Consolidation of Memory

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ABSTRACT: Animal studies have proven useful in addressing aspects of memory formation and consolidation that cannot be readily answered in research with humans. In particular, they offer the possibility of controlling both the extent and locus of brain lesions, and the exact nature of the experiences to be remembered. Taking advantage of these possibilities, recent studies indicated that the graded retrograde amnesia often seen after lesions to the hippocampal system is not uniform across lesion site and task, nor is it an indication that all of the remembered information available in intact subjects becomes available after hippocampal system lesions made a long time after learning. Rather, these studies support the notion that information is stored in both hippocampal and extrahipocampal sites, and that retrieval from different sites involves access to different kinds of information. The strongest evidence in support of this view is the set of findings indicating that when remote memories are retrieved, in either human or animal subjects that have suffered hippocampal system damage, these memories are not qualitatively the same as remote memories retrieved in intact subjects. In sum, memory appears to be rather more dynamic than most current conceptions allow, such that retrieval events trigger new encodings, and these new encodings engage the hippocampal system once again. As a result, older, reactivated memories become more resistant to disruption, and this mechanism helps to explain why graded retrograde amnesia is sometimes seen after brain damage. The use of new neuroimaging techniques, coupled with more sensitive neuropsychological tests in lesioned subjects, should further illuminate the complex nature of memory in coming years. It is likely that animal studies will continue to prove important in these developments. ***Hippocampus 2001;11:56–60.*** **© 2001 Wiley-Liss, Inc.**

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INTRODUCTION

Though the notion of memory consolidation has a long history (see Polster et al., 1991), the exact nature and purpose of the events that transpire after initial registration of information remain obscure. Memory consolidation is inferred from the existence of gradients of retrograde amnesia (RA) after damage to the brain. It is assumed the damage interferes with some time-dependent process that functions to make memory permanently stable. While early ideas about consolidation assumed that the transition from fragile to stable memory occurred in one brain system, more recent views have emphasized the possibility that consolidation reflects an interaction between separable brain systems. In particular, it has been assumed for some time that early, fragile memory depends on the hippocampal system, while later, stable memory does not (e.g., Milner, 1962; Squire, 1992).

Although this view is widely accepted, the data in support of it are equivocal at best (Fujii et al., 2000). One major hurdle is that it is extremely difficult to obtain definitive data from studies with human subjects. Much of the relevant data in humans comes from analysis of retrograde memory defects in patients with various kinds of lesions, and such data are uncontrolled in two important ways. First, the exact nature of the brain damage in these cases is often hard to ascertain, and rarely confined to the brain regions of interest. Second, since the memory content under study involves experiences that happened prior to the brain damage, it is virtually impossible to know exactly what has been stored in the first place, and therefore difficult to know what has been retained and what has been lost. Hence the use of animal models in the analysis of human memory consolidation. The attraction of animal models is that one can, at least in principle, restrict lesions to specific brain regions of interest, and one can also strictly control the experience of the animals prior to making the lesions.[1]

In using animal models, the first question that arises is whether or not RA can be observed at all after disruption of brain function. For a period of 20–30 years this question was answered with respect to relatively short-lasting

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[1]While much of the literature, and this forum, focus on the impact of damage in the hippocampal system, it is important to note that studies have demonstrated RA gradients after damage in other brain regions, such as the entorhinal cortex (Cho and Kesner, 1996; Kornecook et al., 1999). One implication of such findings is that the interactions between the hippocampal formation and neocortex presumed to govern consolidation may not be unique.

RA, on the order of minutes or, at most, several hours. In these studies, the emphasis was on processes occurring within a single brain system, presumed to be responsible for registration and storage of a memory trace. In the past decade, attention has been directed towards intervals of days, months, and even years (in humans), reflecting the idea that memory consolidation can be seen as a long-term process involving interactions among brain systems (e.g., Squire et al., 1984). In both cases, it seems clear that brain damage can cause retrograde amnesia.

RETROGRADE AMNESIA GRADIENTS

Several issues arise in considering RA in animal studies: is it observed across all kinds of learning situations, and, when it occurs, how long does it last and what shape does the RA gradient take? It now seems clear that the existence of RA, and the shape of the RA gradient, vary with a number of factors, including the nature of the task, and the extent of damage to the hippocampal system.

Murray and Bussey (2000), Jarrard (2000), and Squire et al. (2000) recount much of the data from experimental studies of RA in animals, and although these authors disagree over which studies should or should not be included in any such analysis, the overall impression is clear: damage to the hippocampal system after learning can cause RA, and in many studies this RA takes a graded form, such that damage shortly after learning causes a severe or even total impairment, whereas damage sometime later can yield only a mild or even no impairment. This graded RA is the primary empirical result leading to the notion that the hippocampal system is only temporarily critical to memory.[2] However, two important caveats must be noted: whether one sees graded RA or a flat RA function (indicating impairment at all tested retention intervals) seems to depend both on the locus and extent of the brain damage, and on the nature of the task being employed. Leaving these matters aside for the moment, and accepting the reality of graded RA, we must still ask what this fact tells us about the organization and consolidation of memory.

WHAT DOES THE EXISTENCE OF RA GRADIENTS MEAN?

As noted, the standard interpretation of graded RA after hippocampal damage (e.g., Squire and Alvarez, 1995) is that the hippocampus is essential only at the early stages of learning. With time, it is asserted, memory becomes independent of the hippocampus, and damage to that structure no longer has any effect. This interpretation is quite vague on two important questions, and as a consequence has led to some confusion. First, there is the question of whether or not a memory trace is ever "stored" in the hippocampus itself. If so, then during consolidation this memory trace must be either "transferred" to, or replicated in, extrahippocampal structures. If not, then some explanation must be offered for why the hippocampus is critical to memory retrieval and hence performance, even though the memory trace is always stored elsewhere. Second, there is the question of exactly what constitutes "memory" at the various points at which performance is tested. The implicit assumption in the literature is that memory is, at least in qualitative terms, an unchanging entity over time. But there is little reason to accept this assumption: indeed, there is every reason to suspect that different aspects of memory are forgotten at different rates.

Consider, for example, the recent study by Bontempi et al. (1999), which has been taken by some to strongly support the notion that information initially dependent on the hippocampus becomes, with time, dependent on other, presumably neocortical, structures. In this animal study, 2-deoxyglucose imaging showed that when retention was tested shortly after learning, brain activation reflecting response accuracy centered on the hippocampus, but when retention was tested some 25 days later, brain activation reflecting response accuracy centered on the neocortex. A critical fact, clearly seen in the behavioral data, is that performance after 25 days was not the same as after just a few days. The shift in activation from hippocampus to cortex could well reflect a shift in the qualitative nature of the underlying memory trace supporting performance, rather than a "transfer" of the trace from hippocampus to neocortex.

This latter possibility becomes particularly important in evaluating the data from studies of RA and spatial memory, in both animals and humans. Consider the recent paper by Kubie et al. (1999). They reported graded RA, but went on to further analyze the nature of performance in the rats that seemed capable of retrieving spatial memories after a long learning-surgery interval. These same rats were asked to learn a new spatial task, and proved incapable of doing so. Kubie et al. (1999) concluded that when the hippocampus is absent, both performance of previously learned spatial tasks and acquisition of new spatial tasks take a different form than that seen in intact animals. Instead of using, or acquiring, an integrated, map-like representation of the spatial environment, rats without a hippocampus fall back upon a "vector-based" system that can support considerable spatial behavior, but which lacks the flexibility and integral nature of a hippocampal-dependent spatial map. This interpretation is strongly supported by the recent study of Pearce et al. (1998), demonstrating that rats without a hippocampus acquire a spatial task using vectors but not maps.

Another reflection of spatial behaviors supported by multiple systems comes from the work of McDonald and White (1995), who showed that both the caudate and the hippocampus could be important in learning an unambiguous two-choice discrimination task in the eight-arm radial maze (widely separated arms), but that only the hippocampus was important in learning the ambiguous analogue (adjacent arms). The conclusion we draw from these studies is that if performance is spared when hippocampal damage is made some time after learning, this could easily reflect the estab-

[2] An oft-quoted theoretical reason for postulating a temporary role for the hippocampus in memory is the view that the limited number of neurons in the hippocampus would create capacity problems should memories be permanently stored there. Put most simply, there would not be enough room in the hippocampus for a lifetime of memories. Recent data demonstrating life-long neurogenesis in the hippocampal system (e.g., Eriksson et al., 1998) would seem to render this point moot.

lishment of a qualitatively different memory trace, in extrahippocampal circuits, and it is this trace that subsequently supports performance. Under this interpretation, the graded nature of RA reflects the need for time for this new, qualitatively different trace to be established. In fact, Packard and McGaugh (1996) showed that with training, rats switch from place learning dependent on the hippocampus to response learning dependent on the caudate. It is entirely reasonable to suppose that the hippocampus can play a helpful (but not essential) role in the establishment of this new trace. What is critical here is that the memory dependent on extrahippocampal circuits is not necessarily the same as the memory that would be observed if hippocampal circuits were also available. And, by extension, that performance in intact animals can reflect a unique memory contribution of the hippocampal system.

Much the same conclusion can be derived from the study of contextual fear conditioning. Fanselow (2000) and Anagnostaras et al. (2000) carried out an extensive series of studies on this phenomenon. The original study showed that hippocampal lesions had no retrograde effect on fear conditioning to a tone conditioned (CS), but impaired fear conditioning to the context in which conditioning occurred *if* the lesions were made within 7 days of training, *but not* if the lesions were made 28 days later (Kim and Fanselow, 1992). Fanselow (2000) argued that when a hippocampal lesion is made *prior to* context conditioning, some learning will occur, but it will necessarily involve circuits outside the hippocampus. When, conversely, context conditioning is carried out *prior to* the hippocampal lesion, learning occurs within the hippocampus itself, and that is why RA is observed if a lesion is made shortly thereafter. Fanselow (2000) views the absence of RA when 28 days intervene between conditioning and the lesion as reflecting a process by which "with the aid of the hippocampus, this memory becomes permanently stored in other, probably cortical, structures" (p. 80). But note that Fanselow (2000) also argues that the hippocampus is critical for the formation of an "integrated representation of the context" (p. 76), and that "the hippocampal-independent system might be able to acquire fear of some aspects of the context" (p. 79). The clear implication of these results, and views, is that the contextual representation to be found in the hippocampus is integrated and map-like, while the contextual representation formed in the absence of the hippocampus captures only some aspects of the context, e.g., it could involve simple associations between fear and individual elements of the training situation (Nadel and Willner, 1980; Nadel et al., 1985). We would argue that in the 28 days between learning and lesion, just this kind of elemental association between fear and some aspects of the context is being established in the cortex, and that this simpler memory trace suffices to account for the presence of contextual fear in animals given lesions this long after learning.

The same considerations might come into play in helping us understand the results of comparable studies in humans. Teng and Squire (1999) reported considerable sparing of remote spatial memory in a patient with extensive medial temporal lobe damage. In describing this patient's ability to retrieve autobiographical memories from early in life, it is claimed that "neither the quantity nor the quality of his recollections can be distinguished from those of controls" (Squire et al., 2000). However, recent findings from another patient with similarly extensive medial temporal lobe damage call this conclusion into question (Rosenbaum et al., submitted). This patient (K.C.) has been tested on an extensive battery of tests of remote spatial memory. While partially confirming Teng and Squire (1999) in that there was considerable sparing of remote spatial memory, Rosenbaum et al. (2000) also showed that there were persisting deficits in some aspects of spatial knowledge. Thus, remote spatial memories that can be retrieved are not qualitatively and quantitatively the same as those observed in control subjects. Much the same conclusion has been reached from a study of autobiographical memory in temporal lobe patients (Viskontas et al., 2000; Nadel et al., 2000): when increasingly sensitive measures are used, persistent deficits in remote memory are observed *at all time points*.

Overall, our analysis of RA gradients suggests that for certain materials (map-like spatial representations, autobiographical memory), hippocampal system damage will always yield deficits. Other kinds of representations, even some that benefit from the presence of the hippocampus, can survive, and can support behavior. This in turn suggests that critical aspects of integrated spatial representations and autobiographical memories are stored within the hippocampal system itself, and that damage in this system will always cause retrieval deficits. Observing these deficits requires sensitive tests, and careful behavioral analysis, but when this is done the result is clear.

WHAT DOES THE ABSENCE OF GRADED RA MEAN?

As we have seen, the extant data demonstrate that in some circumstances, after damage in the hippocampal system, RA is observed at all time points. This appears to be particularly the case when spatial learning (or episodic memory) is concerned.

But what does this absent gradient mean? We have suggested one interpretation, namely, that the hippocampal system is involved in spatial (and episodic) memories regardless of their age. Others have proposed an alternative: that the absence of a gradient results from the fact that the hippocampal system is critical not to the actual storage of spatial memories, but to performance of spatial tasks (Knowlton and Fanselow, 1998; Squire et al., 2000). This position is difficult if not impossible to distinguish empirically from the view that the hippocampal system is important for actually storing spatial information. But, leaving this aside for the moment, what else can be said about this notion?

One relevant point is that this notion seems to accept the idea that the hippocampus plays some special role in processing spatial information that it does not play in processing nonspatial information, since flat RA functions are not observed in nonspatial tasks. While this is a position we are fairly comfortable with, it does not appear to be consistent with the functional role attributed to the hippocampus in other writings. Thus, Squire et al. (2000) state 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." Proponents of this position presumably should argue that the hippocampus would be critical to performance (but

not storage) of all kinds of relational tasks, spatial or not. Recent neuroimaging data (Nagode and Pardo, 2000), however, count against this view. While the hippocampus was activated during the acquisition of a putatively nonspatial relational task (transitive inference), it was *not* activated during the probe trials when subjects had to utilize their relational information. Since these probe trials were given only 1 h after acquisition, it cannot reasonably be claimed that consolidation had rendered the hippocampal system no longer necessary. Thus, this "performance" explanation of flat RA functions appears to be inconsistent with the abstract relational interpretation of the hippocampal role in memory.

A recent study by Ramos (2000) attempts to deal with the performance issue in an animal study. Rats with hippocampal lesions were trained on a four-arm maze within which one particular arm (and location in space) was always rewarded, no matter where the animal started the trial. When all four arms were identical, rats with hippocampal lesions were incapable of learning the task. However, if during learning the goal arm was indicated by a sandpaper floor insert, rats with hippocampal lesions were capable of acquiring the task. After acquisition, when the floor insert was removed during a retention test 24 h later, the lesioned rats performed at normal level. However, the same rats, when retested 24 days later, displayed a significant deficit in the absence of the floor insert. This study shows that rats with hippocampal lesions who can perform a spatial task nonetheless have an impairment in long-term consolidation of that task, thus demonstrating that there is not a decisive link between performance and retrograde amnesia. The results are quite perplexing nonetheless. One possible explanation, following from the analyses given earlier, is that the form of spatial memory acquired by the lesioned rats reflects vector-based learning, and that this learning suffices for performance 24 h after training. The deficit observed at 24 days would then reflect a critical role of the hippocampal system in the long-term consolidation of this extrahippocampal form of spatial memory.

REACTIVATION, REENCODING, AND MEMORY CONSOLIDATION

In our recent analyses of memory consolidation (Nadel and Moscovitch, 1997, 1998; Moscovitch and Nadel, 1998), we suggested that each reactivation of a memory leads to a new encoding event within the hippocampus. This new encoding event causes the creation of a new memory trace, and it is the proliferation of these sparsely encoded, distributed traces that renders more remote memories increasingly resistant to loss following damage in the hippocampal system. There is evidence from animal studies suggesting that reactivation of a memory trace can lead to effects like these, although the evidence at present is far from conclusive.

Sara (2000) reviewed the literature concerned with reminder effects in animal memory. In a typical experiment, animals would be trained on a task, and then given a retention test sometime later. A retention interval is chosen that yields relatively poor performance, indicating that forgetting has occurred. In a separate group of animals, just prior to the delayed retention test, a "reminder" of the training is administered. This can take the form of placing the animal in the training context (but not delivering either a CS or an unconditioned stimulus (UCS), or placing the animal in a new context and delivering the CS alone or UCS alone. In either case, what is observed the following day when retention of original training is assessed is significantly less forgetting.

This is perhaps not so surprising. More surprising is the following sort of finding: animals are trained on a task, and then given brain lesions sometime later. An interval between training and lesion is chosen that would yield a null effect, i.e., enough time apparently has transpired for memory consolidation to occur. At this point, just prior to the end of this interval, and before the lesion, a "reminder" treatment is applied. Now the brain lesion has the effect of impairing subsequent performance (see Land et al., in press). It is as if reactivating a memory trace renders it fragile once again (note that the study by Gaffan (1993) conforms to this design, since the animals trained sometime before the lesion were given a retention test just prior to surgery).

These results make little sense within standard consolidation theory, but they are consistent with the "reactivation yields reencoding" assumption of the multiple trace theory proposed by Nadel and Moscovitch (1997). Additional evidence consistent with this notion comes from a recent neuroimaging (fMRI) study (Nadel et al., 2000) in which subjects were asked to retrieve either recent or remote memories while being scanned. Hippocampal activation was equally robust during retrieval of remote and recent memories. This suggests that when a remote memory is retrieved, the hippocampal system is reactivated, and perhaps a new encoding event follows.

The critical remaining question is whether the remote memory that is retrieved in this situation has been stored entirely outside the hippocampal system, or if parts of it were represented within the hippocampal system. Neuroimaging studies unfortunately cannot tease apart these two possibilities, but lesion studies can. If the memory was stored entirely outside the hippocampal system, then remote memories retrieved either in amnesic patients, or in lesioned animals, should be qualitatively the same as in normal intact subjects. As we have already argued above, this does not appear to be the case in the animal studies: remote memories retrieved in lesioned subjects are not the same as remote memories available to intact subjects.[3] Similar findings in human amnesics were reported recently (Viskontas et al., 2000; Westmacott and Moscovitch, 2000; Nadel et al., 2000) for tests of autobiographical memory. No matter how remote, memories retrieved by amnesic subjects are not qualitatively the same as those available to intact subjects.

In sum, the data suggest that remote memories are partially stored in extrahippocampal sites, and partially in hippocampal sites. When such a memory is retrieved in an intact subject, both sites are reactivated, and a new encoding event is triggered in the

[3]There is a caveat here. In some cases intact subjects could forget the information acquired during learning, such that both intact subjects and lesioned subjects perform at the same chance level on a delayed retention test (see results of Mumby et al., 1999). In this scenario, one cannot talk of consolidation of memory into extrahippocampal sites simply because at this long retention interval there is no evidence of memory in either lesioned or intact subjects.

hippocampal system. This new encoding event can apparently "restart" the consolidation clock, as observed by Land et al. (in press).

CONCLUSIONS

Animal studies have helped to illuminate several aspects of memory consolidation that human studies alone cannot fully explicate. In particular they have suggested that the form of memory preserved when hippocampal lesions are made after long retention intervals differs from the memory that would be observed were the hippocampal system functional. This observation in turn helps us understand that the process of memory consolidation does not simply involve a shift of memory from hippocampal to extrahippocampal dependence. Rather, it involves complex interactions between independent systems responsible for different aspects of memory. Exactly what these systems are responsible for, and how they interact over time, remain challenges for the future.

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