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Spatial memory deficits in a virtual reality eight-arm radial maze in schizophrenia

Elena A. Spieker [a], Robert S. Astur [b], Jeffrey T. West [a], Jacqueline A. Griego [c], Laura M. Rowland [a,*]

[a] Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD 21228, United States
[b] Department of Psychiatry, Yale University, New Haven, CT 06511, United States
[c] Institute of Cognitive Science, University of Osnabrück, 49076 Osnabrück, Germany

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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.

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 (Green et al., 2000; Sharma and Antonova, 2003; Floresco et al., 2005). Unfortunately, learning and memory impairments in SZ are relatively unaffected by current antipsychotic treatments, which primarily alleviate positive symptoms (Harvey and Keefe, 2001; Carter, 2005; 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 (Deicken et al., 1998; Baare et al., 2001; 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 (Otto et al., 1997; Liu and Bilkey, 1999). 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 healthy controls (HC). These studies showed humans use similar spatial strategies to solve the RAM task as rodents (Packard and McGaugh, 1996; Iaria et al., 2003). 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 HC. The relationships between RAM performance measures and psychiatric symptom severity, memory,

* Corresponding author at: Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228, United States. Tel.: +1 410 402 6803; fax: +1 410 402 6077.
E-mail address: lrowland@mprc.umaryland.edu (L.M. Rowland).

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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 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 HC 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 in. 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 Fig. 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 min to find all rewards, and if the 5 min 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

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