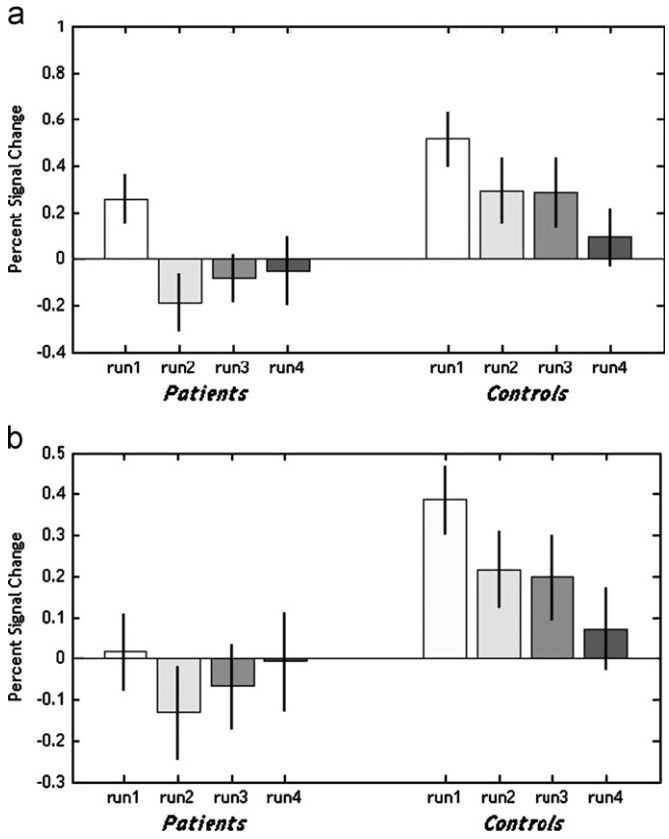

Fig. 3. PSC in the hippocampus, threshold p value < 0.001. (a) Between-group analysis displaying PSC in right hippocampus (14,−36,6). (b) Between-group analysis displaying PSC in left hippocampus (−14,−36,6).

complete the task more often than patients, took less time, and made fewer errors. Both groups showed hippocampal activity, but however, controls had significantly more posterior hippocampal activity while performing the task than the patient group. This was also demonstrated by the PSC graph where controls demonstrated significant signal change in the posterior part of their hippocampus whereas patients only had significant positive signal change in the first run.

In order to control for the level of difficulty of the task in both groups, the analysis was repeated on the successful trials only. As seen in Fig. 3a, an analysis of the successful trials resulted in no significant differences between groups, demonstrating that they performed equally well on the selected trials. However, the fMRI analysis revealed that the control group had significantly more BOLD activity in the hippocampus compared to the patient group. Hence, patients showed significantly lower activity in the hippocampus relative to matched controls even in successful trials. The PSC graphs demonstrated that these patients only had significant signal change for the first trial of the wayfinding task and no significant signal changes for the remaining trials.

Several studies have demonstrated allocentric spatial memory deficits in patients with schizophrenia (Hanlon et al., 2006; Weniger and Irle, 2008; Folley et al., 2010; Girard et al., 2010). Weniger and Irle (2008) conducted a study in which healthy controls and patients with schizophrenia had to navigate in a virtual park and solve a virtual maze. These two tasks assessed allocentric and egocentric strategies, respectively. Interestingly, patients and controls did not differ significantly on navigation strategies used while performing both tasks (determined by a questionnaire). However, patients had difficulties learning their way in the allocentric virtual park, as their performance on the task differed significantly from that of controls. On the other hand, no significant differences were found between groups for the virtual maze that required egocentric strategies. Based on the results of Weniger and Irle (2008), one could not attribute the allocentric deficit in schizophrenia to impairment in navigational abilities, as the patient group was as efficient as the control group in the egocentric virtual maze task. In concordance with the Weniger study, differences observed in patients and controls are likely not due to impairments in navigational abilities in patients but to an impairment in the ability to bind together events and the spatial features of the environment.

Folley et al. (2010) investigated the function of the hippocampus in schizophrenia using a virtual Morris Water Maze task and fMRI. Behavioral results of their study are consistent with our results, as participants with schizophrenia made more errors, traveled greater distances, and spent more time in the task. Though they did not find significant differences in the activity of the hippocampus while patients were engaged in the task relative to controls, they did find a positive correlation between the hippocampal BOLD signal and the efficiency of the task in the control group but not in the patient group. Due to structural and functional anomalies of the hippocampus in schizophrenia, it would be interesting to investigate with fMRI the navigation strategies within this population. MRI studies with virtual navigation demonstrated that several strategies can be used, namely, spatial memory strategies dependent on the hippocampus and stimulus–response strategies that are dependent on the caudate nucleus (Bohbot et al., 2007). In order to navigate successfully individuals with schizophrenia might be using a different strategy to compensate for the lack of neuro-functionality of the hippocampus.

The results of the current research demonstrate altered hippocampus functioning in schizophrenia during a wayfinding task whereby participants had to find a target location by the shortest route possible, even when the task was performed successfully. This may reflect a binding deficit, creating a recall impairment of the landmark relationships, as stipulated by the contextual binding hypothesis (Boyer et al., 2007). The study results are generalizable to a stable population on atypical antipsychotics. This may not be representative of the hippocampal deficit in a larger population. Nonetheless, abnormalities at the level of the hippocampal formation in schizophrenia have been demonstrated by converging evidence from neuropathological findings (Arnold et al., 1995; Benes et al., 1991; Harrison and Eastwood, 2001; Zaidel et al., 1997) and by different neuroimaging techniques (Nelson et al., 1998; Weiss et al., 2005; Wright et al., 2000). These studies have confirmed the reduced volume, decreased neuronal size, and neuron disarray in the hippocampus of individuals with schizophrenia. Based on this evidence, it can be hypothesized that the contextual binding deficit of schizophrenia is a direct consequence of structural and biochemical abnormalities in the hippocampus. Furthermore, these abnormalities may have a direct impact on other brain regions, such as the prefrontal cortex. Memories influence learning and behavior; therefore if events are not encoded properly, this will have important consequences on other cognitive processes, such as executive functioning. A contextual binding

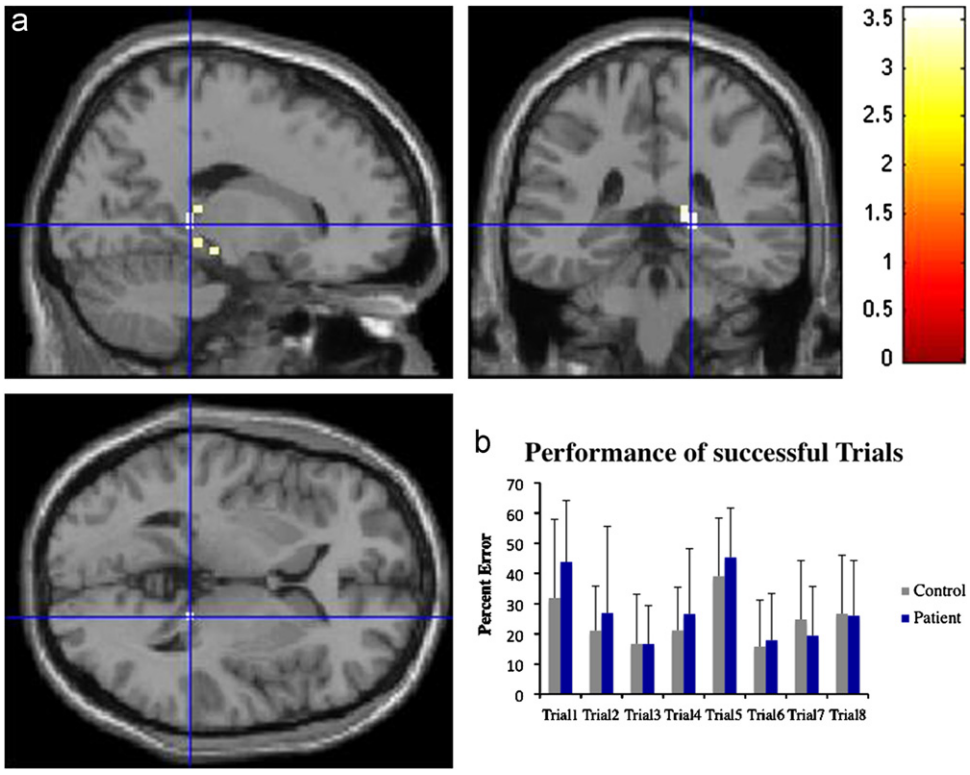

Fig. 4. Between-group analysis of successful trials. (a) Differences (healthy controls > patients) in hippocampal BOLD activity. (b) Difference between controls and patients for the percent error variable (i.e. total distance traveled+distance remaining to reach the goal compared to shortest distance needed to reach goal location).

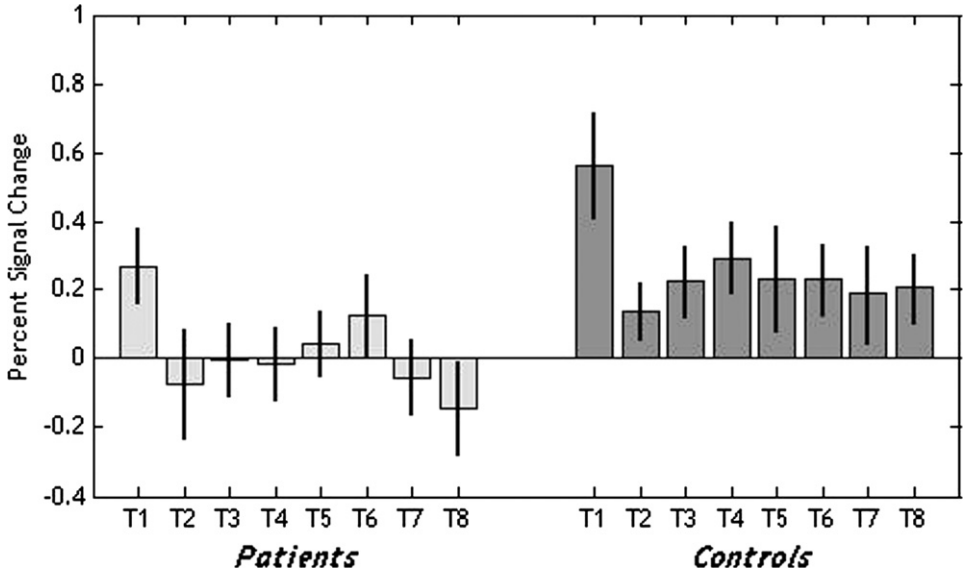

Fig. 5. PSC in the right hippocampus (18,−36,2) threshold value 0.001, for successful trials in patients and controls.

deficit can have important psychological repercussions. If the events are not bound properly, the information provided to other brain regions (e.g. prefrontal cortex) may be erroneous. Since past events influence the processing of new events, individuals with schizophrenia may not be able to use memories for past events with great flexibility to guide and control their behavior, affect, and beliefs (Boyer et al., 2007; Danion et al., 1999; Gray et al., 1991).

The focus of this study was on the ability to bind information together during a 'deeper level' of encoding. Since studies on contextual binding demonstrate that individuals with schizophrenia are capable of encoding the target information (e.g. landmark and orientation) adequately (Burglen et al., 2004; Rizzo et al., 1996a), but are unable to bind the target information together with its contextual features, we did not measure visuospatial working memory. However, the inclusion of a visuospatial working memory task (e.g. spatial span and visual reproduction) would be beneficial for future studies to determine whether visuospatial working memory can influence performance on a navigation task. In this study, the control task also produced significant hippocampal BOLD activity; therefore, only the experimental task was

reported and discussed. It is thought that the task of following the arrows on the ground may have been too simple, so participants had the chance to think of the experimental condition while doing the task or they could have learned spatial information about the control virtual town. Activity in the control task was previously noted (Etchamendy et al., 2012). In fact, Etchamendy et al. (2012) showed that asking participants to engage simultaneously in the control and in a mental task such as counting backwards from 1000 was sufficient to completely eliminate the significant fMRI activity observed in the hippocampus during the virtual navigation control task. It is also possible that the novelty of the environment in the control task of our study activated the hippocampus. Since, the virtual town was already familiar to participants, the conjunction of both tasks (virtual town task and control task) could explain why there was no difference in hippocampal activity between the two tasks. Having no control task should not affect between-group analysis focusing on the hippocampus, as visuo-motor variance is the same in both groups.

5. Conclusion

It has been hypothesized that individuals with schizophrenia have an episodic memory deficit, more specifically, a contextual binding deficit. Since the hippocampus is critical for contextual binding and episodic memory, it was hypothesized that patients with schizophrenia would show a deficit in information processing in the hippocampus, measured with fMRI. In this study it was proposed that visuospatial navigation is an appropriate measure of contextual binding because it precisely explores the capacity to bind an event with its spatial context. Behavioral results of the navigation task demonstrated that control participants successfully completed more trials than patients, took less time to achieve the task, and made fewer errors. fMRI results demonstrated that healthy control participants had significantly more hippocampal activity while performing the task than the patient group. This was also the case when only successful trials were considered. The decreased hippocampal activity in schizophrenia patients might be responsible for their contextual binding deficit, which may explain the episodic memory deficit observed in this population.

Acknowledgments

This study was funded by the Canada Foundation for Innovation, the University of Ottawa Medical Research Fund, the Ontario Ministry of Development and Trade, the Royal Ottawa Health Care Foundation and CIHR fund number 64381 to V.B. A.-A. Ledoux is supported by the Canadian Institutes of Health Research, and the University of Ottawa. We thank Philippe Fossati M.D., Ph.D., François Rousseau, Ph.D., Catherine Smith, M.A., Guylaine Veillette, Benjamin Deschamps, M.Sc., and Kyoko Konishi.

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