Consolidation and the Medial Temporal Lobe Revisited: Methodological Considerations

Elisabeth A. Murray* and Timothy J. Bussey

Laboratory of Neuropsychology, National Institute of Mental Health, Bethesda, Maryland

ABSTRACT: It is widely believed that new memories are stored in the medial temporal lobe structures in the short term, but then are reorganized over time as the neocortex gradually comes to support stable long-term storage. On this view, the medial temporal lobe structures play a time-limited role in information storage. This putative process of reorganization, known as consolidation, is supported by some clinical findings in humans and by some data from nonhuman animals. Here we review prospective studies of retrograde memory in nonhuman animals, with particular emphasis on experimental design. In considering the evidence for a time-limited role for the medial temporal lobe in information storage, we note that there are alternative interpretations for at least some of the findings typically cited in support of the consolidation process. In addition, we suggest that some studies arguing against the consolidation view should probably be given more weight than they have so far received. Finally, we observe that different structures in the medial temporal lobe are unlikely to operate together as a single functional unit mediating a single consolidation process. Although evidence for a time-limited role for medial temporal lobe structures in memory is at present equivocal, future studies that consider some of the alternative accounts we and others have identified will provide a clearer picture of the mechanisms underlying information storage and retrieval in the brain. ***Hippocampus 2001;11:1–7.*** **Published 2001 Wiley-Liss, Inc.†**

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INTRODUCTION

Consolidation of information is thought to be mediated by structures in the medial temporal lobe (MTL) and related medial thalamic structures. This idea has arisen, in part, to explain the findings obtained in several studies in human subjects that have examined retrograde memory, i.e., memory for events that occurred prior to brain trauma. Korsakoff's amnesics, subjects who have become amnesic after surgery for aneurysms of the anterior communicating artery, and nonalcoholic amnesic subjects with damage reportedly limited to the hippocampal formation, all exhibited a pattern of retrograde amnesia characterized by more profound loss of recent as opposed to remote memories (the so-called "temporal gradient") (Gade and Mortensen, 1990; Reed and Squire, 1998). Thus, the pattern of memory loss suggests a gradual process of reorganization or consolidation in which the contribution of certain MTL or medial thalamic structures gradually wanes, and the neocortex comes to support stable, long-term memory. Although alternative explanations of the pattern of retrograde memory impairment (ones not invoking the notion of consolidation) have been offered (Gade and Mortensen, 1990; Nadel and Moscovitch, 1997), the prevailing view is still in favor of the consolidation hypothesis.

It is widely appreciated that clinical populations do not provide a satisfactory answer to questions regarding the fate of information stored prior to brain trauma (Squire, 1992). For example, in some populations (e.g., those with Korsakoff's syndrome) it is difficult to distinguish anterograde from retrograde amnesia, and almost all brain-damaged clinical patients have a lesion that is difficult to specify, and which is unlikely to be limited to a given brain structure. Furthermore, human studies are necessarily retrospective, and thus it is difficult to know exactly when information was acquired, or how well it was learned. Moreover, it has been suggested that some types of memory change character over time (although not necessarily by virtue of the passage of time per se). For example, episodic autobiographical memories are thought to become less "event"-like and more "fact"-like over time (Cermak and O'Connor, 1983). Prospective studies using animals allow investigators to determine with much greater precision the site of brain damage, the time of acquisition of information, and the strength and nature of the original learning. Consequently, several prospective studies of retrograde memory in nonhuman animals have been conducted, and many of these have found that ablations of certain MTL structures yield retrograde memory loss with the aforementioned temporal gradient signature. The pattern of results in experimental studies with nonhuman animals therefore appears to parallel the pattern observed in clinical studies, and has provided support for the consolidation hypothesis. Because experimental evidence from nonhuman animals is an especially critical component of our knowledge base concerning the mechanisms of information storage in the brain, such studies should be encouraged. At the same time, these studies need to be critically evaluated.

Prospective studies of retrograde memory are accompanied by a unique set of methodological issues, such as the choice of between- vs. within-subjects designs, the

*Correspondence to: E.A. Murray, Ph.D., Laboratory of Neuropsychology, National Institute of Mental Health, Building 49, Room 1B80, Bethesda, MD 20892-4415. E-mail: eam@ln.nimh.nih.gov
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number of time points necessary to reveal a temporal gradient where one exists, and whether a study must include substantial forgetting at remote time points in control subjects. It has been claimed that certain features of experimental design, such as forgetting by normal control subjects, are necessary for unequivocal interpretation of the data in the operated subjects (Salmon et al., 1985). In other cases, studies have been excluded from consideration, presumably because of perceived failings in one or more of these aspects of design (Milner et al., 1998; Squire and Knowlton, in press). In this article, we examine specific theoretical and methodological issues concerning prospective studies of retrograde memory carried out in nonhuman animals to gain a more complete picture of the current status of the consolidation debate. Selected studies are cited as examples throughout, but no attempt is made to provide an exhaustive review. Taking these methodological considerations into account, we then reevaluate the weight of experimental evidence in support of the hypothesis that MTL structures mediate consolidation of information.

METHODOLOGICAL CONSIDERATIONS

Typically, prospective studies of retrograde memory assess retention of material learned prior to a brain operation, in which a cerebral ablation or disconnection is performed. Alternatively, the effects of manipulations other than brain surgery (e.g., electroconvulsive shock, administration of drugs or other agents, electrical stimulation of the brain) may be investigated. For present purposes, we will limit our discussion to ablation studies. We now turn to our discussion of methodological considerations, focusing primarily on those that may influence the outcomes of prospective studies of retrograde memory. A summary of the features of a number of studies of retrograde memory in nonhuman animals is provided in Table 1.

Within-Subjects vs. Between-Subjects Designs

By far the most important decision an investigator faces in designing a prospective study of retrograde memory is whether to use a within- or between-subjects design. (For present purposes, a "within-subjects" design refers to a study in which each animal is presented with material for acquisition at two or more different learning-surgery intervals or "time points." In a "between-subjects" design, different groups of animals are used to acquire data for the different learning-surgery intervals.) Many studies have used a within-subjects design, which is associated with some potential drawbacks. Specifically, it is difficult either to predict or to control the development of a learning set for material learned at different time points prior to surgery, and in arranging for equivalent amounts of training across those time points. These two topics are taken up next.

Learning set

In studies employing within-subject designs, there will be opportunity for the development of a learning set over the course of the preoperative learning period, and this may cloud interpretation of the effects of a brain lesion. Indeed, in some studies using within-subject designs, the animals appear to have learned the material at different time points at different rates. For example, Zola-Morgan and Squire (1990) trained monkeys on several sets of object discrimination problems at 16, 12, 8, 4, and 2 weeks prior to removal of the hippocampal formation (hippocampus proper, dentate gyrus, subicular complex) plus underlying parahippocampal cortex and entorhinal cortex. The monkeys were given a different set of problems for acquisition at each time point and, in addition, received a fixed number of training trials for each problem at each time point (or training episode) regardless of learning rate. Examination of the data revealed that there was a significant effect of training episode (see note 18, Zola-Morgan and Squire, 1990), which indicates that problems administered at later time points (recent) were learned faster than those administered at the early time points (remote). A similar analysis holds for the study carried out by Wiig et al. (1996). In that study, each rat learned one problem at each of five time points (8, 6, 4, 2, and 1 week) prior to lesions of the perirhinal cortex, the fornix, or the two combined. As in the study by Zola-Morgan and Squire (1990), there were clear differences in the rate at which animals learned the discrimination problems across time points. Again, lesions yielded greater disruption of the recently (relative to remotely) acquired problems.

Although both of these studies reported a temporally graded memory loss in animals that received lesions in the MTL, and therefore both appear to support the consolidation hypothesis, we might ask whether there is an alternative interpretation of the data in those situations in which there is clear development of a learning set by subjects prior to operation. When a learning set develops, recent and remote problems may be encoded in different ways and/or by different brain regions. For example, several theoretical accounts stress a role for the hippocampal formation in rapid acquisition of information (McClelland et al., 1995; Squire and Zola-Morgan, 1983; Wise and Murray, 1999), and for the neocortex in slower acquisition. If animals learned later (recent) problems more rapidly than early (remote) problems, then MTL lesions might be expected to disrupt the retention of recently acquired information to a greater extent than the remotely acquired information, which is precisely the outcome reported. In other words, if different information encoding and storage systems are differentially engaged in the acquisition of information across time points, the retention (or retrieval) of that information might likewise be differentially affected by a brain lesion. Thus, in at least some cases, there is an alternative to the "consolidation" interpretation of those studies reporting a temporal gradient of information loss.

It can be appreciated that animals are less likely to develop a learning set if there are few, as opposed to many, learning episodes. Indeed, Thornton et al. (1997) chose to use only two time points for precisely this reason, and these authors successfully achieved equivalent learning rates (at least in terms of sessions to criterion) at those time points. It may be no accident that some of the studies reporting a temporally extensive memory loss (i.e., no gradient) after operation have used only two time points (Gaffan, 1993; Thornton et al., 1997). Moreover, examination of Table 1 reveals that in 7 of 8 cases where learning set could be evaluated, a learning

TABLE 1.

*Summary of Retrograde Amnesia Studies in Nonhuman Animals**

Study	Animal	Lesion	Task	Within- or between-subjects?	Number of time points	Acquisition: functional criterion or fixed number of trials?	Evidence of normal forgetting?	Evidence for preoperative learning set?	Result
Anagnostaras et al. (1999)	Rat	Electrolytic dorsal HC	Context and tone fear conditioning	Within	2: 1 and 51 days	Fixed number of tone-shock pairings	No	Not reported	Context: graded RA Tone: no RA
Bolhuis et al. (1994)	Rat	IBO HC IBO SUB	Water maze	Between	2: 3 and 14 days	Fixed	Yes	N/A	Flat RA
Cho et al. (1993)	Mouse	IBO EC	Two-choice discrimination in radial maze	Within	4: 3 days; 2, 4, and 6 weeks	Fixed	Yes	Yes	Graded RA
Cho and Kesner (1996)	Rat	Elecrolytic EC Aspiration PC	Two-choice discrimination in radial maze	Within	4: 1 day; 2, 4, and 6 weeks	Criterion	No	No	EC: graded RA PC: flat RA
Cho et al. (1995), experiment 1	Rat	Electrolytic HC Electrolytic EC Aspiration PC	Two-choice discrimination in radial maze	Within	2: 1 and ~3 days	Criterion	No	No (errors) Yes (sessions)	HC, EC: graded RA PC: No RA
Cho et al. (1995), experiment 2	Rat	Electrolytic HC Electrolytic EC	Two-choice discrimination in radial maze	Within	2: 1 and ~3 days	Criterion	No	Yes	EC: graded HC: flat RA
Gaffan (1993)	Monkey	FNX	Scene discrimination	Within	2: 1 day and 6.5 months	Criterion	Yes	Can't assess[a]	Flat RA
Kim et al. (1995)	Rabbit	Aspiration HC	Trace eyeblink conditioning	Between	2: 1 day, 1 month	Criterion	No	N/A	Graded RA
Kim and Fanslow (1992)	Rat	Electrolytic HC	Context and tone fear conditioning	Between	4: 1, 7, 14, and 28 days	Fixed number of tone-shock pairings	No	N/A	Context: graded RA Tone: no RA
Maren et al. (1997)	Rat	NMDA dorsal HC	Context and tone fear conditioning	Between	3: 1, 28, and 100 days	Fixed number of tone-shock pairings	No	N/A	Context: graded RA Tone: flat RA
Salmon et al. (1987)	Monkey	Aspiration HC, AMY, EC	Concurrent object discrimination	Within	5: 2, 4, 8, 16, and 32 weeks	Criterion	No	Yes	Flat RA
Thornton et al. (1997)	Monkey	Aspiration combined EC + PR	Concurrent object discrimination	Within	2: 1 and 16 weeks	Criterion	Yes	No (sessions) Yes (errors)	Flat RA
Wiig et al. (1996)	Rat	Electrolytic FNX, PR, and combined FNX + PR	Single object discrimination	Within	5: 1, 2, 4, 6, and 8 weeks	Criterion	No	Yes	FNX: graded RA PR: flat RA[b] PR + FNX: flat RA[b]
Winocur (1990)	Rat	Electrolytic dorsal HC, MD thalamus	Socially acquired food preference	Between	4: 1, 2, 5, and 10 days	Fixed	Yes	N/A	HC: graded RA MD thalamus: graded RA
Zola-Morgan and Squire (1990)	Monkey	HC + EC + PH + SUB	Object discrimination	Within	5: 2, 4, 8, 12, and 16 weeks	Fixed	Yes	Yes	Graded RA

*HC, hippocampus; SUB, subiculum; EC, entorhinal cortex; PC, parietal cortex; FNX, fornix; AMY, amygdala; PR, perirhinal cortex; PH, parahippocampal cortex.

[a]Cannot assess because task parameters differed at the two time points.

[b]These operated groups differed from controls at the most remote time point, and no evidence was given of a linear trend to indicate a gradient.

set had developed. Perhaps more importantly, in 5 of the 7 cases where a learning set had developed, a retrograde gradient was reported, and 1 of the 2 studies reporting no gradient (Thornton et al., 1997) actually had only equivocal evidence of a learning set. Thus, future within-subjects studies should employ designs that minimize or negate altogether the development of a learning set for material acquired prior to operation (Cho and Kesner, 1996). For example, one could establish the learning set to asymptotic levels before training at the most remote time point.

As was the case for the development of a learning set, outlined above, there may be other ways in which a within-subjects design leads to difficulties in interpretation of the data derived from prospective studies of retrograde memory. For example, in a within-subjects design the influence of retroactive and proactive interference on learning and retention might be expected to differ at remote and recent time points, in a way that might interact with the effects of a brain lesion. Another concern is that when material is acquired at different absolute times there is a chance that the context in which this material is learned will vary across time points, and that this associated contextual information will influence subsequent retrieval. With a between-subjects design, all the subjects can be trained at the same time, thereby ensuring that all information is learned in a similar context. Of course, this latter approach necessarily entails that the retention tests be given at different times (to achieve different intervals between learning and retention), so contexts for learning and retention cannot both be equated in a single condition of an experiment. Given enough subjects, however, one could include both these conditions (subjects trained concurrently and subjects tested concurrently) in a single experiment. In summary, several possible sources of potentially artifactual temporal gradients can be avoided through the use of between-subjects designs.

Amount of training

It would seem an obvious and desirable goal to achieve an equivalent amount of training for the material presented for acquisition at each time point, for each group, in a prospective study of retrograde memory. After all, only if equivalent amounts of training are provided at each of the time points can one accurately interpret the effects of brain lesions (i.e., the independent variable) on retention of the material acquired at the various learning-surgery intervals (i.e., the dependent variable). Amount of training becomes particularly difficult to evaluate in studies using within-subjects designs. For example, should one strive to equate training across time points for "total number of trials" (or sessions), or should one use a "functional criterion" (e.g., a learning criterion of 90% correct responses)? If "amount of training" for material presented at different learning-surgery intervals is equivalent according to one measure, it might not be so according to the other. Salmon et al. (1987) pointed out that one advantage of using animals in retrograde memory experiments is that unlike in studies in humans, the "strength" of learning across time points can be matched by training animals to a functional criterion. Since then, this group abandoned this method in favor of training for a set number of trials (Zola-Morgan and Squire, 1990). One advantage of training for a fixed number of trials is that the amount of exposure to training materials is then equilibrated across time points. The disadvantage of course is that the "strength" of training is not necessarily equilibrated. If the strength of training varies in a systematic fashion, this, too, might lead to a spurious retrograde gradient, as may be the case when a learning set develops (see above). In any event, there appears to be no correct answer to the question of how best to equate groups when using within-subjects designs. The design features of each individual study need to be considered against the background of those of other studies, and of the hypothesis being tested.

A separate issue is whether "equivalent" training is a necessary aspect of an experimental design. At least one study (Gaffan, 1993) used an unorthodox design that led to different amounts of training at different time points, and this may be one reason some authors (Milner et al., 1998; Squire and Knowlton, 2000) have excluded the findings of that study from consideration. Because this exclusion may have resulted in neglect of a study that contains data arguing against the prevailing view, it is worth examining the precise way in which "unequal" training might have affected the experimental outcome. Gaffan (1993) trained monkeys to discriminate complex naturalistic scenes at two time points (approximately 6 months and 1 week) before surgery (fornix transection) or rest (controls). The method of training was slightly different for the scene discriminations learned at the two time points, and there was more accumulated training (in terms of numbers of trials) for the remote relative to the recent set of problems. (It should also be noted that there were more problems presented for acquisition at the remote relative to the recent time point.) Nevertheless, the animals were trained to the same functional criterion, i.e., 90% correct responses for each set. A few days before surgery or rest, all monkeys received a retention test (consisting of one trial per problem) of the material that had been learned at both time points. After fornix transection, the monkeys showed a clear loss of information relative to the controls—a loss that was equivalent for the recently and remotely acquired material. As already indicated, one unorthodox aspect of Gaffan's (1993) study was that the monkeys were given more training on the first (remote) set of problems than on the second (recent) set. Because one would predict that the "extra" training on the remote problem set should, if anything, act to protect information storage from disruption by MTL damage, thereby increasing the probability of observing a temporal gradient, this study should not, on this basis, be excluded from consideration.

Another unusual feature of the experimental design in Gaffan (1993), as alluded to earlier, was that all monkeys received a preoperative retention test of the material that had been learned at both time points. Again, one could argue that the monkeys' extra experience on the retention test would act to reduce the chances of forgetting of the remote set and thereby increase the likelihood of obtaining a temporal gradient. To our knowledge, there are no theoretical grounds for thinking that the retention test involving the remotely learned material would differentially *increase* the probability of forgetting of that material relative to the recently learned material, or that the retention test involving the recently learned material would differentially *decrease* the probability of

forgetting that material relative to the remotely learned material, either of which might warrant exclusion of this study from consideration. On this view, it seems that the findings from Gaffan (1993) should be considered together with those from other studies assessing the effects of MTL lesions, despite the unorthodox aspects of experimental design.

Advantages of within-subjects designs

The foregoing discussion suggests that, when attempting to map structure to function in studies of retrograde memory, a between-subjects design provides significant advantages over a within-subjects design. There are other instances, however, in which within-subjects designs are warranted. For example, a within-subjects design will more directly mimic the clinical phenomenon: if the purpose of a study is to model the retrograde amnesia seen in clinical patients, a closer approximation to this phenomenon would be attained by examining memory within individual subjects. Another aspect of the human situation that cannot be realized in a between-subjects design is that, in humans, memory for events gets "tested" occasionally, by virtue of occasional extra-experimental retrieval of information in the interim between original learning and later testing for retention. This, too, can be modeled in a within-subjects design. Indeed, the preoperative retention test used by Gaffan (1993) can be thought of as an attempt to model just this kind of occasional retrieval that presumably occurs in human subjects.

Within-subjects designs may be called for on other occasions, in addition to modeling retrograde amnesia in human subjects. Consider the following example. A study by Kim and Fanselow (1992), using a between-subjects design, reported a temporal gradient for context (but not cue) conditioning after dorsal hippocampal lesions, as measured by the amount of freezing behavior upon exposure to the context (or cue) alone. Although these authors offered a mnemonic account of the pattern of results (Kim and Fanselow, 1992; Maren et al., 1997), it was possible that the findings could be explained by hyperactivity in the hippocampal subjects, i.e., a performance deficit. Because there is substantial individual variability in the levels of hyperactivity of hippocampectomized rats, Anagnostaras et al. (1999) used a within-subjects design to distinguish between these possibilities. As it turned out, their rats with dorsal hippocampal lesions still exhibited a temporal gradient for conditioning to context, a finding favoring the mnemonic account. Thus, the study of Anagnostaras et al. (1999) is a good illustration of the deliberate and successful application of a within-subjects design to test competing hypotheses.

Summary

In prospective studies of retrograde memory in nonhuman animals, there are several drawbacks to the use of within-subjects designs. Use of between-subjects designs, as opposed to within-subjects designs, should have at least two benefits: 1) the training at each time period can with confidence be assumed to be equivalent, and 2) the animals can be assumed to have learned the material the same way. Indeed, the same stimulus material can be used for every subject in the experiment at every learning-surgery interval evaluated, a factor that would greatly decrease variance and increase sensitivity of the test. Accordingly, from the point of view of mapping structure to function, the use of between-subjects designs is preferable. Nevertheless, as we have seen, the use of within-subjects designs has some advantages, perhaps the strongest among them being the ability to mimic the clinical phenomenon.

Number of Time Points

Another decision that needs to be made in designing a prospective study of retrograde memory is how often (and how frequently) to present information for acquisition prior to surgery. One obvious advantage of using multiple (i.e., more than two) learning-surgery intervals is that it serves to outline the time course of the putative consolidation process. In addition, in situations where little is known about the time course of information storage (e.g., testing with a new task or new species), use of multiple time points should increase the probability of finding and defining the limits of the window of the putative consolidation period. Two time points, however, are certainly sufficient to reveal a temporal gradient where one exists (e.g., Kim et al., 1995). Thus, although there are some advantages to assessing retention of information learned at several time points prior to trauma/surgery, there would appear to be no absolute requirement for the "multiple time-point" feature of experimental design.

Forgetting in Normal Controls

If there is no forgetting in the control subjects over the period investigated, and no temporal gradient in the operated group, it is possible that even more remote time periods, had they been investigated, might have revealed a gradient (Salmon et al., 1987). To the extent that one has demonstrated retention of information in control subjects that ranges from good to poor, this argument is no longer valid. A demonstration of forgetting in normal controls, however, does not appear to be imperative in prospective studies of retrograde memory. Certainly, there are instances in the literature of forgetting in controls with no evidence of a temporal gradient in the operated group (Bolhuis et al., 1994; Gaffan, 1993; Thornton et al., 1997) and, conversely, of no forgetting in controls with the appearance of a temporal gradient (Kim and Fanselow, 1992). Consequently, the detection or occurrence of a temporally graded memory loss would seem to be independent of the demonstration of forgetting in controls.

Site of Lesion and Type of Stimulus Material

If we assume that there is a consolidation mechanism operating in the MTL, there still remains the issue of the neural basis of the putative process. One view posits that MTL structures (namely, the entorhinal cortex, perirhinal cortex, hippocampal formation, and parahippocampal cortex) work together as a single functional unit (Zola-Morgan et al., 1994). (On anatomical grounds, this system is considered also to include the fornix, the main fiber bundle connecting the hippocampal formation with the medial diencephalon.) There are two related issues that deserve mention in this regard. First, according to this unitary-function view, any con-

solidation process mediated by the MTL would be expected to be mediated by the entire set of structures. If so, it is surprising that certain discussions of retrograde amnesia in nonhuman animals (Milner et al., 1998; Squire and Knowlton, 2000) have excluded from consideration the effects of perirhinal cortex damage (Wiig et al., 1996) or of perirhinal plus entorhinal cortex damage (Thornton et al., 1997), limiting consideration to the effects of damage to the remaining MTL structures. Surely, if the underlying assumption is that MTL structures are functioning together in memory, one cannot pick and choose which studies using MTL lesions should be considered, but must consider them all or provide justification for exclusion. Moreover, if we wish to know whether the MTL in particular has a role in the consolidation of memories, then studies investigating brain regions outside the MTL would be of considerable interest. What would it mean for the MTL consolidation hypothesis if lesions of brain regions outside the MTL led to temporally graded retrograde amnesia? As it happens, just such results have been reported. Winocur (1990), for example, reported a temporally graded memory loss following lesions of the dorsomedial thalamus. Although the prevailing view allows for a temporally limited role for medial thalamic structures in memory, other results are more difficult to explain. Liang et al. (1982) reported a temporal gradient for memory of a one-trial inhibitory avoidance task following lesions of the amygdala. The latter finding suggests that consolidation, in the sense used here, may not be the private domain of the hippocampus and related structures. Such studies cast doubt on the prevailing view and indicate that many brain regions may have a time-limited role in memory. Alternatively, as discussed above, it may be that something about the design of certain studies of retrograde memory can lead to artifactual temporal gradients.

Second, there is accumulating evidence that the MTL structures make selective contributions to memory (Aggleton et al., 1997; Bussey et al., 1999; Gaffan, 1994; Mishkin et al., 1997; Murray et al., 1996; Murray, 2000), which suggests the distinct possibility of multiple consolidation mechanisms. Lack of data prevents any firm conclusions in this regard, but some findings are consistent with this idea. For example, as indicated earlier, Zola-Morgan and Squire (1990) found that lesions including the hippocampal formation plus the underlying entorhinal cortex and parahippocampal cortex yielded a temporally graded retrograde memory deficit for object discriminations. Thornton et al. (1997) likewise trained monkeys on object discriminations, but in contrast to the findings of Zola-Morgan and Squire (1990), found an equally severe impairment for the retention of both recently and remotely learned material, i.e., no temporal gradient, after perirhinal plus entorhinal cortex lesions. Thus, "hippocampal" damage led to loss of information learned up to 4 weeks prior to operation, whereas perirhinal plus entorhinal cortex damage led to loss of information learned at least 16 weeks prior to operation. In both studies, the type of learning (visual object discrimination problems) was similar, and the retention measure (percent correct responses on critical trials) was similar as well. Taken together, the results suggest at least two possibilities: 1) the hippocampus and perirhinal cortex have different time courses of consolidation; or 2) the perirhinal cortex serves as a permanent site of storage, at least for certain kinds of information.

As another example, Murray et al. (1993) found that hippocampal lesions yielded virtually no disruption in monkeys' retention of visual stimulus-stimulus associations learned immediately preoperatively. Given the good postoperative retention at this single "recent" time point, it would appear that the hippocampus is not necessary for consolidation, at least not for this kind of material. Because the monkeys required a large number of sessions to learn the visual stimulus-stimulus associations, and acquired them gradually over the course of about 6 weeks, one might argue that consolidation occurred earlier than the admittedly arbitrary 90% criterion endpoint we imposed. Even so, other monkeys in the same study that had been trained in the same manner showed extremely poor retention of the same preoperatively learned material after combined lesions of the amygdala and hippocampus that included much of the underlying perirhinal, entorhinal, and parahippocampal cortex. Thus, as was the case for our earlier example, this outcome is incompatible with the idea that the MTL structures operate together as a single functional unit in mediating a single consolidation process. Accordingly, the unitary-function view appears to be in need of modification. Future work will need to assess separately the role of each of the MTL structures in information storage and retrieval.

In conclusion, different regions in the MTL appear to process different types of information, and there may be different, anatomically separate consolidation processes for these types of information. Thus, a more complete understanding of information storage, and of the putative consolidation processes, will require systematic examination of retrograde amnesia for different types of material (e.g., object information, spatial information).

CONCLUSIONS

In summary, a consideration of several of the design features employed in prospective studies of retrograde memory leads to two important conclusions. First, there are alternative interpretations for at least some of the data that are usually cited in support of the consolidation hypothesis of MTL function. Temporally graded memory loss may in some cases reflect an interaction of the type of learning with a given brain lesion rather than a shift of storage from one brain region to another. Second, some studies that have been discounted because of their use of unorthodox designs should probably be given more weight than they have so far received. Such studies need to be evaluated on an individual basis to assess their implications regarding the MTL consolidation hypothesis. Even taking these two conclusions into account, however, there is no clear-cut answer to the question, "Does the MTL play a time-limited role in information storage?" As additional information accumulates, and as some of the alternative accounts we and others have identified are evaluated, a clearer picture of the mechanisms underlying information storage will undoubtedly emerge.

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