ELSEVIER

Neuropsychologia 43 (2005) 1580–1590

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

# Retrograde amnesia in rats with lesions to the hippocampus on a test of spatial memory

Gordon Winocur [a, b, c, d, *], Morris Moscovitch [b, c], Douglas A. Caruana [e], Malcolm A. Binns [b]

[a] *Department of Psychology, Trent University, Ont., Canada*
[b] *Rotman Research Institute, Baycrest Centre for Geriatric Care, 3560 Bathurst Street, Toronto, Ont., Canada M6A 2E1*
[c] *Department of Psychology, University of Toronto, Toronto, Canada*
[d] *Department of Psychiatry, University of Toronto, Toronto, Canada*
[e] *Center for Studies in Behavioral Neurobiology, Department of Psychology, Concordia University, Canada*

Received 29 October 2004; received in revised form 24 January 2005; accepted 25 January 2005
Available online 23 February 2005

**Abstract**

The present study examined remote spatial memory in a test that spans several months to determine whether remote memories are spared relative to more recent ones, as predicted by models of memory consolidation. At 3, 6 or 12 months of age, groups of rats received forced-choice training as to the location of food reward in a cross maze. At 12.5 months, rats received bilateral neurotoxic lesions to the hippocampus or a control surgical procedure and 2 weeks later their memory for the spatial location was tested. Their performance was compared to that of rats with hippocampal or control lesions with no prior training on several measures of savings. The hippocampal group with no pre-training, as expected, was severely impaired in learning the location of the food reward. Compared to this group, rats with hippocampal lesions that were pre-trained consistently performed better at the shortest training–surgery interval but not at the longer ones. That is, rats with hippocampal lesions exhibited retrograde amnesia at all training–surgery intervals and a forgetting curve that paralleled that of the control groups. The results were interpreted within a framework that distinguishes between relational and associative context, and as providing evidence that the hippocampus is necessary for the retention and retrieval of memories that are bound to relational context, regardless of the age of the memory.


*Keywords:* Hippocampus; Retrograde amnesia; Spatial memory; Rats; Brain-damage; Cross-maze; Forgetting

## 1. Introduction

Research into remote memory following medial temporal lesions (MTL) has yielded two patterns of retrograde amnesia (RA) in rats, monkeys and humans. One pattern is characterized by a temporal gradient in which remote pre-morbid memories are retained better than recent memories (e.g., Kim & Fanselow, 1992; Winocur, 1990; Zola-Morgan & Squire, 1990; for review, see Squire, Clark, & Knowlton, 2001). Indeed, retention of remote memory may be normal. Traditionally, this pattern has been interpreted in terms of consolidation theory (Squire, 1992), which states that a period of time is required to form enduring representations. The hippocampus and related MTL structures are said to be necessary for memory retention (and retrieval) only until the consolidation process is complete, after which memories can be recovered directly from extra-hippocampal structures.

A second general pattern of RA has been observed in which memory loss is severe and extensive for the entire period that is tested (Sutherland et al., 2001; Warrington & Sanders, 1971). In some cases, RA parallels the normal forgetting curve, with superior memory for recently acquired information (Viskontas, McAndrews, & Moscovitch, 2000). In other cases, there is no gradient to speak of, with all memories being equally inaccessible (for review, see Fujii, Moscovitch, & Nadel, 2001). Contrary to consolidation theory, these

* Corresponding author. Tel.: +1 416 785 2500x3592; fax: +1 416 785 2474.
*E-mail address:* gwinocur@rotman-baycrest.on.ca (G. Winocur).

0028-3932/$ – see front matter 
doi:10.1016/j.neuropsychologia.2005.01.013

results indicate that the hippocampus and related structures can contribute indefinitely to memory retention and retrieval. This view is broadly consistent with multiple trace theory (MTT), which posits that the hippocampal complex is needed for maintaining and recovering detailed representations of some kinds of memories, regardless of their age (Moscovitch, 2002; Nadel & Moscovitch, 1997).

In attempting to resolve the discrepancy between the two patterns of RA, Rosenbaum, Winocur, and Moscovitch (2001) proposed that the respective patterns were linked to context-dependent and context-free memories in animals, which may correspond to episodic and semantic memory in humans. Context-dependent memories are those in which the complex of cues that defines the target event are linked relationally to each other in spatial (e.g., allocentric cues in water, radial arm and cross mazes) or non-spatial (e.g., configural learning) ways, or both. By contrast, context-free memories exist separately from the relational context, but may be supported by associations formed with elements of the context independently of each other (associative context; e.g., food smell in the food-preference task (Winocur, 1990) and conditional or background stimuli in avoidance conditioning (Winocur, Rawlins, & Gray, 1987). Our view, in line with a growing body of evidence that links hippocampal function to the process of forming contextual associations (Anagnostaras, Gale, & Fanselow, 2001; Nadel & Willner, 1980; Winocur, 1997; Winocur et al., 1987), is that hippocampal lesions affect only those remote memories that are dependent on relational context. The distinction between relational and associative context is similar to the distinctions made by Sutherland and Rudy (1989) between configural and simple associations and by Anagnostaras, Gale, and Fanselow (2001) between unified representations and elemental associations.

It follows from our position that if a memory is always dependent on relational context, the hippocampus will always be implicated and that damage to the structure will disrupt performance regardless of when the memory was formed. Spatial memory prototypically relies on relational context and, consequently, performance on tests of this type of memory should be impaired following hippocampal lesions at all delays after acquisition. The following experiment provides a direct test of this prediction by assessing the effects of hippocampal lesions on remote spatial memory.

It is well known that rats with hippocampal lesions are reliably impaired in learning spatial locations in various tasks, where successful performance depends on effective use of relational cues in the environment (McDonald & Hong, 2000; Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978, 1979; Olton, Becker, & Handelmann, 1979; Winocur, 1982). By comparison, relatively few studies have examined remote spatial memory in rats with hippocampal lesions, and most of them used variations of the Morris Water Maze with retention intervals from 2 to 15 weeks (Bolhuis, Stewart, & Forrest, 1994; Mumby, Astur, Weisend, & Sutherland, 1999; Sutherland et al., 2001; see also Kubie, Sutherland, & Muller, 1999 who used a dry-land version of the water maze). For the most part, hippocampal rats appeared to show extensive memory loss without a temporal gradient (but see Ramos, 1998). However, these studies are inconclusive as to whether the hippocampal contribution is time dependent. In at least two cases (Mumby et al., 1999; Sutherland et al., 2001), control performance deteriorated markedly over the testing interval, reducing the difference between hippocampal and control groups and giving the impression that the memory deficit had diminished over time. The difficulty is further compounded because even the controls performed at near floor levels at the longer intervals (see Squire et al., 2001, for a similar critique).

What is needed is a test of spatial memory in which control performance is above chance even at long intervals. As well, it is important that the intervals be sufficiently long to allow for the possibility of long-term or prolonged consolidation, if indeed it occurs. To this end, we selected a cross-maze task, on which normal rats showed savings over retention intervals spanning several months. Different groups of rats were trained on the cross-maze at 3, 6 or 12 months of age, then subjected to hippocampal or control surgery at about 12.5 months of age and tested 2 weeks later for 3 days. In addition, separate groups of rats with hippocampal or control lesions, with no prior training, were administered the cross-maze task as a test of spatial learning. This condition was included to assess the effects of previous training, over and above any new learning during the test phase, and to confirm the effects of hippocampal lesions on spatial learning. If there were savings, previously trained rats with control lesions should perform better than their untrained counterparts at some or all of the delays; at issue, is whether this holds true for rats with hippocampal lesions.

Consolidation theory posits that the contribution of the hippocampus is time-dependent, even for memories of relational context. As a result, a temporal gradient should be observed following hippocampal lesions, with impairment at short delays before consolidation is complete, but normal performance at long delays when memory has been fully consolidated. By contrast, our view and that of MTT predict that hippocampal lesions will lead to impaired performance at all delays because the spatial nature of the task ensures that the memories will always be dependent on relational context and, necessarily, will rely on the hippocampus.

To test these predictions, we examined performance on the first trial of day 1 testing, which would be the purest measure of memory for the pre-operatively learned spatial location. In addition, we examined the rate of re-learning over 10 trials of day 1, the assumption being that pre-operatively acquired spatial memory would facilitate re-learning. As a final measure of savings, we assessed total performance over 3 days of testing. In all cases, controls should show savings at long training-test intervals. According to consolidation theory, rats with hippocampal lesions should show greater savings at the longer intervals, whereas MTT predicts that impairment at the longer intervals should be at least comparable to that at the shorter intervals.