

# Retrograde amnesia: neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding<sup>☆</sup>

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## Abstract

Many lesion experiments have provided evidence that the hippocampus plays a time-limited role in memory, consistent with the operation of a systems-level memory consolidation process during which lasting neocortical memory traces become established [see Squire, L. R., Clark, R. E., & Knowlton, B. J. (2001). Retrograde amnesia. *Hippocampus* 11, 50]. However, large lesions of the hippocampus at different time intervals after acquisition of a watermaze spatial reference memory task have consistently resulted in temporally ungraded retrograde amnesia [Bolhuis, J. J., Stewart, C. A., Forrest, E. M. (1994). Retrograde amnesia and memory reactivation in rats with ibotenate lesions to the hippocampus or subiculum. *Quarterly Journal of Experimental Psychology* 47B, 129; 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. *Behavioural Brain Research* 106, 97; Sutherland, R. J., Weisend, M. P., Mumby, D., Astur, R. S., Hanlon, F. M., et al. (2001). Retrograde amnesia after hippocampal damage: recent vs. remote memories in two tasks. *Hippocampus* 11, 27]. It is possible that spatial memories acquired during such a task remain permanently dependent on the hippocampus, that chance performance may reflect a failure to access memory traces that are initially unexpressed but still present, or that graded retrograde amnesia for spatial information might only be observed following partial hippocampal lesions. This study examined the retrograde memory impairments of rats that received either partial or complete lesions of the hippocampus either 1–2 days, or 6 weeks after training in a watermaze reference memory task. Memory retention was assessed using a novel ‘reminding’ procedure consisting of a series of rewarded probe trials, allowing the measurement of both free recall and memory reactivation. Rats with complete hippocampal lesions exhibited stable, temporally ungraded retrograde amnesia, and could not be reminded of the correct location. Partially lesioned rats could be reminded of a recently learned platform location, but no recovery of remote memory was observed. These results offer no support for hippocampus-dependent consolidation of allocentric spatial information, and suggest that the hippocampus can play a long-lasting role in spatial memory. The nature of this role—in the storage, retrieval, or expression of memory—is discussed. © 2004 Elsevier Ltd. All rights reserved.

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## 1. Introduction

While there is evidence indicating that the hippocampus plays a temporary role in certain forms of memory, spatial

memories may depend permanently on the integrity of the hippocampus (Bolhuis, Stewart, & Forrest, 1994; Mumby, Astur, Weisend, & Sutherland, 1999; Sutherland, Weisend, Mumby, Astur, & Hanlon, 2001). We now present a study addressing whether this disparity stems from two experimental factors that, although of little apparent theoretical significance, often constitute key differences between experiments, namely the size of the lesion and the testing protocol.

The transformation of memory from a labile initial state to a permanent, durable form that can last a lifetime remains

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poorly understood, despite over a century of scientific interest in the problem (Ribot, 1883). In humans, damage to the temporal lobes or hippocampus alone often results in a disproportionate impairment of recently acquired declarative memories, with relative sparing of memories formed in the more distant past, a phenomenon known as graded retrograde amnesia (e.g. Kapur & Brooks, 1999; Reed & Squire, 1998; Rempel-Clower, Zola, Squire, & Amaral, 1996; Scoville & Milner, 1957; Teng & Squire, 1999). This differential sparing of more remote memories has also been induced experimentally by lesioning the hippocampal formation in animals at different times after training (Anagnostaras, Maren, & Fanselow, 1999; Cho, Beracochea, & Jaffard, 1993; Cho & Kesner, 1996; Clark, Broadbent, Zola, & Squire, 2002; Kim & Fanselow, 1992; Kubie, Sutherland, & Muller, 1999; Maren, Aharonov, & Fanselow, 1997; Ramos, 1998; Takehara, Kawahara, Takatsuki, & Kirino, 2002; Uretsky & McCleary, 1969; Wiig, Cooper, & Bear, 1996; Winocur, McDonald, & Moscovitch, 2001; Zola-Morgan & Squire, 1990; see Squire, Clark, & Knowlton (2001) for review). These studies are complemented by functional imaging data from both rodents and humans indicating that hippocampal activity is sometimes preferentially associated with the retrieval of recent, rather than remote, memory (Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999; Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Haist, Bowden Gore, & Mao, 2001; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003). Observations such as these have led to the concept of hippocampus-dependent memory consolidation. The so-called ‘standard model’ suggests that interactions between the hippocampus and the cortex after learning result in the stabilization of memories outside the hippocampus (Squire & Alvarez, 1995). These memories are therefore spared if hippocampal damage takes place once a memory consolidation process has terminated.

However, a number of pieces of evidence do not support this model (Nadel & Moscovitch, 1997). In some cases, both in humans and animals, retrograde amnesia is equally severe for both recent and remote memories (Bolhuis et al., 1994; Cipolotti et al., 2001; Mumby et al., 1999; Sanders & Warrington, 1971; Sutherland et al., 2001; Viskontas, McAndrews, & Moscovitch, 2000). Likewise, functional imaging often reveals substantial hippocampal activity even following the retrieval of remote memory (Maguire & Frith, 2003; Ryan et al., 2001). The existence of temporally ungraded retrograde amnesia has led to the proposition of an alternative hypothesis, the multiple trace theory, according to which certain memories are permanently mediated by cortico-hippocampal traces (Moscovitch & Nadel, 1998; Nadel & Moscovitch, 1997). Specifically, the theory holds that each reactivation of a memory leads to the formation of additional traces (Nadel & Moscovitch, 1997). Temporally graded retrograde amnesia can then be explained by the proliferation of memory traces over time: provided that hippocampal damage is incomplete, remote memories, represented by a larger number of traces, will be better preserved

than recently acquired memories. According to a later version of the theory (Rosenbaum, Winocur, & Moscovitch, 2001), this model only applies to contextually rich memories, not to those that are context-free or semantic in character; it is suggested that the latter might exhibit a time-limited dependence on the hippocampus as the ‘standard’ model predicts (Rosenbaum et al., 2001). Alternatively, the hippocampus may never be required under these circumstances (cf. Vargha-Khadem et al., 1997).

These two theories of the preservation of remote episodic or relational memory after hippocampal damage make contrasting predictions. One prediction of the multiple trace theory is that partial damage to the hippocampus can result in a temporal gradient of retrograde amnesia, whereas a complete hippocampal lesion will lead to ‘flat’, i.e. temporally ungraded, amnesia. In contrast, the standard model predicts a temporal gradient favouring remote memory irrespective of the extent of the lesion. The capricious nature of human neuronal injury results in most, if not all, human amnesic subjects having only partial hippocampal damage. However, variability in the locus and extent of extra hippocampal damage may also account for some of the apparent discrepancies concerning gradients of human retrograde amnesia (Reed & Squire, 1998; Rempel-Clower et al., 1996).

In considering the effects of lesion size, it might be relevant that watermaze studies of retrograde amnesia have generally employed large hippocampal lesions (e.g. Bolhuis et al., 1994; Mumby et al., 1999; Sutherland et al., 2001), compared to the less extensive septal (dorsal) hippocampal lesions often used in studies of retrograde amnesia for non-spatial information (e.g. Kim & Fanselow, 1992; Maren et al., 1997; Winocur, 1990). Although reports exist of temporally graded retrograde amnesia for spatial information following dorsal hippocampal lesions (Ramos, 1998), and also for non-spatial information following large hippocampal lesions (Clark et al., 2002; Winocur et al., 2001), the effect of lesion size on retrograde spatial memory has never been systematically investigated; see Jarrard (2001).

A further issue is that the memories shown by humans or animals with partial hippocampal damage are likely to be weak, as only a subset of the stored traces will be available; and a failure of memory retrieval, rather than storage, should always be considered (de Hoz, Martin, & Morris, 2004). Not only may the detection of such memories be difficult, but the possibility of seeing differences as a function of the age of the memory may be small unless cueing techniques are deployed to aid memory retrieval. This problem is compounded by the fact that long-term retention of spatial memory in intact rodents is often poor, requiring the use of reacquisition as a measure of memory (Kubie et al., 1999; Mumby et al., 1999; Ramos, 1998; Sutherland et al., 2001); however, the use of a savings measure confounds retrieval and re-learning. Certain cueing techniques, such as merely re-exposing the animals to the contextual or apparatus cues may aid memory reactivation without incurring any re-learning (Gisquet Verrier & Schenk, 1994; Gold, Haycock, Marri, & McGaugh,

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