

## Impairment on the hippocampal-dependent virtual Morris water task in schizophrenia

Faith M. Hanlon<sup>a,b,c,d,\*</sup>, Michael P. Weisend<sup>a,c,d</sup>, Derek A. Hamilton<sup>c</sup>,  
Aaron P. Jones<sup>c,d</sup>, Robert J. Thoma<sup>a,b,c,d</sup>, Mingxiong Huang<sup>e</sup>, Kimberly Martin<sup>d</sup>,  
Ronald A. Yeo<sup>c</sup>, Gregory A. Miller<sup>b,f</sup>, Jose M. Cañive<sup>b,d</sup>

<sup>a</sup> *The Mental Illness and Neuroscience Discovery (MIND) Institute, 1101 Yale Blvd. NE, Albuquerque, New Mexico 87106, USA*

<sup>b</sup> *Department of Psychiatry, University of New Mexico School of Medicine, MSC09 5030, 1 University of New Mexico, Albuquerque, New Mexico 87131, USA*

<sup>c</sup> *Department of Psychology, University of New Mexico, Logan Hall, Albuquerque, New Mexico 87131, USA*

<sup>d</sup> *New Mexico VA Health Care System, 1501 San Pedro SE, Albuquerque, New Mexico 87108, USA*

<sup>e</sup> *Department of Radiology, University of California San Diego and VA San Diego Health Care System, 3350 La Jolla Village Drive, San Diego, California 92161, USA*

<sup>f</sup> *Departments of Psychology and Psychiatry and Beckman Institute Biomedical Imaging Center, 603 E. Daniel St., University of Illinois, Urbana-Champaign, Illinois 61820, USA*

Received 8 September 2005; received in revised form 23 May 2006; accepted 25 May 2006

Available online 14 July 2006

---

### Abstract

Traditional neuropsychological tests of visual and verbal memory have been used to evaluate memory deficits in schizophrenia. However, these tests cannot be used in non-human animal research, which is important for the discovery of treatments that will improve cognition and for study of the etiology of schizophrenia. To help bridge the gap between human and non-human animal research on hippocampal function in schizophrenia, this study sought to characterize the behavioral performance exhibited by patients using the Morris water task (MWT). The MWT has been shown in human and non-human animal studies to be hippocampus-dependent. In the virtual MWT, human subjects navigate a computer-generated on-screen environment to escape from the “water” by locating a platform. Patients with schizophrenia and controls performed two versions of the virtual MWT: a hippocampal-dependent hidden-platform version, relying on allocentric navigational abilities, and a non-hippocampal-dependent visible-platform version, relying on cued-navigational abilities. Patients traveled further and took longer to find the hidden platform over training blocks and spent less time in the correct quadrant during a probe trial. There was no deficit in the visible-platform condition. These findings identify a behavioral impairment on a hippocampal-dependent task in schizophrenia and support using the MWT in testing animal models of schizophrenia.

© 2006 Elsevier B.V. All rights reserved.

**Keywords:** Memory; Hippocampus; Morris water task; Allocentric; Schizophrenia; Spatial

---

\* Corresponding author. Departments of Psychiatry and Psychology, University of New Mexico, The MIND Institute, 1101 Yale Blvd. NE, Albuquerque, NM 87106, USA. Tel.: +1 505 272 5194; fax: +1 505 272 8248.

E-mail address: [ghanlon@themindinstitute.org](mailto:ghanlon@themindinstitute.org) (F.M. Hanlon).

## 1. Introduction

Kraepelin et al. (1919) were convinced that schizophrenia involves brain abnormalities and speculated that hallucinations and thought disorder were related to damage to the temporal lobes. With the advent of electromagnetic and hemodynamic neuroimaging, neuropsychological and postmortem techniques, neural mechanisms in schizophrenia have received increased attention. Multiple abnormalities have been documented in schizophrenia brains, with temporal lobe deficits, specifically in hippocampus, potentially playing a significant role. Neuropsychological assessment of hippocampal function in patients with schizophrenia has traditionally been conducted with visual and verbal memory tasks related to temporal-lobe function. This approach, however, does not fully exploit the large body of data and theory emerging from non-human animal studies of hippocampal function.

Investigators have described the neuropsychological impairment seen in schizophrenia as a “generalized deficit” (Blanchard and Neale, 1994). Nevertheless, specific cognitive abilities, such as attention, executive function and memory, have been found to contribute substantially to this generalized deficit (Goldman et al., 1996). Saykin et al. (1991, 1994) studies show a particularly large memory impairment relative to attention and executive function in unmedicated patients with schizophrenia. They determined that impaired visual and particularly verbal learning and memory distinguished patients from normal controls better than other neuropsychological variables, and they related these deficits to those found after temporal-hippocampal damage. Gruzelier et al. (1988) administered a battery of neuropsychological tests to patients with schizophrenia and normal controls, also finding a generalized deficit, but with the most striking deficits again emerging on memory tasks involving temporal-hippocampal function. Wexler et al. (1998) reported specific verbal memory deficits in schizophrenia that were independent of attentional and perceptual impairments. This verbal memory deficit is the best indicator for poor social and occupational functioning in schizophrenia (Green, 1996; Green and Neuchterlein, 1999). Among verbal memory deficits, recall is affected more than recognition (Clare et al., 1993; Johnson et al., 1977; Nacmani and Cohen, 1969). Episodic memory (memory for events) and semantic memory (memory for facts), which together are often referred to as declarative memory, seem to be affected in patients with schizophrenia more than is procedural memory (Cirillo and Seidman, 2003; Clare et al., 1993; Goldberg et al., 1993; Gras-

Vincendon et al., 1994; Kazes et al., 1999; McKenna et al., 1990; Tamlyn et al., 1992; Weiss and Heckers, 2001). This relative deficit in declarative memory suggests a hippocampal locus in schizophrenia (Squire, 1987; Squire et al., 2004).

Although the tests used to date to describe memory deficits in patients with schizophrenia are similar to those used after hippocampal damage in humans, they cannot be used in non-human animal research. Non-human animal research is important not only for the discovery of interventions that will ameliorate cognitive deficits in schizophrenia but for the discovery of the etiology of schizophrenia (Hanlon and Sutherland, 2000; Le Pen et al., 2000; Lipska et al., 1993; Lipska and Weinberger, 2000). Until recently, research on hippocampal function in schizophrenia has generally not taken advantage of the large amount of information acquired from non-human animal studies.

To help bridge the gap between human and non-human animal research on hippocampal function in schizophrenia, the present study sought to characterize the behavioral performance of patients with schizophrenia on a task well known to rely on the hippocampus. Theories of hippocampal function are based to a large degree on studies of amnesic patients with hippocampal damage and on studies of animals with intentional hippocampus lesions. The hippocampus has been hypothesized to be necessary for: (1) construction and storage of spatial information in the form of allocentric spatial cognitive maps (O’Keefe and Nadel, 1978); (2) declarative (explicit information) rather than procedural (implicit information) memory (Squire, 1987); and (3) disambiguating the relations between stimuli that combine to form unique representations during the encoding and recall of information (Cohen and Eichenbaum, 1993; Rudy and Sutherland, 1995; Sutherland and Rudy, 1989). All of these hypotheses predict a spatial impairment after hippocampal damage. All three propose that, to navigate to a goal in an allocentric spatial environment, the subject must build a representation of the goal in relation to distal cues (constellations of cues) to form a cognitive map and must be able to use this information flexibly regardless of where in the environment the subject begins navigating. Because the hidden-platform version of the Morris water task (MWT) relies on this ability, all of the above theories predict a deficit on this task after hippocampal damage.

A considerable body of theoretical and empirical research with human and non-human animals has established the MWT as a quintessential hippocampal task. In the traditional hidden-platform version of the

MWT, the platform is submerged just below the water surface in a large circular pool of opaque water, and a rat is released from one of the four cardinal compass points (Morris, 1981). The rat must learn to escape from the water by locating this hidden platform. Virtual navigation tasks consisting of a computer-generated display of a pool filled with water (virtual MWT (VMWT); Astur et al., 1998; Chamizo et al., 2003; Hamilton et al., 2002; Hamilton and Sutherland, 1999; Moffat and Resnick, 2002; Sandstrom et al., 1998) and a computer-generated circular arena (C-G arena; Jacobs et al., 1997, 1998; Thomas et al., 2001) have been developed for human testing. When performing the species-relevant MWT, rats and humans with hippocampal damage are unable to use spatial cues in the environment to locate a hidden platform (allocentric spatial ability) as controls do (Astur et al., 2002; Morris et al., 1982; Sutherland et al., 1982; Sutherland et al., 1983). If the hidden platform is removed after training during a probe trial, the normal human and rat will persist in searching where the platform had been located (Astur et al., 2002; Hamilton and Sutherland, 1999; Morris, 1981), indicating that they had learned the spatial location of the hidden platform. In contrast, rats and humans with hippocampal damage do not exhibit a preference for a particular area of the pool during a probe trial, signifying that they have not learned the location of the platform, thus exhibiting an allocentric spatial deficit. Importantly, hippocampal-damaged rats and humans do not differ from controls in their capacity to navigate to a visible platform in the same environment by relying on cued navigational abilities or simple associations between stimuli, demonstrating intact motivation, perception and motor skills. Studies have also shown a deficit on the VMWT in other human populations believed to have hippocampal damage, the elderly and children with fetal alcohol syndrome (Driscoll et al., 2003; Hamilton et al., 2003; Moffat and Resnick, 2002). The deficit in the elderly may not be due to ability to construct a spatial map, however, but to ability to find a particular location within that map (Laurance et al., 2002).

Although the VMWT does not involve proprioceptive or vestibular cues comparable to those involved in real navigation, the available data suggest that the psychological processes involved in place navigation in real and virtual environments are remarkably similar (Hamilton et al., 2002). In addition, it has been shown that patients with bilateral vestibular lesions exhibit spatial learning deficits on the VMWT (Schautzer et al., 2003; Brandt et al., 2005). Of particular importance to the present report, the psychological processes involved in navigating based upon a constellation of visual cues

are considered by most researchers interested in biological mechanisms in this behavior to be dependent upon hippocampal circuitry as reviewed in the theories above. Collectively, these data support the conclusion that vestibular and proprioceptive signals are not necessary for virtual place learning, and spatial learning deficits in humans can be detected in the VMWT in their absence.

These and other studies have provided evidence of the dependence of the MWT and VMWT on the hippocampus. Unfortunately, the MWT and other hippocampus-reliant tasks well grounded in the non-human animal literature have not been widely used in schizophrenia research. Two recent studies, Titone et al. (2004) and Hanlon et al. (2005), have begun to bridge this gap by using tasks (transitive inference (TI) and transverse patterning (TP), respectively) that rely on relational mnemonic abilities that have been shown to rely on the hippocampus in non-human animal research (TI: Dusek and Eichenbaum, 1997; TP: Alvarado and Rudy, 1995a,b; Alvarado et al., 2002; Rondi-Reig et al., 2001). Both studies found a behavioral deficit in patients with schizophrenia on these tasks, with the Hanlon et al. (2005) study also finding a hippocampal activation deficit with magnetoencephalography. Although these are important studies in that they found a hippocampal impairment in patients with schizophrenia on tasks shown with non-human animals to depend on the hippocampus, neither task has the body of theoretical development and empirical data supporting its hippocampal dependence that is available for the MWT. In addition, the MWT has already been employed to assess hippocampal function in animal (Andersen and Pouzet, 2004; Beraki et al., 2005; Flagstad et al., 2005; Hanlon and Sutherland, 2000; Lecourtier et al., 2004; Le Pen et al., 2000; Mattsson et al., 2002; Silva-Gomez et al., 2003) and human (Rowland et al., 2005) models of schizophrenia. Thus, investigating whether patients with schizophrenia exhibit an impairment on the VMWT is overdue.

The present project sought to characterize MWT performance in patients with schizophrenia. Patients were hypothesized to show a behavioral impairment on the hidden-platform version of the VMWT compared to control subjects. Patients should take more time and take longer paths to locate the hidden platform, and during the probe trial (with the platform removed) patients should spend less time in the quadrant where the hidden platform was previously located. In contrast, normal performance was expected for navigation to the visible platform. Because the visible-platform version is not sensitive to hippocampal damage, it is an important

control task for establishing that the subject is able and motivated to use the keyboard to navigate through the water toward a goal in order to escape the pool.

## 2. Materials and methods

### 2.1. Participants

Forty-four male subjects were included, 22 controls (19 right-handed) and 22 patients with schizophrenia (19 right-handed). Two of the patients were treated with conventional antipsychotics (haloperidol) and 20 with novel antipsychotics (5 on clozapine, 4 on aripiprazole, 4 on olanzapine, 2 on risperidone, 4 on quetiapine and 1 unknown due to enrollment in a double-blind drug study). Patients were recruited from the Albuquerque VA Health Care System and from the University of New Mexico Health Sciences Center. Selection criteria for patients with schizophrenia were: (1) diagnosis of schizophrenia determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV SCID-Clinician Version; First et al., 1996); (2) no history of any other psychiatric diagnosis (other than past substance abuse or one past depressive episode); (3) continuous treatment with one antipsychotic medication for at least 3 months; (4) no history of head injury with loss of consciousness for more than 1 min; (5) no hospitalization in past 3 months; (6) age 20–60; (7) no history of neurological problems (e.g. epilepsy, head trauma, stroke, brain tumor); and (8) signed informed consent. Recruitment of normal controls was done from the local community through word of mouth. Selection criteria for control subjects were: (1) no history of psychiatric dysfunction as determined by the SCID (other than past substance abuse or one past depressive episode); (2) no reported history of attention deficit hyperactivity disorder or learning disabilities; (3) no history of head injury with loss of consciousness for more than 1 min; (4) age 20–60; (5) no history of neurological problems; and (6) signed informed consent.

Patients and controls did not differ in age (controls:  $M=33.8$ ,  $S.D.=8.6$ ; 17 in the 20–40 range, 4 in the 41–50 range and 1 in the 51–60 range; patients:  $M=36.8$ ,  $S.D.=10.9$ ; 14 in the 20–40 range, 7 in the 41–50 range and 1 in the 51–60 range;  $F(1,42)=1.0$ ,  $p=0.326$ ) or parental education (controls:  $M=13.3$  years,  $S.D.=3.1$ ; patients:  $M=12$  years,  $S.D.=2.3$ ;  $F(1,42)=2.4$ ,  $p=0.129$ ). Patients were moderately ill, with mean years since symptom onset of 17.8 ( $S.D.=9.4$ ). They had a Positive and Negative Symptom Scale (PANSS) mean positive score of 13.6 ( $S.D.=3.4$ ), negative score

of 15.0 ( $S.D.=4.9$ ), general score of 30.1 ( $S.D.=6.8$ ) and total score of 58.7 ( $S.D.=12.9$ ).

### 2.2. Procedures

Task procedures were those of Hamilton et al. (2003). Subjects were tested on two versions of the task. In both versions, navigation to a goal (platform) was measured with a computerized (virtual) version of the MWT (VMWT; Hamilton et al., 2003; Hamilton and Sutherland, 1999). The subject navigates in a virtual environment consisting of a room with a square floor-plan and a circular pool in the center (Fig. 1). All four walls of the room are identical in appearance except for a different landmark flush with the wall to use as spatial cues (four landmarks in total; Fig. 1). The landmarks are placed off-center vertically by a fixed amount and placed off-center horizontally so that a subject could not find the platform by taking a straight trajectory from any starting location toward a landmark. The field of view is 48°, which allows participants to view one or two cues simultaneously on the display. The surface of the pool consists of an opaque, blue pattern that is patterned (tiled) via anti-aliasing of the original images to reduce (if not eliminate) any grid-like pattern that could be detected by the subject. The pool contains a square platform, 1.75% of the pool area. For analysis the pool's area was divided into four quadrants (Fig. 1).

The VMWT was run on an IBM-compatible computer with a 17" color monitor. Arrow keys on the keyboard were used to navigate through the virtual environment. Subjects were able to navigate forward, but not backward, and to turn left and right using the keyboard arrow keys (UP, LEFT and RIGHT). Also, forward movement in the pool was accompanied by the sound of moving water. The subject's position in the pool was collected in  $x, y$  coordinates recorded by the computer every 100 ms. Auditory feedback was controlled by the computer and was presented via speakers. When the platform location was discovered, a bell sounded and a verbal message saying the platform has been found appeared on the screen. When the duration of the trial exceeded 60 s without the platform location being found, an aversive tone sounded, the platform became visible and a verbal message saying the platform is visible appeared on the screen.

In the first version of this task the subject was to learn to virtually swim to the hidden platform to escape from the water. The subjects escaped from the water as quickly as they could by finding the hidden platform that was under the surface of the water. The hidden location was in a fixed position over trials. Each

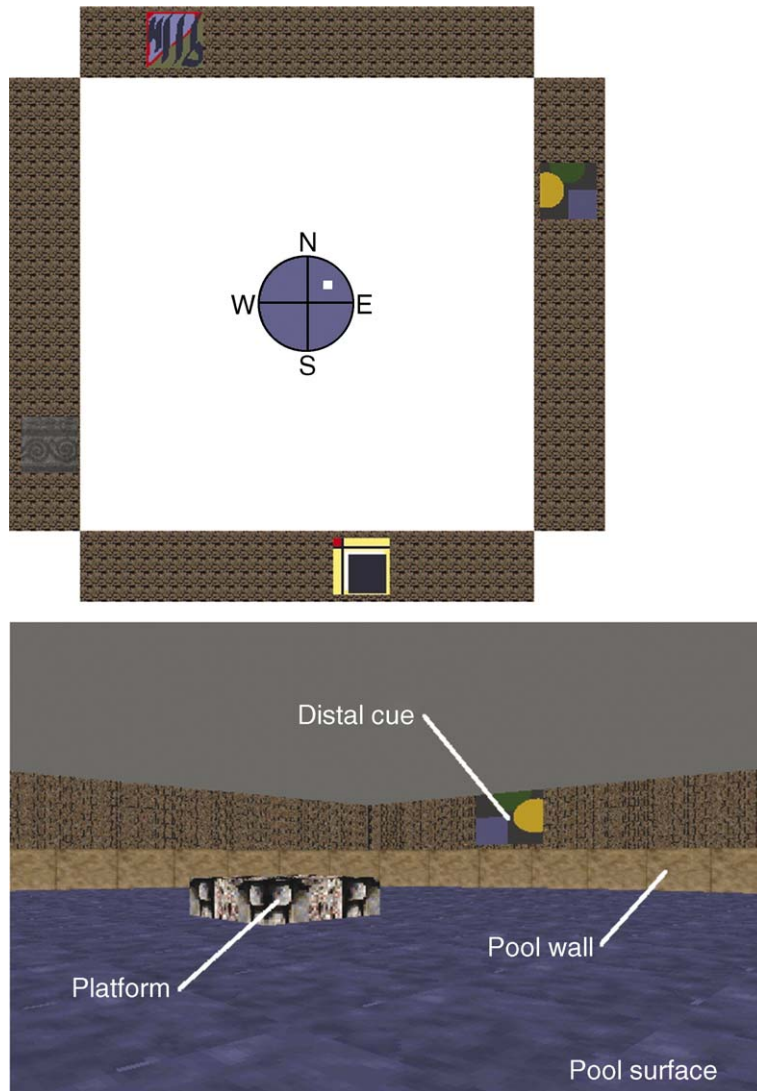


Fig. 1. VMWT environment. Upper panel: an aerial view of the virtual environment, with the four vertical walls flattened. The circular pool is positioned in the center of the room. The hidden platform is shown as a white square within the pool. There are four walls with a cue placed on each. Lower panel: subject's view from the center of the pool. The visible platform, a distal cue, the pool surface and two pool walls are shown.

participant received 24 training trials in six blocks of four trials, with each of four different starting locations occurring six times. Starting positions were chosen according to a pseudorandom sequence. If the platform was found within 60 s, the subject remained on the platform for 5 s, during which time they could rotate and view the environment but could not leave the platform. The display was then removed and a 2 s intertrial interval followed. For the hidden-platform version of the VMWT, subjects were given the following instructions:

For this task you will view a virtual environment on the monitor. You can move through the environment

using the arrow keys on the keyboard (UP, LEFT, AND RIGHT). You will be placed in a circular pool of water from which you must escape by climbing onto a platform. Your goal is to climb onto the platform as quickly as possible. However, the platform is submerged just below the surface of the water, so you will not be able to see the platform. You will have to find it by swimming around the pool. You will begin facing the wall of the pool. Because you cannot move backwards you will need to turn before you can move out into the pool. When you cross over the platform, you will be stopped and raised out of the water, and you will see a message

saying that you have found the platform. You will also hear a bell indicating that you have found the platform. If you do not find the platform within 60 seconds, the platform will become visible, and you will see a message prompting you to swim to the visible platform. If this message appears, you should look around the environment until you see the platform and then swim to it. Regardless of whether you find the platform when it is visible or hidden, you will stay on the platform for a few moments, then the screen will fade out and you will begin another trial. You will complete several trials, and the hidden platform will be in the same location each time. You can use the pictures on the walls of the environment to help you locate the hidden platform.

No other information about the task was given. For this version, latency to find the platform was recorded, along with swim path length.

After the hidden-platform trials, a probe trial was presented, in which the platform was removed, and the subject (uninformed about the removal) swam for 45 s trying to locate the platform. The starting location for the probe trial was selected pseudorandomly from the two starting locations furthest from the learned platform location (S and W starting points in Fig. 1). Percentage of time spent in what had been the platform quadrant (NE quadrant in Fig. 1) and total path length were the dependent measures for the probe trial.

In the second version of the task, presented after the first for all subjects, the subject swam to a visible platform. The platform location was in a fixed position over trials and was in the same location as the hidden platform. The height of the platform above the water surface was approximately half of the height of the pool wall (Fig. 1). Subjects were run for eight trials, with each of four starting locations occurring twice. Again, there was a 60 s trial duration, with starting positions chosen with the same pseudorandom sequence as the hidden-platform version. Latency and path length to find the platform were recorded. Once the subject finished both versions, s/he was interviewed and asked to rate the difficulty of the task (10 point scale: 1=very easy, 10=very difficult), whether the cues helped navigation, whether s/he thought the platform and starting locations were varied or fixed, and about experience with playing video games (e.g., hours per day).

Control subjects were expected to exhibit monotonic improvement in performance with practice, whereas it was hypothesized that the patient group would learn at a slower rate, if at all. Accordingly, a univariate linear trend analysis was conducted to investigate group

differences in latency and distance to locate the platform across blocks of trials. Subject age in years was used as a covariate to address possible affects of age on VMWT performance (Driscoll et al., 2003). This was allowable because the groups did not differ in age (Miller and Chapman, 2001).

### 3. Results

#### 3.1. Hidden-platform version

Over the 24 trials of training, patients with schizophrenia ( $M=40\%$ ,  $S.D.=15$ ) spent less time in the correct quadrant than did controls ( $M=49\%$ ,  $S.D.=11$ ;  $F(1,42)=4.87$ ,  $p=0.033$ ). The upper panel of Fig. 2 illustrates that patients tended to take longer than controls to locate the hidden platform (group  $F(1,41)=3.55$ ,  $p=0.067$ ). Latency did not decrease linearly with practice for subjects generally (linear block  $F(1,41)=1.43$ ,  $p=0.239$ ) nor differentially by age (age  $\times$  linear block  $F(1,41)=0.17$ ,  $p=0.681$ ), although age was related to latency to locate the hidden platform (age  $F(1,41)=14.02$ ,  $p=0.001$ ). Importantly, after identical performance in block 1, patients did not benefit from practice as much as controls did (group  $\times$  linear block  $F(1,41)=5.11$ ,  $p=0.029$ ). Investigating the simple effect of group in each block confirmed that patients took longer to locate the hidden platform in the last three blocks (block 4,  $p=0.004$ ; block 5,  $p=0.043$ ; block 6,  $p=0.005$ ).

Fig. 2 (lower panel) shows search distance as a function of group and block, and Fig. 3 shows sample search paths. In contrast to search time, there was no overall group difference in distance to locate the hidden platform (group  $F(1,41)=1.28$ ,  $p=0.265$ ). Search distance did not decrease with practice for subjects generally (linear block  $F(1,41)=3.03$ ,  $p=0.089$ ) nor differentially by age (age  $\times$  linear block  $F(1,41)=1.92$ ,  $p=0.174$ ). Age did not share significant variance with distance traveled (age  $F(1,41)=0.2$ ,  $p=0.658$ ). However, controls' distance decreased with practice (group  $\times$  linear block  $F(1,41)=6.64$ ,  $p=0.014$ ). Exploring that interaction, patients took a longer path than did controls to locate the hidden platform in the last block of trials ( $F(1,42)=6.11$ ,  $p=0.018$ ). In summary, patients did not improve in latency and distance traveled with practice as control subjects did.

#### 3.2. Probe trial

Fig. 4 shows that patients spent less time in the correct quadrant of the pool during the probe trial than

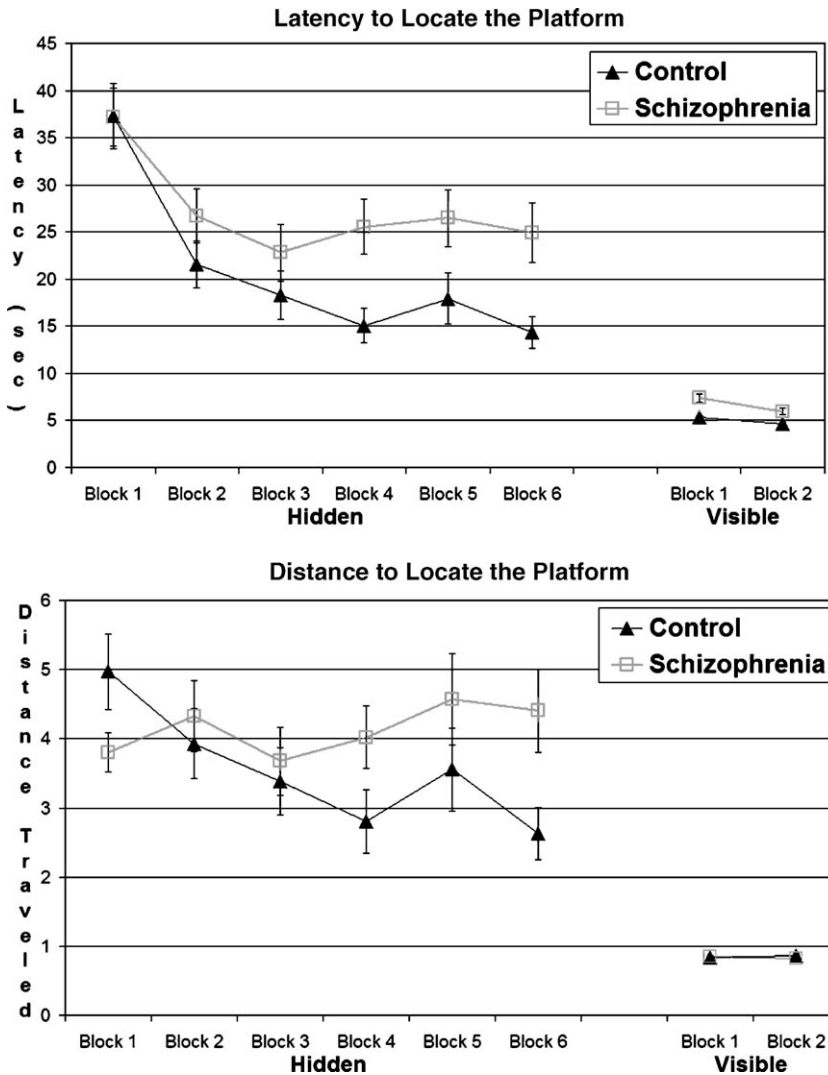


Fig. 2. Upper panel: mean latency to locate platform. Lower panel: mean distance traveled. Search path length was quantified as the ratio of distance traveled (in pixels) to the diameter of the pool. Bars indicate S.E. Note: S.E. bars are not apparent around means for the visible version of the task because the values were very small.

did controls,  $F(1,42)=6.49, p=0.015$ . Importantly, there was no difference between patients and controls in mean path length during the probe trial,  $F(1,42)=1.91, p=0.174$ , verifying that both groups were searching for the platform and that patients were involved in the task.

### 3.3. Visible-platform version

The upper panel of Fig. 2 illustrates subjects' speed in locating the visible platform, which did not decrease with practice for subjects generally (linear block  $F(1,41)=1.13, p=0.295$ ) nor differentially by age (age  $\times$  linear block  $F(1,41)=0.03, p=0.863$ ). As with

the hidden-platform version, age shared significant variance with latency to locate the visible platform (age  $F(1,41)=8.21, p=0.007$ ) but not with distance to locate the platform (age  $F(1,41)=1.33, p=0.255$ ). Patients took longer to find the visible platform (group  $F(1,41)=16.55, p<0.001$ ), but groups did not differ in practice effects (group  $\times$  linear block  $F(1,41)=2.43, p=0.127$ ), in percent time spent in the correct quadrant (controls:  $M=58\%$ ,  $S.D.=3$ ; patients:  $M=57\%$ ,  $S.D.=3$ ;  $F(1,42)=1.58, p=0.215$ ) or in path length to reach the visible platform ( $F(1,41)=0.06, p=0.811$ ; lower panel of Fig. 2). The distance traveled did not improve with practice overall (linear block  $F(1,41)=0.6, p=0.445$ ) nor differentially by group (group  $\times$  linear block  $F(1,41)=$

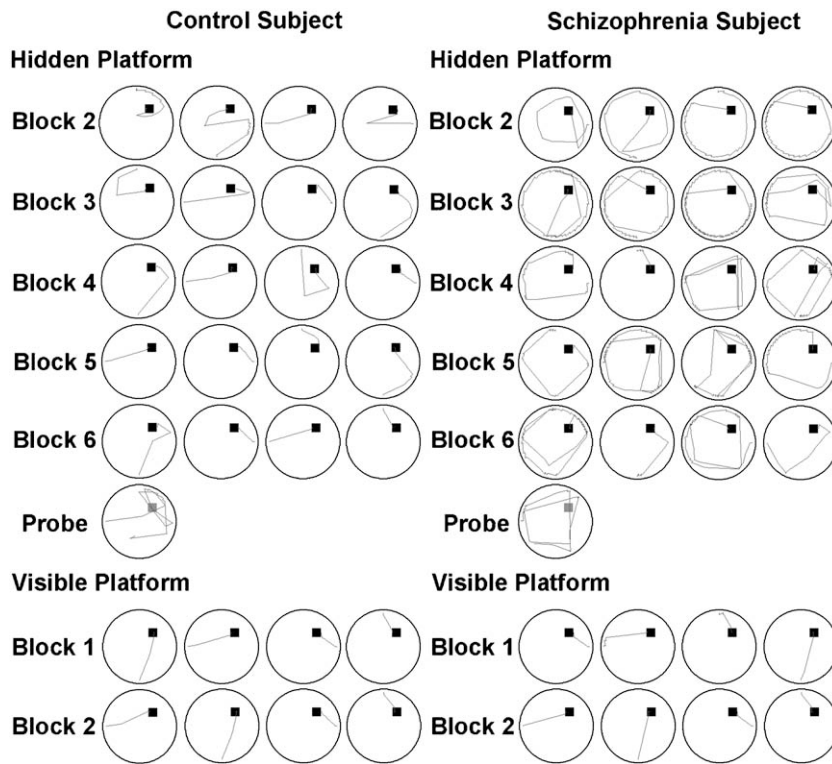


Fig. 3. Search paths for hidden- and visible-platform trials for one control subject and one schizophrenia patient who performed at mean level for their respective groups on percent of time spent in the correct quadrant during the probe trial. Trials are organized from left to right and by blocks of trials. The search paths for the first block of trials during the hidden-platform version were not quantified. The black square indicates where the hidden and visible platforms were located, and the gray line within the circle is the subject's search path. The column after the hidden-platform trials includes the search path during the probe trial, the gray square indicating where the platform was located prior to removing it.

2.05,  $p=0.16$ ) or age (age  $\times$  linear block  $F(1,41)=0.75$ ,  $p=0.393$ ). Therefore, patients did not show detectable behavioral impairments on the visible-platform version.

#### 3.4. Debriefing questionnaire

Fewer patients ( $N=15$ ) than controls ( $N=22$ ) reported that the cues on the walls helped in locating the hidden platform ( $\chi^2(1)=8.32$ ,  $p=0.004$ ). There was no group difference in number of participants correctly reporting that the platform stayed in the same location ( $\chi^2(1)=1.47$ ,  $p=0.226$ ; 14 controls and 10 patients) or that each trial began in a different location ( $\chi^2(1)=2.07$ ,  $p=0.150$ ; 19 controls and 15 patients). Nearly all participants (21 controls and 20 patients) reported playing video games in their lifetime, with similar rates of current video-game play (frequency of playing video games,  $\chi^2(1)=1.64$ ,  $p=0.441$ ; 9 controls and 13 patients did not currently play them, 6 controls and 5 patient rarely played, and 7 controls and 4 patients sometimes played; hours per week playing video games, controls:  $M=0.97$  h, S.D.=1.54, patients:  $M=0.72$  h,

S.D.=1.75;  $F(1,42)=0.25$ ,  $p=0.617$ ). Task difficulty was rated as fairly easy overall ( $M=4$ , S.D.=2.01) on a scale from 1 (easy) to 10 (difficult), although patients rated it as more difficult than controls (controls:  $M=3.09$ , S.D.=1.54, patients:  $M=4.91$ , S.D.=2.05;  $F(1,42)=11.10$ ,  $p=0.002$ ). For the entire sample, the more difficult the task was rated, the worse the performance (overall latency:  $r=0.656$ ,  $p<0.001$ ; overall distance:  $r=0.381$ ,  $p=0.011$ ; percent time spent in the correct quadrant during the probe trial:  $r=-0.429$ ,  $p=0.004$ ).

#### 3.5. Relationship between the VMWT and transverse patterning task

Ten of the control subjects and 10 of the patients with schizophrenia in the present sample were also included in the Hanlon et al. (2005) study, in which subjects performed the hippocampal-dependent transverse patterning (TP) task and several non-hippocampal control tasks (elemental, feature-neutral, and rock, paper, scissors). The hippocampal specificity of the VMWT performance in the present study was explored by

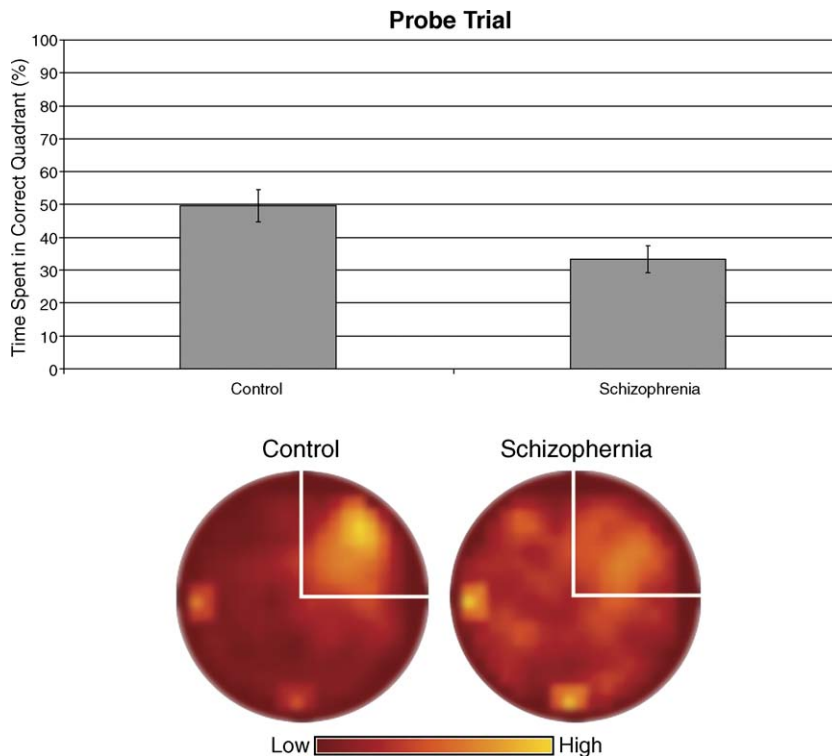


Fig. 4. The bar graph illustrates time in the correct quadrant during the probe trial. Bars indicate S.E. The pseudocolor circles show average composite dwell time for each group during the probe trial. Prior to platform removal for the probe trial, it was located in the upper right quadrant. Areas in yellow depict regions occupied for a relatively high percentage of the time, whereas areas in red were occupied a relatively low percentage of the time.

examining its relationship to the hippocampal-dependent TP task and control task performance available from the Hanlon et al. (2005) study. In this subset of 20 subjects, the higher the percentage of time spent in the correct quadrant during the probe trial on the VMWT, the higher the percentage of correct responses on TP after training ( $r=0.464$ ,  $p=0.039$ ). Therefore, the better subjects performed on the VMWT once trained, the better they performed on TP. This relationship was not found for any of the control tasks (% correct after training) used in the Hanlon et al. (2005) study, evidence that present VMWT results are specific to hippocampal-dependent processes.

#### 4. Discussion

Present results suggest a hippocampal deficit in patients with schizophrenia, using a task with well established theoretical and empirical backing, thus helping to bridge the gap between knowledge of hippocampal function in human clinical research and non-human animal research. Findings support the use of the MWT in developing and testing animal models of schizophrenia, because direct comparisons of hippo-

campal function across species can be performed. Thus, present results are relevant to theories of hippocampal dysfunction in schizophrenia and to animal models concerning the importance of early hippocampal damage.

Patients with schizophrenia were impaired on the hippocampal-dependent hidden-platform version of the VMWT. Patients were slower and had longer search paths than controls. Patients also spent less time in the correct quadrant during training. When tested for their knowledge of platform location in the probe trial, patients spent less time in the correct quadrant, verifying their performance deficit on the task using a standard measure of rodent spatial memory in the MWT. It has been recognized that multiple strategies and sources of stimulus control can be used simultaneously during place navigation (Sutherland and Hamilton, 2004), including the control of navigation by spatial relations, headings to individual cues and approach-avoidance tendencies to mention a few. Based on analysis of search paths during the probe trial (Figs. 3 and 4) and self-report measures indicating that visual cues were not helpful, the observed impairment suggests that patients failed to utilize any effective strategies for navigating

directly to the place where the hidden platform was located and that navigation in patients was not controlled by conspicuous visual cues as observed in controls. Failure to utilize effective strategies to solve the task likely contributed to patients reporting the task as more difficult than control subjects. Debriefing indicated that the group performance difference was not due to differences in experience playing video games. Overall, results support the first hypothesis, that patients with schizophrenia would show a deficit on this hippocampal-dependent task.

Results for percent time spent in the correct quadrant are similar to those found in other studies using the VMWT that have found an impairment in a specific population. This consistency begins to establish norms for the task. In the present study, controls averaged 50% and patients 33% of their time in the correct quadrant, a 17% difference. [Hamilton et al. \(2003\)](#) found that fetal alcohol syndrome (FAS) children (27%) spent less time in the correct quadrant during the probe trial of the VMWT than did age-matched controls (53%). [Driscoll et al. \(2003\)](#) found a similar impairment in an elderly group (~26%) compared to a younger control group (~42%). [Astur et al. \(2002\)](#) examined patients with unilateral hippocampal resections and found impairment on the VMWT, regardless of which hemisphere sustained the resection. Instead of percent of time spent in the correct quadrant during the probe trial, Astur and colleagues reported distance traveled in the correct quadrant and found that patients spent approximately 14% of the total distance traveled in the correct quadrant vs. 52% for controls. This large deficit was not expected for patients with schizophrenia, as they are hypothesized to have compromised hippocampi but not extensive loss of function. [Astur et al. \(2002\)](#) stated that evidence for using a ‘spatial’ strategy would be traveling 40% or more of the total distance during the probe trial in the correct quadrant of the pool. This was based on the finding that, after bilateral ibotenic acid lesions to hippocampus, rats spent  $\sim 33 \pm 7\%$  of their distance in the correct quadrant of the MWT ([Mumby et al., 1999](#)). Applying this criterion to the present data on latency, 68% of the schizophrenia sample failed to use a ‘spatial’ strategy vs. 23% for the control sample ( $p=0.006$ ).

As a control task for the hidden-platform version of the VMWT, the visible-platform version of the VMWT is not sensitive to hippocampal damage. In the present case, it showed that patients were able to use the keyboard to navigate through the water toward a goal to escape the pool and had a normal amount of motivation to do so. Patients with schizophrenia took longer to

reach the visible platform than did controls. However, the absolute magnitude of the difference was small, as both groups quickly located the visible platform, with little variability (controls averaged 5 s, S.D.=0.69, and patients 6.6 s, S.D.=1.69). Examination of swim path data indicated that this difference was not due to differences in navigational strategies. It could be due to variation in use of the keys (e.g., tapping on them vs. holding them down). When the percent time spent in the correct quadrant and the distance to reach the visible platform were assessed, patients did not differ from controls. Thus, it appears that patients with schizophrenia are not impaired on this non-hippocampal-dependent version of the VMWT. Overall, these data show that patients were adequately proficient at navigating with the keyboard and motivated to do so.

Caution with regard to the conclusion of a ‘specific’ hippocampal deficit based on present data is appropriate. The visible-platform version of the VMWT is an informative comparison task because it is the standard control task used in both human and non-human animal research. However, it is not psychometrically comparable to the hidden-platform version, as it is considerably easier to learn and perform. Task difficulty can be an important confound in group comparisons ([Chapman and Chapman, 1973](#)). Therefore, in order to conclude that patients with schizophrenia exhibit a specific hippocampal deficit based on this task, research that includes a psychometrically comparable control task is essential, such as was done in the [Hanlon et al. \(2005\)](#) study of the TP task and three control tasks.

A second reason for caution is that, although it is clear that the hidden-platform VMWT depends heavily on the hippocampus, the present study cannot rule out a contribution from frontal systems as well. Damage to frontal areas causes deficits on the task in rat ([Kolb et al., 1994, 1983; Sutherland et al., 1982](#)). This relationship has not been investigated in human subjects. Obviously, the hippocampus is embedded in a variety of neural circuits, and no single study can rule out possible involvement of all other regions. Future research could relate schizophrenia and nonpatient performance to tissue volume in hippocampus and frontal areas or could use electroencephalography (EEG), magnetoencephalography (MEG) or functional magnetic resonance imaging (fMRI) during the task to evaluate hippocampal and possible frontal involvement. Such research would strengthen conclusions regarding a hippocampus-specific origin of the schizophrenia VMWT performance deficit.

The lack of a psychometrically comparable control task and the possibility of a contribution from frontal or

other areas, however, do not alter the present finding of a behavioral deficit in schizophrenia on a hippocampal-dependent variant of the VMWT. The hippocampal specificity of this deficit was supported by using data available from the Hanlon et al. (2005) study, finding a relationship between VMWT and TP performance, which was not found with control tasks. Thus, in combination with recent work using a different set of carefully matched tasks, in which patients exhibited a deficit on the hippocampal-dependent TP task and not on psychometrically equivalent non-hippocampal-dependent control tasks (Hanlon et al., 2005), present results are compatible with a hippocampal deficit in schizophrenia.

Demonstration of a behavioral deficit in schizophrenia with tasks sensitive to hippocampal function in both human and non-human animals encourages cross-species work to develop interventions to ameliorate cognitive deficits and to test theories of the etiology of schizophrenia. For example, it is possible that various cognitive training regimens or antipsychotic medications could differentially affect specific aspects of cognitive performance. Due to the small number of patients on each medication type, the relationship between medication status and VMWT performance was not explored in the present sample. However, it has been examined in rat, finding that acute administration of an assortment of antipsychotic medications resulted in differential affects on MWT performance (Ploeger et al., 1992; Skarsfeldt, 1996). Therefore, future research using this task would benefit from examining the potential interaction of medication status and VMWT performance in human and non-human animal research. In regard to investigating etiological theories, Weinberger (1987, 1997; Weinberger et al., 1986) has proposed that, in the absence of obvious traumatic or perinatal brain damage, brain pathology in schizophrenia should often be considered to result from developmental abnormalities. More specifically, schizophrenia may be the result of early damage in some parts of the brain that adversely affects maturation in other parts of the brain. Lipska et al. (1993), Lipska and Weinberger (2000) and Weinberger et al. (1992) suggested a dysfunction in a prefrontal-limbic network in schizophrenia and proposed a neurodevelopmental model involving initial damage to the hippocampus that then disrupts normal development of prefrontal cortex. Accordingly, Lipska et al. (1993) developed an animal model of schizophrenia, showing that early damage to ventral hippocampus in rat produces late-emerging abnormalities in behaviors related to the dopamine system,

prefrontal cortex function and social behavior (Lipska et al., 1993; Lipska et al., 1995; Lipska and Weinberger, 1994, 2000; Sams-Dodd et al., 1997). To further test this theory, Hanlon and Sutherland (2000) damaged the limbic area in neonatal rats, measuring adult performance on the MWT and on tasks sensitive to dopamine and prefrontal cortex function. They found a deficit on all three tasks, concluding that early limbic damage results in sustained hippocampal dysfunction that subsequently fosters prefrontal and dopamine system deficits. This adult deficit on the MWT was also found by Le Pen et al. (2000) after selective neonatal ventral hippocampal lesions in rats. The present finding of VMWT impairment is not only consistent with this schizophrenia neurodevelopmental model and associated animal model but suggests possibilities for testing etiological theories involving the hippocampus.

In summary, present results confirmed an allocentric spatial navigation impairment, with sparing of cued navigation, in schizophrenia using the hippocampal-dependent VMWT. These findings suggest a hippocampal deficit in schizophrenia that may play a role in the memory impairments found in this population. The VMWT may also be useful in evaluating other memory disorders (e.g., Alzheimer's disease, temporal lobe epilepsy, FAS, post-traumatic stress disorder) that could benefit from a cross-species test of hippocampal function.

### Acknowledgements

This research was supported by grants from NIMH (R01 MH65304) to Jose M. Cañive, the Mental Illness and Neuroscience Discovery (MIND) Institute to Jose M. Cañive and Faith M. Hanlon, and from the University of New Mexico School of Medicine Research Allocation Committee (RAC) to Roland R. Lee. The authors wish to thank Robin Douglas, Fernando Torres, Lawrence Calais, Jeanne Schneider and Juan Bustillo for their recruitment efforts, and Claudia Tesche and Paul Amrhein for their advice.

### References

- Alvarado, M.C., Rudy, J.W., 1995a. Rats with damage to the hippocampal-formation are impaired on the transverse-patterning problem but not on elemental discriminations. *Behav. Neurosci.* 109, 204–211.
- Alvarado, M.C., Rudy, J.W., 1995b. A comparison of kainic acid plus colchicine and ibotenic acid-induced hippocampal formation damage on four configural tasks in rats. *Behav. Neurosci.* 109, 1052–1062.

- Alvarado, M.C., Wright, A.A., Bachevalier, J., 2002. Object and spatial relational memory in adult rhesus monkeys is impaired by neonatal lesions of the hippocampal formation but not the amygdaloid complex. *Hippocampus* 12, 421–433.
- Andersen, J.D., Pouzet, B., 2004. Spatial memory deficits induced by perinatal treatment of rats with PCP and reversal effect of D-serine. *Neuropsychopharmacology* 29, 1080–1090.
- Astur, R.S., Ortiz, M.L., Sutherland, R.J., 1998. A characterization of performance by men and women in a virtual Morris water task: a large and reliable sex difference. *Behav. Brain Res.* 93, 185–190.
- Astur, R.S., Taylor, L.B., Mamelak, A.N., Philpott, L., Sutherland, R.J., 2002. Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. *Behav. Brain Res.* 132, 77–84.
- Brandt, T., Schautzer, F., Hamilton, D.A., Bruning, R., Markowitsch, H.J., Kalla, R., Darlington, C., Smith, P., Strupp, M., 2005. Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans. *Brain* (Sep 1, Electronic publication ahead of print).
- Beraki, S., Aronsson, F., Karlsson, H., Ogren, S.O., Kristensson, K., 2005. Influenza A virus infection causes alterations in expression of synaptic regulatory genes combined with changes in cognitive and emotional behaviors in mice. *Mol. Psychiatry* 10, 299–308.
- Blanchard, J.J., Neale, J.M., 1994. The neuropsychological signature of schizophrenia: generalized or differential deficit? *Am. J. Psychiatry* 151, 40–48.
- Chamizo, V.D., Aznar-Casanova, J.A., Artigas, A.A., 2003. Human overshadowing in a virtual pool: simple guidance is a good competitor against locale learning. *Learn. Motiv.* 34, 262–281.
- Chapman, L.J., Chapman, J.P., 1973. Problems in the measurement of cognitive deficit. *Psychol. Bull.* 79, 380–385.
- Cirillo, M.A., Seidman, L.J., 2003. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. *Neuropsychol. Rev.* 13, 43–77.
- Clare, L., McKenna, P.J., Mortimer, A.M., Baddeley, A.D., 1993. Memory in schizophrenia: what is impaired and what is preserved? *Neuropsychologia* 31, 1225–1241.
- Cohen, N.J., Eichenbaum, H., 1993. *Memory, Amnesia, and the Hippocampal System*. MIT Press, Cambridge, MA.
- Driscoll, I., Hamilton, D.A., Petropoulos, H., Yeo, R.A., Brooks, W. M., Baumgartner, R.N., Sutherland, R.J., 2003. The aging hippocampus: cognitive, biochemical and structural findings. *Cereb. Cortex* 13, 1344–1351.
- Dusek, J.A., Eichenbaum, H., 1997. The hippocampus and memory for orderly stimulus relations. *Proc. Natl. Acad. Sci. U. S. A.* 94, 7109–7114.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1996. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Clinician Version*. American Psychiatric Press, Washington, DC.
- Flagstad, P., Glenthøj, B.Y., Didriksen, M., 2005. Cognitive deficits caused by late gestational disruption of neurogenesis in rats: a preclinical model of schizophrenia. *Neuropsychopharmacology* 30, 250–260.
- Goldberg, T.E., Torrey, E.F., Gold, J.M., Ragland, J.D., Bigelow, L.B., Weinberger, D.R., 1993. Learning and memory in monozygotic twins discordant for schizophrenia. *Psychol. Med.* 23, 71–85.
- Goldman, R.S., Axelrod, B.N., Taylor, S.F., 1996. Neuropsychological aspects of schizophrenia. In: Grant, I., Adams, K.M. (Eds.), *Neuropsychological Assessment of Neuropsychiatric Disorders*, second ed. Oxford University Press, New York, pp. 504–525.
- Gras-Vincendon, A., Danion, J.M., Grange, D., Bilik, M., Willard-Schroeder, D., Sichel, J.P., Singer, L., 1994. Explicit memory, repetition priming and cognitive skill learning in schizophrenia. *Schizophr. Res.* 13, 117–126.
- Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am. J. Psychiatry* 153, 321–330.
- Green, M.F., Neuchterlein, K.H., 1999. Should schizophrenia be treated as a neurocognitive disorder? *Schizophr. Bull.* 25, 309–318.
- Gruzelier, J., Seymour, K., Wilson, L., Jolley, A., Hirsch, S., 1988. Impairments on neuropsychologic tests of temporohippocampal and frontohippocampal functions and word fluency in remitting schizophrenia and affective disorders. *Arch. Gen. Psychiatry* 45, 623–629.
- Hamilton, D.A., Sutherland, R.J., 1999. Blocking in human place learning: evidence from virtual navigation. *Psychobiology* 27, 453–461.
- Hamilton, D.A., Driscoll, I., Sutherland, R.J., 2002. Human place learning in a virtual Morris water task: some important constraints on the flexibility of place navigation. *Behav. Brain Res.* 129, 159–170.
- Hamilton, D.A., Kodituwakku, P., Sutherland, R.J., Savage, D.D., 2003. Children with fetal alcohol syndrome are impaired at place learning but not cued-navigation in a virtual Morris water task. *Behav. Brain Res.* 143, 85–94.
- Hanlon, F.M., Sutherland, R.J., 2000. Changes in adult brain and behavior caused by neonatal limbic damage: implications for the etiology of schizophrenia. *Behav. Brain Res.* 107, 71–83.
- Hanlon, F.M., Weisend, M.P., Yeo, R.A., Huang, M.X., Lee, R.R., Thoma, R.J., Moses, S.N., Paulson, K.M., Miller, G.A., Cañive, J.M., 2005. A specific test of hippocampal deficit in schizophrenia. *Behav. Neurosci.* 119, 863–875.
- Jacobs, W.J., Laurance, H.E., Thomas, K.G.F., 1997. Place learning in virtual space: I. Acquisition, overshadowing, and transfer. *Learn. Motiv.* 28, 521–541.
- Jacobs, W.J., Thomas, K.G.F., Laurance, H.E., Nadel, L., 1998. Place learning in virtual space: II. Topographical relations as one dimension of stimulus control. *Learn. Motiv.* 29, 288–308.
- Johnson, J.H., Klingler, D.E., Williams, T.A., 1977. Recognition in episodic long-term memory in schizophrenia. *J. Clin. Psychol.* 33, 643–647.
- Kazes, M., Danion, J.M., Robert, P., Berthet, L., Amado, I., Willard, D., Poirier, M.F., 1999. Impairment of consciously controlled use of memory in schizophrenia. *Neuropsychology* 13, 54–61.
- Kolb, B., Sutherland, R.J., Whishaw, I.Q., 1983. A comparison of the contributions of the frontal and parietal association cortex to spatial localization in rats. *Behav. Neurosci.* 97, 13–27.
- Kolb, B., Buhmann, K., McDonald, R., Sutherland, R., 1994. Dissociation of the medial prefrontal, posterior parietal, and posterior temporal cortex for spatial navigation and recognition memory in the rat. *Cereb. Cortex* 6, 664–680.
- Kraepelin, E., Barclay, R.M., Robertson, G.M., 1919. *Dementia Praecox and Paraphrenia*. E & S Livingstone, Edinburgh, Scotland.
- Laurance, H.E., Thomas, K.G.F., Newman, M.C., Kaszniak, A.W., Nadel, L., Jacobs, W., 2002. Older adults map novel environments but do not place learn: findings from a computerized spatial task. *Aging Neuropsychol. Cogn.* 9, 85–97.
- Lecourtier, L., Neijt, H.C., Kelly, P.H., 2004. Habenula lesions cause impaired cognitive performance in rats: implications for schizophrenia. *Eur. J. Neurosci.* 19, 2551–2560.

- Le Pen, G., Grottick, A.J., Higgins, G.A., Martin, J.R., Jenck, F., Moreau, J.L., 2000. Spatial and associative learning deficits induced by neonatal excitotoxic hippocampal damage in rats: further evaluation of an animal model of schizophrenia. *Behav. Pharmacol.* 11, 257–268.
- Lipska, B.K., Weinberger, D.R., 1994. Subchronic treatment with haloperidol and clozapine in rats with neonatal excitotoxic hippocampal damage. *Neuropsychopharmacology* 10, 199–205.
- Lipska, B.K., Weinberger, D.R., 2000. To model a psychiatric disorder in animals: schizophrenia as a reality test. *Neuropsychopharmacology* 23, 223–239.
- Lipska, B.K., Jaskiw, G.E., Weinberger, D.R., 1993. Postpubertal emergence of hyperresponsiveness to stress and to amphetamine after neonatal excitotoxic hippocampal damage: a potential animal model of schizophrenia. *Neuropsychopharmacology* 9, 67–75.
- Lipska, B.K., Swerdlow, N.R., Geyer, M.A., Jaskiw, G.E., Braff, D.L., Weinberger, D.R., 1995. Neonatal excitotoxic hippocampal damage in rats causes post-pubertal changes in prepulse inhibition of startle and its disruption by apomorphine. *Psychopharmacology* 122, 35–43.
- Mattsson, A., Ogren, S.O., Olson, L., 2002. Facilitation of dopamine-mediated locomotor activity in adult rats following cholinergic denervation. *Exp. Neurol.* 174, 96–108.
- McKenna, P.J., Tamlyn, D., Lund, C.E., Mortimer, A.M., Hammond, S., Baddeley, A.D., 1990. Amnesic syndrome in schizophrenia. *Psychol. Med.* 20, 967–972.
- Miller, G.A., Chapman, J.P., 2001. Misunderstanding analysis of covariance. *J. Abnorm. Psychol.* 110, 40–48.
- Moffat, S.D., Resnick, S.M., 2002. Effects of age on virtual environment place navigation and allocentric cognitive mapping. *Behav. Neurosci.* 116, 851–859.
- Morris, R.G.M., 1981. Spatial localization does not require the presence of local cues. *Learn. Motiv.* 12, 239–260.
- Morris, R.G.M., Garrud, P., Rawlins, J.N.P., O'Keefe, J., 1982. Place navigation impaired in rats with hippocampal lesions. *Nature* 297, 681–683.
- Mumby, D.G., Astur, R.S., Weisend, M.P., Sutherland, R.J., 1999. Retrograde amnesia and selective damage to the hippocampal formation: memory for places and object discriminations. *Behav. Brain Res.* 106, 97–107.
- Nacmani, G., Cohen, B.D., 1969. Recall and recognition free learning in schizophrenics. *J. Abnorm. Psychiatry* 74, 511–516.
- O'Keefe, J., Nadel, L., 1978. *The hippocampus as a cognitive map*. Clarendon Press, Oxford.
- Ploeger, G.E., Spruijt, B.M., Cools, A.R., 1992. Effects of haloperidol on the acquisition of a spatial learning task. *Physiol. Behav.* 52, 979–983.
- Rondi-Reig, L., Libbey, M., Eichenbaum, H., Tonegawa, S., 2001. CA1-specific N-methyl-D-aspartate receptor knockout mice are deficient in solving a nonspatial transverse patterning task. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3543–3548.
- Rowland, L.M., Astur, R.S., Jung, R.E., Bustillo, J.R., Lauriello, J., Yeo, R.A., 2005. Selective cognitive impairments associated with NMDA receptor blockade in humans. *Neuropsychopharmacology* 30, 633–639.
- Rudy, J.W., Sutherland, R.J., 1995. Configural association theory and the hippocampal formation: an appraisal and reconfiguration. *Hippocampus* 5, 375–389.
- Sams-Dodd, F., Lipska, B.K., Weinberger, D.R., 1997. Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behaviour in adulthood. *Psychopharmacology* 132, 303–310.
- Sandstrom, N.J., Kaufman, J., Huettel, S.A., 1998. Males and females use different distal cues in a virtual environment navigation task. *Cogn. Brain Res.* 6, 351–360.
- Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, D.B., Stafiniak, P., 1991. Neuropsychological function in schizophrenia: selective impairment in memory and learning. *Arch. Gen. Psychiatry* 48, 618–624.
- Saykin, A.J., Shtasel, D.L., Gur, R.E., Kester, D.B., Mozley, L.H., Staliniak, P., Gur, R.C., 1994. Neuropsychological deficits in neuroleptic naïve patients with first-episode schizophrenia. *Arch. Gen. Psychiatry* 51, 124–131.
- Schautzer, F., Hamilton, D., Kalla, R., Strupp, M., Brandt, T., 2003. Spatial memory deficits in patients with chronic bilateral vestibular failure. *Ann. N. Y. Acad. Sci.* 1004, 316–324.
- Silva-Gomez, A.B., Bermudez, M., Quirion, R., Srivastava, L.K., Picazo, O., Flores, G., 2003. Comparative behavioral changes between male and female postpubertal rats following neonatal excitotoxic lesions of the ventral hippocampus. *Brain Res.* 973, 285–292.
- Skarsfeldt, T., 1996. Differential effect of antipsychotics on place navigation of rats in the Morris water maze. A comparative study between novel and reference antipsychotics. *Psychopharmacology* 124, 126–133.
- Squire, L.R., 1987. *Memory and Brain*. Oxford University Press, New York, NY.
- Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. *Annu. Rev. Neurosci.* 27, 279–306.
- Sutherland, R.J., Hamilton, D.A., 2004. Rodent spatial navigation: at the crossroads of cognition and movement. *Neurosci. Biobehav. Rev.* 28, 687–697.
- Sutherland, R.J., Rudy, J., 1989. Configural association theory: the role of the hippocampal formation in learning, memory, and amnesia. *Psychobiology* 17, 129–144.
- Sutherland, R.J., Kolb, B., Whishaw, I.Q., 1982. Spatial mapping: definitive disruption by hippocampal or frontal cortical damage in the rat. *Neurosci. Lett.* 31, 271–276.
- Sutherland, R.J., Whishaw, I.Q., Kolb, B., 1983. A behavioral-analysis of spatial localization following electrolytic, kainite-induced or colchicines-induced damage to the hippocampal formation in the rat. *Behav. Brain Res.* 7, 133–153.
- Tamlyn, D., McKenna, P.J., Mortimer, A.M., Lund, C.E., Hammond, S., Baddeley, A.D., 1992. Memory impairment in schizophrenia: its extent, affiliations and neuropsychological character. *Psychol. Med.* 22, 101–115.
- Thomas, K.G.F., Hsu, M., Laurance, H.E., Nadel, L., Jacobs, W.J., 2001. Place learning in virtual space: III. Investigation of spatial navigation training procedures and their application to fMRI and clinical neuropsychology. *Behav. Res. Methods Instrum. Comput.* 33, 21–37.
- Titone, D., Ditman, T., Holzman, P.S., Eichenbaum, H., Levy, D.L., 2004. Transitive inference in schizophrenia: impairments in relational memory organization. *Schizophr. Res.* 68, 235–247.
- Weinberger, D.R., 1987. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch. Gen. Psychiatry* 44, 660–669.
- Weinberger, D.R., 1997. The biological basis of schizophrenia: new directions. *J. Clin. Psychiatry* 58, 22–27.
- Weinberger, D.R., Berman, K.F., Zec, R.F., 1986. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Arch. Gen. Psychiatry* 43, 114–124.

- Weinberger, D.R., Berman, K.F., Suddath, R., Torrey, E.F., 1992. Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance and regional cerebral blood flow study of discordant monozygotic twins. *Am. J. Psychiatry* 149, 890–897.
- Weiss, A.P., Heckers, S., 2001. Neuroimaging of declarative memory in schizophrenia. *Scand. J. Psychol.* 42, 239–250.
- Wexler, B.E., Stevens, A.A., Bowers, A.A., Sernyak, M.J., Goldman-Rakic, P.S., 1998. Word and tone working memory deficits in schizophrenia. *Arch. Gen. Psychiatry* 55, 1093–1096.