Retrograde Amnesia

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ABSTRACT: In humans, the phenomenon of temporally graded retrograde amnesia has been described in the clinic and the laboratory for more than 100 years. In the 1990s, retrograde amnesia began to be studied prospectively in experimental animals. We identified 13 published studies in which animals were given equivalent training at two or more separate times before damage to the fornix or hippocampal formation. Eleven of these studies found temporally graded retrograde amnesia, with the extent of amnesia ranging from several days to a month or two. We consider these studies and also suggest why temporally graded retrograde amnesia has sometimes not been observed. Although the evidence in favor of temporally graded retrograde amnesia is substantial, the inference from this work, that memory is reorganized as time passes, is rather vague and depends on mechanisms yet to be identified. It is therefore encouraging that many opportunities exist for moving beyond purely descriptive studies to studies that involve treatments or manipulations directed toward yielding information about mechanisms. *Hippocampus 2001;11:50–55.*
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INTRODUCTION

For more than 100 years, clinical reports of human memory impairment have described the phenomenon of temporally graded retrograde amnesia (Ribot, 1881; Russell and Nathan, 1946), i.e., that in memory-impaired patients remote memory often appears spared relative to recent memory. Quantitative studies of retrograde amnesia began in the 1970s (Sanders and Warrington, 1971; Squire et al., 1975; Squire, 1975). Although temporally graded amnesia was frequently observed, reports of extended, ungraded amnesia have also appeared (reviewed by Hodges, 1994; Squire and Alvarez, 1995). Some progress has been made towards understanding when retrograde amnesia is graded or ungraded by focusing on which specific anatomical structures and connections are damaged. For example, many cases of extended, ungraded retrograde amnesia have involved damage to structures in the neocortex of the lateral and anterior temporal lobe (Kapur, 1993; Squire and Alvarez, 1995). By contrast, temporally graded retrograde amnesia is most often associated with damage to the structures of the medial temporal lobe (Kapur and Brooks, 1999; Reed and Squire, 1998). In cases of temporally graded human amnesia where detailed neuropathological and neuropsychological information is available, bilateral damage was limited to the CA1 field of the hippocampus proper (patients R.B. and G.D., Zola-Morgan et al., 1986; Rempel-Clower et al., 1996) or to structures within the hippocampal formation (the CA1 fields, dentate gyrus, subiculum, and entorhinal cortex) (patients L.M. and W.H., Rempel-Clower et al., 1996; Beatty et al., 1987; Salmon et al., 1988; for an additional patient see Victor and Agamanolis, 1990).

Despite improved understanding of the neuroanatomy of retrograde amnesia, it is nevertheless the case that studies in patients necessarily depend on retrospective methods. As a result, it is difficult to sample memory

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equivalently across past time periods and correspondingly difficult to compare performance scores across time periods. Yet, knowing the shapes of the performance curves across past time periods is imperative if retrograde amnesia is to be fully understood (Squire, 1992). For these reasons, it was a welcome development when prospective studies of retrograde amnesia began in earnest in the 1990s, using animal models of human amnesia. As outlined by Murray and Bussey (2001), the prospective study allows precision with respect to the timing and strength of original learning; and the use of experimental animals brings other important factors under experimental control, including especially the locus and extent of the lesion.

Most of the studies carried out to date have focused on the effects of hippocampal formation or fornix lesions on memories acquired at different times before surgery. Anagnostaras et al. (2001) raise concerns about studies that have used excitotoxins to damage the hippocampus, suggesting that excitotoxic lesions may damage structures outside the hippocampus. Murray and Bussey (2001) point out the advantages of between-subject designs for studies of retrograde amnesia, where different groups of animals are trained at each time point of interest prior to surgery. We are aware of 13 published studies to date, in which animals were given equivalent amounts of training at two or more distinct times before bilateral damage to the hippocampal formation or the fornix. The results of these studies are presented in chronological order in Figure 1. Eight studies involved aspiration or electrolytic (i.e., non-excitotoxic) lesions, and six used a between-subjects design. Together, the studies involved five different species (cats, monkeys, rabbits, rats, and mice) and a wide variety of spatial and nonspatial tasks, including context fear conditioning, trace eyeblink conditioning, object discrimination learning, and place learning in the water maze. The results were similar with different lesion techniques and with between-group and within-group designs.

Before considering this collection of studies, it is useful to mention two studies of retrograde amnesia that do not appear in Figure 1. One study had only three animals in the operated group, a numerically small impairment in the operated group, and a non-optimal design for studying retrograde amnesia (Gaffan, 1993). Nevertheless, the operated group, in fact, exhibited temporally graded retrograde amnesia. However, it is difficult for us to interpret the overall pattern of results, which was strongly influenced by the unusual performance of a single control animal that (like the operated group) retained remotely learned material *better* than recently learned material. In the second study, animals were trained on two consecutive discrimination problems, each of which required an average of 2 or 3 days (Cho et al., 1995). Training on one problem was completed, on average, 3.7 days before hippocampal or entorhinal surgery, and training on the second problem was completed 1 day before surgery. The pattern of data is in fact not incompatible with temporally graded retrograde amnesia. However, because no time interval intervened between the training of the two tasks, this study cannot address questions about recent and remote memory that are relevant to the phenomenon of retrograde amnesia.

Of the 13 studies summarized in Figure 1, 11 found temporally graded retrograde amnesia (all but studies 6 and 12, which are discussed below). The extent of retrograde amnesia ranges from about 5 days (study 2) to a month or more (studies 3, 8, and 10). Interestingly, in all 11 studies that found temporally graded retrograde amnesia, the shape of the retrograde amnesia curve is upward-going to the right. That is the operated groups retained remotely acquired memories better than recently acquired memories. As discussed elsewhere (Squire, 1992), this feature of temporally graded retrograde amnesia is especially important to the idea that the structures damaged in amnesia have a temporary role, and that memories initially depend on these structures but become independent as time passes.

Although most studies of retrograde amnesia in experimental animals have focused on the hippocampal formation, a few studies have explored the effects of lesions in the adjacent cortex, or of larger lesions that include both the hippocampal formation and adjacent cortex. In one study, conjoint perirhinal-entorhinal lesions in monkeys impaired the retention of object discrimination problems similarly, whether they were learned 1 week or 16 weeks before surgery (Thornton et al., 1997). No temporal gradient of retrograde amnesia was observed. A second study compared the effects of perirhinal lesions or combined perirhinal-fornix lesions in rats on visual discrimination problems learned 1–8 weeks before surgery (Wiig et al., 1996). The results for both these groups resembled the effects of fornix lesions alone (Fig. 1, study 9), except that the performance of discriminations learned 8 weeks before surgery was significantly impaired.

Finally, in a third study, monkeys with large medial temporal lobe lesions that included the amygdala, hippocampal formation, and perirhinal and parahippocampal cortices were impaired similarly in the retention of 100 object discrimination problems that had been learned from 2–32 weeks before surgery (Salmon et al., 1987). Some incidental damage to the inferotemporal cortex (area TE) was present in all four operated animals.

The available data from experimental animals thus suggest that retrograde amnesia is more extensive after large medial temporal lobe lesions, or after conjoint perirhinal-entorhinal cortex lesions, than after lesions limited to the hippocampus or the entorhinal cortex. Damage lateral to the medial temporal lobe may also increase the extent of retrograde amnesia. The available findings from human patients are consistent with this conclusion. First, damage limited to the CA1 field of the hippocampus (patients R.B. and G.D.) causes a limited retrograde amnesia, involving perhaps 1 or 2 years. More extensive damage, but damage still limited to the hippocampal formation (patients L.M. and W.H.), causes extensive temporally graded retrograde amnesia covering as much as 15–25 years. Finally, large medial temporal lobe lesions, albeit lesions that extend laterally to include anterior fusiform gyrus (patient E.P., Reed and Squire, 1998), produce extensive retrograde amnesia covering 40–50 years. Nevertheless, memories for facts and events from early life appear to be intact. Similarly, patient H.M. (Scoville and Milner, 1957), who sustained bilateral resection of the medial temporal lobes at age 27, is also reported to have access to memories from early life (for additional discussion, see Rempel-Clower et al., 1996). These observations, taken together, suggest that temporally graded retrograde amnesia becomes more extensive as damage extends beyond the hippocampus.

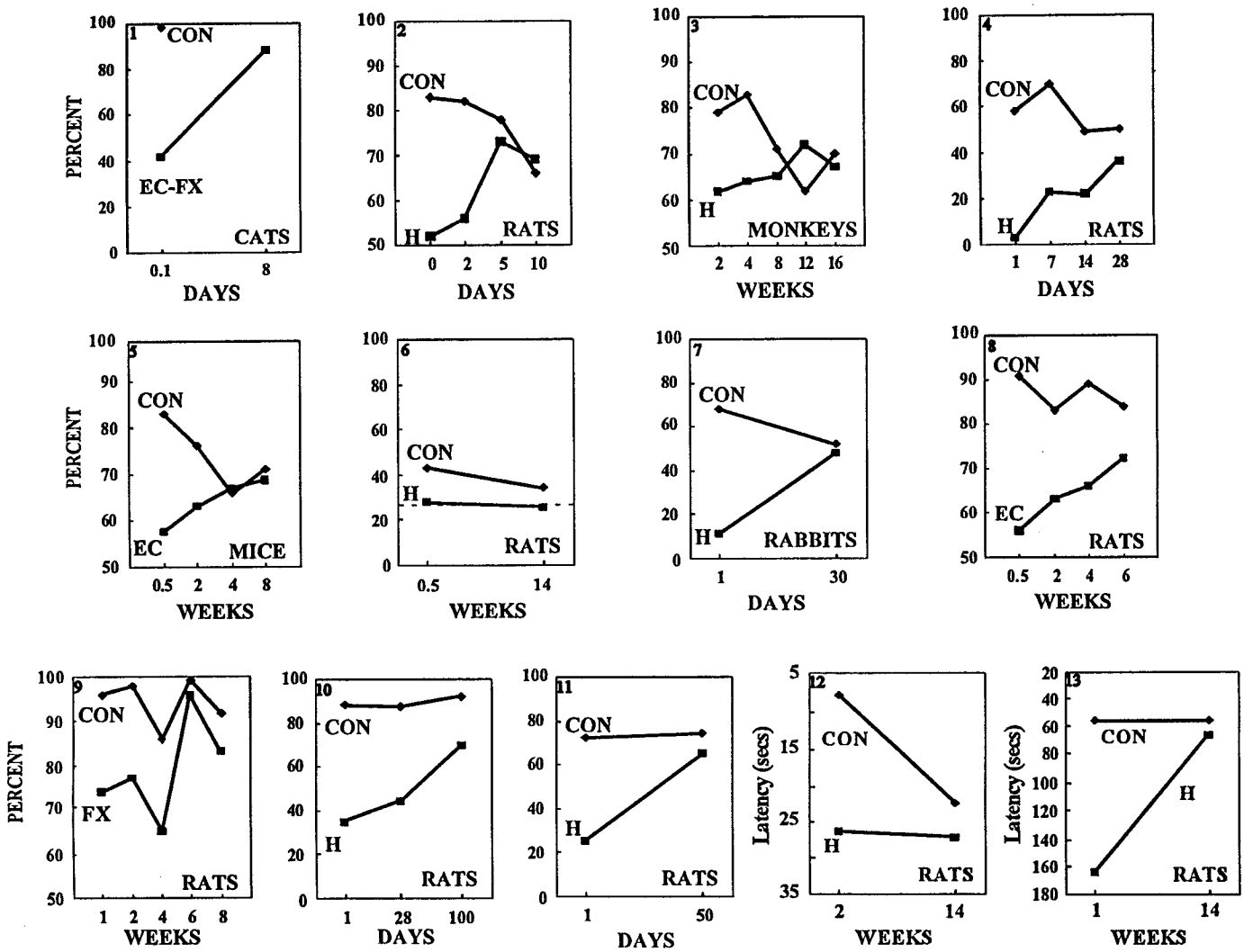

FIGURE 1. Summary of findings from 13 studies that examined retrograde amnesia prospectively. In each case, an equivalent amount of training was given at each of two or more times before damage to the hippocampal formation or fornix, and retention was assessed shortly after surgery. Data show performance of control (CON) and operated animals (H, hippocampus; EC, entorhinal cortex; FX, fornix) as a function of training-surgery interval. Performance scores are in percent (0–100 or 50–100) so that a high score reflects good retention. In studies 12 and 13, the performance score is the latency to find a hidden goal, and here a low score reflects good retention. (Note here that the axis has been constructed so that low latency scores, like high percent scores, appear at the top of each panel.) In study 6, the dotted line denotes chance performance. Study 1, Uretsky and McCleary, 1969; adapted from their Figure 2. Study 2, Winocur, 1990; adapted from his Figure 2. Study 3, Zola-Morgan and Squire, 1990; adapted from their Figure 2. Study 4, Kim and Fanselow, 1992; adapted from their Figure 2. Study 5, Cho et al., 1993; adapted from their Figure 3. Study 6, Bolhuis et al., 1994; adapted from their Figure 4A. Study 7, Kim et al., 1995; adapted from their Figure 3, first retention day. Study 8, Cho and Kesner, 1996; adapted from their Figure 4. Study 9, Wiig et al., 1996; adapted from their Figure 4A. Study 10, Maren et al., 1999; adapted from their Figure 4A. Study 11, Anagnostaras et al., 1999; adapted from their Figure 3C. Study 12, Mumby et al., 1999; adapted from their Figure 5. Study 13, Kubie et al., 1999; adapted from their Figures 3 and 5, first five retention trials.

This pattern of findings implies that the hippocampus itself is important for memory for a relatively short period of time after learning and that the adjacent perirhinal and parahippocampal cortices remain important for a longer time. Thus, these cortices may have an intermediate function between the hippocampus proper and the association areas of, for example, the temporal and parietal neocortex, which are thought to be permanent repositories of long-term memory. This idea that the reorganization or consolidation of memory occurs in stages has also been developed by others (Eichenbaum et al., 1999). At the same time, it is important to note that the few available studies of experimental animals with large medial temporal lobe lesions have not yet documented the extended, temporally graded retrograde amnesia that has been described in patients with large medial temporal lobe lesions.

New data presented in the accompanying articles, and not illustrated in Figure 1, provide some additional information about the nature of retrograde amnesia. Winocur et al. (2001) tested rats with large hippocampal lesions on the retention of a socially-acquired food preference (Galef and Wigmore, 1983). Previously, rats with dorsal hippocampal lesions were found to exhibit tempo-

rally graded retrograde amnesia covering about 5 days (Winocur, 1990) (Fig. 1, study 2). In the new study, nearly complete dorsal and ventral hippocampal lesions produced virtually the same result. Earlier studies have also found temporally graded retrograde amnesia in animals with nearly complete lesions of the hippocampus (Fig. 1, studies 7 and 13). It had been suggested that complete lesions of the hippocampus, or perhaps complete lesions of medial temporal lobe structures, should lead to a loss of memory (especially autobiographical memory) that extends throughout life and that no gradient of retrograde amnesia should be observed (Nadel and Moscovitch, 1997). The results of studies like the new one described by Winocur et al. (2001) count against this suggestion, at least when only the hippocampus is considered.

Alternatively, if the idea proposed by Nadel and Moscovitch (1997) is meant to apply instead to the entire medial temporal lobe, then one can turn to the findings from patient E.P. (Reed and Squire, 1998; Stefanacci et al., 2000). E.P. has extensive bilateral medial temporal lobe lesions, but is nevertheless capable of excellent autobiographical remembering from his early life. Neither the quantity nor quality of his recollections can be distinguished from those of controls (Reed and Squire, 1998). These findings count against the suggestion that the medial temporal lobe is needed for recovering remote memories (Nadel and Moscovitch, 1997) and favor instead the view that remote memories are independent of medial temporal lobe structures.

Interestingly, Reed and Squire (1998) described a second postencephalitic patient (G.T.), who also has nearly complete medial temporal lobe damage bilaterally but whose lesion extends laterally to involve much of the left and right temporal lobes. G.T. is severely impaired at autobiographical remembering and can produce virtually no episodic memories from any period in his life. The findings from G.T., and from other severely impaired patients, are consistent with the idea that extensive, ungraded retrograde amnesia occurs when there is lateral temporal cortical damage in addition to medial temporal lobe pathology (Squire and Alvarez, 1995; Kapur, 1993).

Two new studies of retrograde amnesia in rats are described by Sutherland et al. (2001), which are of particular interest with respect to the widely discussed role of the hippocampus in spatial memory. In the two studies, rats learned two different problems in the water maze at either 1 day, 1 week, 2 weeks, 4 weeks, or 15 weeks before hippocampal surgery (NMDA lesions). One study involved a two-choice visible platform discrimination. On the first eight trials of retention, the rats with hippocampal lesions were impaired even at the longest (15-week) training-surgery interval (Sutherland et al., 2001, their Fig. 6B). Because it is possible that the retention measure could be complicated by a difficulty in relearning the discrimination (Knowlton and Fanselow, 1998), it would be interesting to know the performance scores on the first retention trial.

The second study involved was the hidden platform version of the Morris water maze. Retention of place memory was first tested using a nonplatform probe trial, and retention was then tested on a trial with the hidden platform present. A temporal gradient of retrograde amnesia was not observed. On both measures of retention, rats with hippocampal lesions were impaired relative to controls when learning occurred only 1 day or 1 week before surgery (and up to 2 weeks before surgery in the case of the second measure). At training-surgery intervals longer than 2 weeks, the poor performance of the control animals appears to have brought their scores too close to the scores of the operated animals for a between-group difference to emerge (Sutherland et al., 2001, their Figs. 6A and 8). Indeed, for the control rats there was no evidence of retention beyond 4 weeks after training. Once more than 4 weeks had passed, control rats performed at chance (25%) on the no-platform probe trial. In addition, after 2 weeks had passed, the swim latency of the control animals to find the hidden platform was similar to their swim latency during the first few trials of initial training (R. Sutherland, personal communication).

There have been other studies of retrograde amnesia and spatial memory in experimental animals (Fig. 1, studies 6, 8, 12, and 13). Of these, two found evidence for sparing of remote spatial memory (studies 8 and 13), and two did not (studies 6 and 12). What might account for the different results? The answer may lie in how long after training the phenomenon of retrograde amnesia can be studied. In the studies that found evidence for sparing of remote spatial memory, the spared memories had been acquired 6 weeks (study 8) or 14 weeks (study 13) before surgery. (Indeed, the data in study 8 suggest that sparing of remote memory might have been even more complete had training-surgery intervals longer than 6 weeks been included in the study.) In these same studies, control animals performed quite well at all the time points studied. In contrast, in the studies that did not find sparing of remote spatial memory (studies 6 and 12; the new study by Sutherland et al., 2001), control animals performed poorly (study 6) or at naive levels beyond 4 weeks after training (study 12; also Sutherland et al., 2001). If memory for these spatial tasks requires many weeks to become independent of the hippocampus, then studies in experimental animals will be unsuccessful at detecting this process unless memory can be studied for many weeks after training.

Recent evidence from humans indicates that remote spatial memory is spared even after large medial temporal lobe lesions. Patient E.P., described earlier, is able to recollect the layout of the neighborhood in which he grew up and from which he moved away as a young adult (Teng and Squire, 1999). He can mentally navigate, construct novel routes, and point correctly to landmarks while imagining himself at various locations. Yet he cannot give any directions to prominent locations in his current neighborhood to which he moved after he became amnesic; and, although he lives less than 2 miles from the Pacific Ocean, he cannot when asked point in the direction of the ocean.

Spatial memory has often been thought to have special status with respect to the function of the hippocampus. However, a number of considerations suggest that spatial memory is better viewed as an example of a broader category that includes both spatial and nonspatial relational (declarative) memory, all of which depends on the integrity of the hippocampus (Squire, 1992; Eichenbaum et al., 1999). The findings for retrograde amnesia and spatial memory, as just reviewed, are consistent with this perspective.

The nature of retrograde amnesia, both graded and ungraded and spatial and nonspatial, has been a central topic in the biology of memory for many years. It is easy to understand why discussion and debate

about retrograde amnesia has been so extended. The relevant experiments take considerable time to be completed, and they are difficult and expensive to carry out. In addition, the idea that has come out of retrograde amnesia studies, namely, that memory is reorganized as time passes and gradually becomes independent of the hippocampus, is rather vague and depends on mechanisms yet to be identified. Nevertheless, the evidence that something like this occurs is substantial. In the case of patients with damage limited to the hippocampal formation, temporally graded retrograde amnesia has been observed repeatedly in the clinic and the laboratory. In the case of experimental animals, 11 of the 13 studies in Figure 1, plus the new study by Winocur et al. (2001), report the phenomenon of temporally graded retrograde amnesia. And plausible explanations are available as to why a few studies do not (two in Fig. 1 plus the two new studies by Sutherland et al., 2001).

While new work will be helpful, particularly work directed at medial temporal lobe structures other than the hippocampal formation and fornix, the time is ripe to move beyond purely descriptive studies. No studies have been done with treatments or manipulations that might identify, for example, what determines the extent of temporally graded retrograde amnesia or what kind of process must occur after training. A number of promising opportunities have become available for approaching such questions: the possibility in behaving animals of recording from cortical neurons that may be part of hippocampus-dependent representations (Higuchi and Miyashita, 1996; Messinger et al., 2000; Erickson and Desimone, 1999), the possibility of interfering selectively with learning, retrieval, or consolidation by temporally controlled manipulation of gene expression (Hood et al., 2000), the possibility of reversibly inactivating the hippocampus or other structures at specific times with pharmacological agents (Riedel et al., 1999), and the possibility of tracking the course of memory reorganization with neuroimaging techniques (Bontempi et al., 1999; Stark and Squire, 2000). The 1990s marked the period in which the phenomenon of temporally graded retrograde amnesia was documented in experimental animals. Perhaps the new decade will yield the first clues about its mechanisms.

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