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Spatial Memory Deficits in a Virtual Reality Eight-Arm Radial Maze in Schizophrenia

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Abstract

Learning and memory impairments are present in schizophrenia (SZ) throughout the illness course and predict psychosocial function. Abnormalities in prefrontal and hippocampal function are thought to contribute to SZ deficits. The radial arm maze (RAM) is a test of spatial learning and memory in rodents that relies on intact prefrontal and hippocampal function. The goal of the present study was to investigate spatial learning in SZ using a virtual RAM. Thirty-three subjects with SZ and thirty-nine healthy controls (HC) performed ten trials of a virtual RAM task. Subjects attempted to learn to retrieve four rewards each located in separate arms. As expected, subjects with SZ used more time and traveled more distance to retrieve rewards, made more reference (RM) and working memory (WM) errors, and retrieved fewer rewards than HC. It is important to note that the SZ group did learn but did not reach the level of HC. Whereas RM errors decreased across trials in the SZ group, WM errors did not. There were no significant relationships between psychiatric symptom severity and maze performance. To our knowledge, use of a virtual 8-arm radial maze task in SZ to assess spatial learning is novel. Impaired virtual RAM performance in SZ is consistent with studies that examined RAM performance in animal models of SZ. Results provide further support for compromised prefrontal and hippocampal function underlying WM and RM deficits in SZ. The virtual RAM task could help bridge preclinical and clinical research for testing novel drug treatments of SZ.

Keywords

radial arm maze; reference memory; working memory; schizophrenia; spatial learning; memory

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Conflict of Interest

All authors declare that there are no conflicts of interest.

Contributors

Elena Spieker wrote the first draft of the manuscript, and was involved in data collection, statistical analyses, and manuscript revisions. Robert Astur created the virtual 8-arm maze task, contributed to the study design and manuscript revisions. Jeffrey West assisted with data collection, statistical analyses, and manuscript revisions. Jacqueline Griego contributed to analyses and revisions of the manuscript. Laura Rowland designed the study and oversaw all aspects of the study including manuscript preparation.

1. Introduction

Learning and memory impairments are present in schizophrenia (SZ) throughout the illness course (Park and Holzman, 1992; Piskulic et al., 2007) and are a primary predictor of psychosocial function (Floresco et al., 2005; Green et al., 2000; Sharma and Antonova, 2003). Unfortunately, learning and memory impairments in SZ are relatively unaffected by current antipsychotic treatments, which primarily alleviate positive symptoms (Carter, 2005; Harvey and Keefe, 2001; Keefe et al., 2007; Mintz and Kopelowicz, 2007). Abnormalities in prefrontal and medial temporal lobe function are thought to contribute to learning and memory deficits in SZ as demonstrated by behavioral and neuroimaging studies (Baare et al., 2001; Deicken et al., 1998; Jessen et al., 2003; Reichenberg and Harvey, 2007).

The radial arm maze (RAM) (Walker and Olton, 1979) is a test of spatial learning and memory in rodents that relies on intact prefrontal (Hasselmo, 2005) and medial temporal lobe (i.e., hippocampal; (for review see Martin and Clark, 2007) neural circuitry. Medial temporal lobe lesions produce learning and memory impairments in standard and delayed nonmatching to sample versions of the RAM in rodents (Liu and Bilkey, 1999; Otto et al., 1997). Optimal performance on the RAM also depends on communication between frontal and temporal lobe structures (Muzzio et al., 2009) since lesions in white matter connecting the hippocampus and prefrontal cortex impair RAM performance (Floresco et al., 1997). The development of virtual reality environments allows tasks developed in rodents, such as the RAM, to be used in humans (Olton and Samuelson, 1976). Such applications have led to evaluations of spatial learning and memory in humans behaviorally (Astur et al., 2004) and with functional magnetic resonance imaging (fMRI) (Astur et al., 2005; Marsh et al., 2010) in HC. These studies showed humans use similar spatial strategies to solve the RAM task as rodents (Iaria et al., 2003; Packard and McGaugh, 1996). FMRI studies of the RAM task reveal hippocampal and frontal activations that corroborate lesion studies in rodents (Astur et al., 2005; Marsh et al., 2010).

The goal of the present study was to investigate spatial learning in SZ using a virtual 8-arm radial maze. The virtual RAM task is ideal for use in SZ because it assesses both reference memory (RM) and working memory (WM) function, and reflects hippocampal and frontal function, respectively. Moreover, the application of the virtual RAM may be used to bridge preclinical and clinical research and thus provide a unique opportunity to test novel pharmacotherapies cross-species. Based on the evidence from other WM and spatial memory tasks, we hypothesized that subjects with SZ would demonstrate spatial learning deficits compared to healthy controls (HC). The relationships between RAM performance measures and psychiatric symptom severity, memory, and visual spatial function, assessed with standardized neuropsychological tests, were explored.

2. Materials and Methods

2.1 Subjects

Thirty-three outpatients with SZ treated with antipsychotic medication and thirty-nine healthy controls (HC) participated in this study. Inclusion/exclusion criteria for volunteers with SZ were: (1) diagnosis of SZ as determined with the Structured Clinical Interview for DSM-IV-TR, Patient Version (SCID-P) (First et al., 1995) (2) no current or past neurological condition, (3) no DSM-IV-TR (American Psychiatric Association, 2000) substance abuse or dependence in the last 6 months, (4) clinically stable as determined by outpatient treatment psychiatrist, (5) stable antipsychotic treatment (same medication, dose for at least 3 months) and (6) right-handed. Inclusion/exclusion criteria for healthy volunteers were: (1) no past or present psychiatric disorder as determined with the

Structured Clinical Interview for DSM-IV-TR, Non-Patient Version (SCID-NP) (First et al., 1996), (2) no first-degree relatives with a diagnosis of a psychotic disorder, (3) no current or past neurological condition, and (4) right-handed.

2.2 Apparatus

A Sony VAIO laptop with a 17" color monitor was used for testing. Auditory feedback was provided through the computer speakers in conjunction with visual stimuli presented on-screen each time a reward was found. A joystick was used to navigate the maze.

2.3 Procedure

All subjects gave written informed consent prior to participation in the study. Subjects with SZ were evaluated for their ability to provide informed consent before signing consent documents. This study was approved by the University of Maryland Internal Review Committee. Subjects with SZ were evaluated for psychopathology with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984). All subjects completed the virtual maze task (described below) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Kenchaiah et al., 2002) to provide indices of attention (digit span and coding tests), immediate and delayed memory (story and list recall tests), language (fluency), visual spatial construction, and combined score as a measure of general cognitive function. Subjects were monetarily compensated for their time.

2.4 Maze Task

Subjects navigated the maze as a first-person explorer of the virtual reality environment (see Figure 1). Movement of the joystick in a given direction panned the screen to that direction to maintain first-person viewpoint. The RAM consisted of 8 wells, 4 of which were baited. The same configuration of rewarded arms was used for all subjects and for all trials. Subjects were instructed to navigate the virtual room using the joystick. They were informed that rewards were located at the ends of 4 wells and the purpose of the task was to locate the rewards as quickly as possible. Auditory notification (pleasant tone) occurred upon location of a reward. Visual notification "Congratulations. You have found all the rewards" appeared upon location of all 4 rewards followed by a 2 second screen blackout. Each subsequent trial started at the middle of the maze and began with a visual message "Please find the rewards again." There were a total of 10 trials of the task. Each trial allotted 5 minutes to find all rewards, and if the 5 minutes elapsed and all 4 four rewards were not found, the trial terminated. Measures recorded for each trial included trial time and distance to completion, WM and RM errors, and number of rewards discovered. A RM error was defined as entry to an arm that was never rewarded. A WM error was defined as entry to an arm that was previously entered.

2.5 Analyses

Mean trial time, distance traveled, number of rewards found, WM errors, and RM errors across the ten trials of the task were analyzed by group using linear mixed models, which account for missing data. RAM data for one trial was lost for one SZ subject.

The relationships between task performance (trial time, WM and RM errors) and (1) BPRS total, positive and negative symptom scores, (2) RBANS memory and visual spatial indices, digit span, and total score, and **(3) illness duration** were computed with Spearman's rank correlations with Bonferroni-corrected alpha set to 0.001. Correlation analyses were restricted for neuropsychological measures because we expected maze measures to be related to standard neuropsychological measures of memory and visual spatial function. The

relationship between task performance (trial time, WM and RM errors) and duration of illness was also examined with bivariate correlations to control for age.

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 18.0. Statistical tests were two-tailed ($\alpha < .05$) unless otherwise stated**.**

3. Results

Subject demographic and clinical characteristics are provided in Table 1. There were no significant differences in age, gender, or ethnicity between groups (all *p*'s > 0.05). As commonly found, subjects with SZ had fewer years of education ($t(70) = 3.28$, $p = 0.002$) and lower RBANS scores ($t(69) = 4.10$, $p < 0.001$) compared to HC. One HC participant completed the maze task but chose not to complete the RBANS.

Maze performance measures were analyzed by 2 (group: SZ, HC) X 10 (trial) mixed models. Age, sex, **education**, and race were included as covariates but did not account for significant amounts of variance in spatial learning in any models (*p*'s > 0.1) and were excluded from analyses. All models included group as the between subjects and trial as the repeated measures factor. Dependent variables included trial time, distance traveled, rewards found, WM errors, and RM errors per trial.

There were significant group by trial interactions for distance traveled ($F(9, 629) = 3.01$, $p = 0.002$), WM errors ($F(9, 629) = 1.95$, $p = 0.043$), and RM ($F(9, 629) = 4.39$, $p < 0.001$) errors. Figure 2 shows how the two groups differ over time for each outcome of interest (trial 1 – 10).

There was a significant main effect of group and trial on all measures (see Table 2). HC took less time ($F(1, 70) = 12.52$, $p = 0.001$), traveled less distance ($F(1, 70) = 6.96$, $p = 0.01$) to locate rewards, found more rewards overall ($F(1, 70) = 8.97$, $p = 0.004$), and made fewer WM ($F(1, 70) = 5.08$, $p = 0.027$) and RM ($F(1, 70) = 9.50$, $p = 0.003$) errors than subjects with SZ.

On average, both groups traveled less distance ($F(9, 629) = 16.21$, $p < 0.001$) in less time ($F(9, 629) = 40.10$, $p < 0.001$), located more rewards ($F(9, 629) = 3.16$, $p = 0.001$), and had fewer WM ($F(9, 629) = 4.70$, $p < 0.001$) and RM ($F(9, 629) = 36.15$, $p < 0.001$) errors as trials proceeded.

Several significant relationships between maze performance and neuropsychological measures were observed. RM errors on the RAM and RBANS digit span ($r = -0.559$, $p < 0.001$) were negatively correlated among HC indicating the better short-term memory performance, the fewer RM errors (Table 3). No additional significant correlations emerged. Among the SZ group, trial completion time was negatively correlated with RBANS digit span ($r = -0.619$, $p < 0.001$) and RBANS total score ($r = -0.599$, $p < 0.001$) indicating the better the short-term memory and general cognitive performance, the better spatial learning performance. The associations between RBANS immediate and delayed memory indices and trial completion time approached trend level significance (Table 4). There were no statistically significant relationships or trends toward significance between BPRS positive and negative symptom severity and task performance measures (all *p*'s > 0.1).

Duration of illness was positively correlated with time and working and reference memory error rates (all *p's* <.001). However, when age was controlled for, all correlations between illness duration and performance were no longer significant at the Bonferroni corrected $p < 0.001$.

4. Discussion

To our knowledge, this is the first study to assess spatial learning performance using a virtual 8-arm radial maze task in SZ. Subjects with SZ displayed impaired spatial learning compared to HC. Subjects with SZ had increased trial completion time and distance traveled, and made more RM and WM errors compared to the control group. These impairments were related to short-term memory and general cognitive function as assessed with RBANS neuropsychological tests. These impairments were related to schizophrenia illness duration, but results should be considered with caution since this effect was at trend significance level when age was controlled. Psychiatric symptom severity was not associated with maze measures; these findings provide additional support that cognitive deficits in SZ are a distinct core feature of the illness (Heinrichs and Zakzanis, 1998).

Since the RAM relies on intact prefrontal (Hasselmo, 2005) and medial temporal lobe (for review see Martin and Clark, 2007) function, performance impairments putatively reflects abnormal prefrontal and hippocampal function. These findings are supported by behavioral and neuroimaging research reporting abnormal prefrontal and medial temporal lobe function associated with learning and memory deficits in SZ (Baare et al., 2001; Deicken et al., 1998; Jessen et al., 2003; Reichenberg and Harvey, 2007). With regards to neurochemistry, spatial learning and memory impairments in SZ may be partially due to abnormal glutamate function. This is supported by research on glutamate N-methyl-d-aspartate receptor (NMDAR) antagonists such as phencyclidine (PCP), ketamine, and MK-801. NMDAR blockade induces positive, negative, and cognitive symptoms resembling those observed in SZ (Rowland, 2005) and impairs performance in the RAM (for a review see Myhrer, 2003) in rodents (Duncan et al., 1998; Gao et al., 1993) and the Morris water maze in humans (Rowland et al., 2005) and rodents (Tsien et al., 1996). Repeated exposure to NMDAR antagonists in rodents, a model of chronic SZ, is linked to cellular and neurochemical alterations in the prefrontal cortex (Jentsch et al., 1997; Mouri et al., 2007; Noda et al., 2000) and deficits in spatial WM on a delayed spatial win-shift procedure in the RAM (Enomoto and Floresco, 2009).

It is important to note that the SZ group learn the task but not to the level of HC. This was indicated by a reduction in trial time, distance traveled, and RM errors in the SZ group. With additional practice it is feasible that subjects with SZ would reach similar performance on these measures as HC. Rats administered PCP required more trials to reach RM error level of HC on the RAM (He et al., 2006). Similarly, subjects with SZ can perform similarly to HC on a hippocampal-dependent task, transverse patterning, but require training (Rowland et al., 2010).

WM errors in the HC group steadily decreased across trials but did not in the SZ group. This suggests there may be a pervasive WM deficit that does not improve with practice on the RAM task in SZ. However, it is also possible that WM errors may improve on this task with a training intervention specifically targeted to improve WM or with a general cognitive remediation program intervention. Cognitive remediation, when combined with psychotherapy, improves global psychosocial function in SZ (McGurk et al., 2007; Wykes et al., 2011). Cognitive training without adjunctive therapy has mixed results. One study consisting of 36 1-hour sessions of computer-based cognitive training among SZ subjects found no improvement in attention and WM performance as assessed with standard neuropsychological tests (Dickinson et al., 2010). In contrast, other studies found that 50 hours of “neuroplasticity-based” computerized training resulted in improvements in verbal learning and memory and global cognition for up to 6 months post-training (Fisher et al., 2010; Genevsky et al., 2010), however, nonverbal WM showed no change (Genevsky et al.,

2010). Virtual reality paradigms such as the RAM may provide information about the potential of cognitive training to improve prefrontal cortex and hippocampal function.

There are some study limitations worth mentioning. The subjects with SZ were clinically stable and treated with antipsychotic medication. It is possible that antipsychotic medication impacts RAM performance. We tried to provide some control over this potential confound by including only subjects with SZ who had been on the same drug and dose for at least 3 months. Studies investigating drug-naïve first-episode subjects would help elucidate the impact of antipsychotic medications on RAM performance. Another possible study limitation is the number of trials used in this study. It is possible that subjects with SZ would have reached HC performance if we administered more than 10 trials. Future studies that incorporate additional trials would help determine if this is the case. Since this was purely a behavioral study the interpretation regarding impaired prefrontal and medial temporal lobe function underlying the RAM performance deficits in SZ is speculative. Future studies to explore neural activation with fMRI would help determine if prefrontal and medial lobe function is indeed compromised during RAM performance in SZ.

Episodic (item and relational) memory and WM, processes assessed with this virtual RAM task, are targets for treatment development in SZ as highlighted by the Cognitive Neuroscience Treatment Research to Improve Cognition in SZ (CNTRICS) (Barch et al., 2009). The virtual RAM task has the potential to bridge preclinical and clinical research for novel drug treatments of cognition in SZ.

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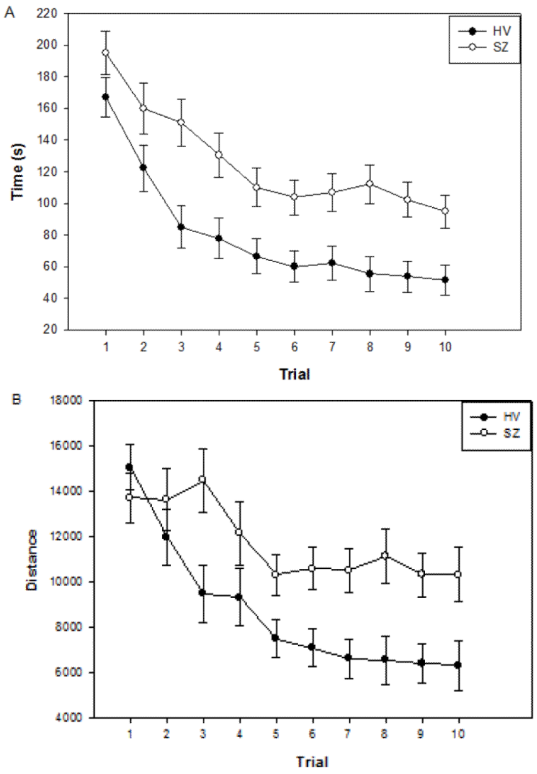
Figure 1.
Arial view of the virtual 8-arm radial maze task.



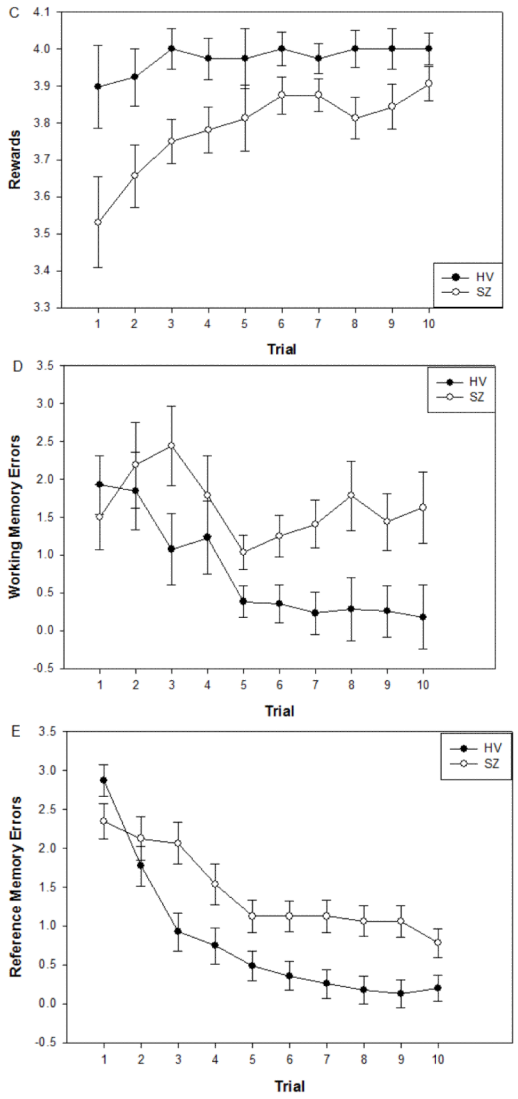


Figure 2.
Mean (SE bars) for (A) time, (B) distance traveled, (C) number of rewards found, (D) number of working memory errors, and (E) number of reference memory errors per trial in the healthy volunteer (HV) and schizophrenia (SZ) groups.

Table 1
Subject demographic and clinical characteristics

	SZ (*n*=33)	HV (*n*=39)	p
Age (years)	40.0 ± 11.9	40.5 ± 11.4	0.845
Gender			0.116
Male	23 (70%)	20 (51%)	
Female	10 (30%)	19 (49%)	
Education (years)	13.0 ± 2.3	14.8 ± 2.4	0.002
RBANS (total)	87.6 ± 15.0	101.9 ± 14.3	<0.001
Immediate Memory	90.5 ± 16.9	101.2 ± 20.0	0.018
Delayed Memory	94.3 ± 13.1	101.0 ± 12.6	0.030
Visuospatial	92.2 ± 18.2	97.8 ± 18.1	0.195
Digit Span Score	9.8 ± 2.4	12.2 ± 2.5	<0.001
Race			0.933
Caucasian	15 (45%)	19 (49%)	
African American	17 (52%)	18 (46%)	
Asian	1 (3%)	0	
Hispanic/Latino	0	2 (5%)	
Psychiatric Ratings			
SANS	21.5 ± 11.5		
BPRS (total)	32.3 ± 7.3		
BPRS (+ subscale)	8.9 ± 4.7		
BPRS (− subscale)	7.9 ± 2.7		
Duration of Illness (years)	16.4 (10.5)		

SZ – subjects with schizophrenia, HV – healthy volunteers, RBANS – Repeatable Battery for the Assessment of Neuropsychological Status, SANS – Scale for the Assessment of Negative Symptoms, BPRS – Brief Psychiatric Rating Scale

Mean ± SD; *n* (%)

Table 2
8-arm performance measures averaged across trials

	SZ (*n*=33)	HV (*n*=39)	p	*Effect size (Cohen's d)*
Average Time (sec)	131.8 ± 83.2	80.1 ± 34.4	.001	0.85
Average Distance (units)	11712.3 ± 6649.7	8608.8 ± 2860.2	.010	0.63
Average Rewards Found	3.73 ± 0.5	3.97 ± 0.08	.004	0.71
Average Working Memory Errors	1.7 ± 2.2	0.8 ± 1.0	.027	0.87
Average Reference Memory Errors	1.5 ± 1.1	0.8 ± 0.7	.003	0.78

SZ – subjects with schizophrenia, HV – healthy volunteers

Mean ± SD

Table 3

The relationship between RBANS and 8-arm measures for the healthy volunteer group (*n*=38)

	(*r*, *p*)		
RBANS Index:	**Time**	**Working Memory Errors**	**Reference Memory Errors**
Digit span	−.183, .272	−.194, .243	**−.559, <.001**
Immediate Memory	−.156, .351	−.219, .186	−.271, .100
Delayed Memory	−.155, .353	−.167, .316	−.346, .033
Visual Spatial	−.040, .813	.069, .679	−.075, .654
TOTAL SCORE	−.216, .192	−.233, .160	−.398, .013

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status

Table 4

The relationship between RBANS, BPRS, duration of illness, and 8-arm measures for the schizophrenia group (*n*=33)

	(*r*, *p*)		
RBANS Index:	**Time**	**Working Memory Errors**	**Reference Memory Errors**
Digit span	**−.619, <.001**	−.503, .003	−.391, .025
Immediate Memory	−.473, .005	−.365, .037	−.398, .022
Delayed Memory	−.450, .009	−.320, .069	−.379, .030
Visual Spatial	−.448, .009	−.382, .028	−.341, .052
RBANS score (total)	**−.599, <.001**	−.478, .005	−.493, .004
BPRS (+ subscale)	.027, .882	.065, .719	−.018, .921
BPRS (− subscale)	.092, .612	−.005, .979	−.026, .885
BPRS (total)	−.028, .876	.002, .993	−.036, .841
Duration of Illness	.733, <.001	.654, <.001 .388, .031	.737, <.001 .472, .007
Age-Controlled	.367, .042		

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status, BPRS – Brief Psychiatric Rating Scale