Retrograde amnesia and memory consolidation: a neurobiological perspective

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The fact that information acquired before the onset of amnesia can be lost (retrograde amnesia) has fascinated psychologists, biologists, and clinicians for over 100 years. Studies of retrograde amnesia have led to the concept of memory consolidation, whereby medial temporal lobe structures direct the gradual establishment of memory representations in neocortex. Recent theoretical accounts have inspired a simple neural network model that produces behavior consistent with experimental data and makes these ideas about memory consolidation more concrete. Recent physiological and anatomical findings provide important information about how memory consolidation might actually occur.

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Introduction

Retrograde amnesia refers to loss of memory for information acquired before the onset of amnesia. Retrograde memory loss almost always occurs in association with anterograde amnesia, which is characterized by an inability to learn new information. Depending on the locus and extent of brain damage, retrograde amnesia can be equivalent across past time periods, or it can be temporally graded (i.e. memories acquired recently are more affected than memories acquired longer ago). Temporally-graded retrograde amnesia has been used to support the concept of memory consolidation, that is, the idea that memory is gradually 'fixed' as time passes after learning. This review focuses on the phenomenon of retrograde amnesia, especially its temporally-graded form, and then explores current ideas about memory consolidation and recent neurobiological findings that suggest how memory consolidation might occur.

Temporally-graded retrograde amnesia

For more than 100 years, clinical reports of human memory impairment have emphasized that retrograde memory loss is typically temporally graded [1,2]. Quantitative studies of human retrograde amnesia first appeared in the 1970s. In their seminal study in 1971, Sanders and Warrington [3] reported that five amnesic patients (one with amnesia pursuant to right temporal lobectomy; three with diencephalic amnesia from alcoholic Korsakoff's syndrome; and one with amnesia from coal gas poisoning) had ungraded retrograde amnesia extending nearly 40 years. This result was notable because it appeared to contradict a century of clinical interpretation based on less rigorous methods.

Several findings during the past two decades have clarified this matter considerably. First, the patient with the right temporal lobectomy (patient N.T.) had a 28-year history of frequent seizures [4,5]. Thus, N.T.'s extensive remote memory impairment might have reflected a failure of new information storage (due to recurrent seizures) rather than retrograde amnesia itself. (Autopsy after the patient's death in 1986 revealed a sclerotic lesion of the left hippocampal formation in addition to the right temporal lobectomy [5].)

Second, it is widely recognized that patients with Korsakoff's syndrome are not an optimal group for studying retrograde amnesia, because their memory impairment typically has a progressive onset and it is difficult to date precisely the time when the amnesia began. In any case, in eight separate quantitative studies of remote memory impairment published since 1971, patients with alcoholic Korsakoff's syndrome have consistently exhibited extensive temporally-graded retrograde amnesia covering a decade or more [6–13]. Thus, the vast majority of patients with alcoholic Korsakoff's syndrome have temporally-graded retrograde amnesia. A few non-Korsakoff patients with bilateral diencephalic damage or basal forebrain damage have also been studied [13,14,15•,16], but the results here are variable, perhaps because the neuroanatomy of the amnesia is itself variable and often incompletely described.

Abbreviation

REM—rapid eye movement.

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Finally, quantitative studies of other patient groups have confirmed the finding that retrograde amnesia can be temporally graded. For example, on a test of former one-season television programs, designed to permit the equivalent sampling of past time periods [17], psychiatric patients prescribed bilateral electroconvulsive therapy (ECT) for depressive illness exhibited temporally-graded retrograde amnesia covering about three years [18]. In addition, patients with amnesia due to anoxia or ischemia, who developed their amnesia on a known date, exhibited temporally-graded retrograde amnesia covering 10–20 years [13], and patients with transient global amnesia exhibited temporally-graded retrograde amnesia covering 20 years or more [19,20].

Retrograde amnesia is not always temporally graded

Although temporally-graded retrograde amnesia is the typical finding in circumscribed human amnesia, it is important to note that some memory-impaired patients have extensive retrograde memory impairment with no evidence of sparing in more remote time periods. The best known examples of this condition are three patients who developed severe amnesia as a consequence of herpes simplex encephalitis (patient S.S. [21], patient D.R.B. (Boswell) [22], and patient R.F.R. [23]) and a fourth patient K.C., who developed amnesia after a closed head injury [24] (for a more recent report of amnesia following an infarction, see [25]). Extensive remote memory impairment has also been described in patients after left temporal lobectomy [26], and in association with dementia from Alzheimer's disease, Huntington's disease, Parkinson's disease, or Pick's disease [27–30].

Finally, it should be noted that severe and sometimes extensive retrograde amnesia, in the absence of any anterograde amnesia at all, is the hallmark of psychogenic (functional) amnesia [31–33].

The association between anterograde and retrograde amnesia

In Russell and Nathan's [2] classic study of more than 1000 patients with closed head injury, the duration of anterograde amnesia was strongly correlated with the extent of retrograde amnesia. In addition, for chronic amnesic patients with temporally-graded retrograde amnesia, a correlation can usually be detected between the severity of anterograde impairment and the extent of the retrograde impairment: correlations ranged between 0.31 and 0.69 based on five different remote memory tests [12]; see also [13]. Such correlations follow naturally from one major view about how the medial temporal lobe memory system and associated diencephalic structures contribute to normal memory functions [34]. Specifically, these structures are essential for establishing information within long-term memory, and they are also essential for a limited period of time after learning [35–38].

Note, however, that this view provides no account for extensive, ungraded forms of retrograde amnesia. Indeed, extensive ungraded retrograde amnesia appears to be a distinct entity. Thus, four recent reports describe not only extensive and apparently ungraded retrograde amnesia, but also retrograde amnesia that appeared disproportionately severe in comparison to anterograde amnesia [26,39–41]. For additional cases and discussion, see reviews [15•,42•].

The most likely possibility is that severe, ungraded retrograde amnesia involves damage to structures in addition to (or other than) the medial temporal lobe and diencephalic structures associated with circumscribed amnesia [43]. The cases cited above all involved damage to neocortex of the anterior and lateral temporal lobe. Such damage would be expected to compromise memory storage sites themselves, that is, knowledge systems [44–46], without altogether destroying the ability to establish new representations. Damage to memory storage sites would produce a constant loss of memory across past time periods, that is, ungraded retrograde amnesia. New representations might still be established to the extent that they are based on different cues or different processing strategies than ones that depend on the damaged tissue, and such representations would therefore be stored at different sites in other knowledge systems.

Temporally-graded retrograde amnesia in patients with damage limited to the hippocampal region

It is reasonable to expect that some of the most useful information about retrograde amnesia should come from patients for whom detailed neuropsychological and anatomical information is available. Four such patients (R.B., G.D., L.M., and W.H.) with bilateral damage to the hippocampal region (i.e. the hippocampus proper, dentate gyrus, and subiculum) have been studied. These four patients had circumscribed memory impairment and no evidence of other cognitive impairment. R.B. [47] and G.D. (N Rempel-Clower, S Zola-Morgan, LR Squire, Soc Neurosci Abstr 1994, 20:1075) developed moderately severe anterograde amnesia following an ischemic event. In both cases, histopathological examination after death revealed a bilateral lesion limited to the CA1 region of the hippocampus. For R.B., retrograde amnesia was mild and limited to one or two years at most. For G.D., retrograde amnesia was difficult to judge because of his low intelligence test scores and poor motivation, but it appeared, as in R.B., to have been quite limited ([13,48]; N Rempel-Clower, S Zola-Morgan, LR Squire, Soc Neurosci Abstr 1994, 20:1075).

Patient L.M. (N Rempel-Clower, S Zola-Morgan, LR Squire, Soc Neurosci Abstr 1994, 20:1075), also termed M.R.L. [49], and patient W.H. [50] had moderately severe anterograde amnesia (W.H.'s anterograde amnesia was more severe than that of R.B., L.M., or G.D.), and both had extensive, temporally-graded retrograde amnesia covering at least 15 years (see also [13,48]). For both patients, post-mortem examination identified a bilateral lesion involving all the cell fields of the hippocampus and the dentate gyrus (N Rempel-Clower, S Zola-Morgan, LR Squire, Soc Neurosci Abstr 1994, 20:1075; N Rempel-Clower, LR Squire, S Zola-Morgan, DG Amaral, unpublished observations). L.M. also had minimal cell loss in layers II and III of the midportion of the entorhinal cortex, probably due to retrograde degeneration associated with damage to the dentate gyrus. W.H. had more substantial cell loss in the entorhinal cortex. An apparently similar amnesic patient with damage to all hippocampal cell fields and much of the dentate gyrus was also described as having a severe, temporally-graded retrograde amnesia [51].

These cases suggest that damage limited to the CA1 field of the hippocampus (patients R.B. and G.D.) causes a very limited retrograde amnesia, whereas more extensive damage (patients L.M. and W.H.) causes extensive, temporally-graded retrograde amnesia.

Prospective studies of retrograde amnesia in experimental animals

Studies of remote memory in amnesic patients necessarily rely on retrospective methods and imperfect tests. As a result it is difficult to compare performance across time periods. Yet the pattern of performance is critical to the interpretation of the data [52]. Five prospective studies have found temporally-graded retrograde amnesia in experimental animals using different species and tasks: object discrimination learning in monkeys [53], context-specific fear conditioning in rats [54], acquired food preference in rats [55], maze learning in mice [56], and trace conditioning of the eyeblink reflex in rabbits [57•]. In each case, animals were trained at different time intervals before they received bilateral lesions of the hippocampal region and/or adjacent, anatomically related cortex, and, in each case, the lesion produced the same pattern of data. Specifically, remote memories were retained better than recent memories. The extent of the retrograde amnesia varied from a few days [55] to about 12 weeks [53].

Two other studies did not find evidence for a temporal gradient of retrograde amnesia following lesions of the hippocampus in rats [58] or fornix transection in monkeys [59]. However, these studies assessed memory at only two different time points (recent and remote), which makes it more difficult to detect a temporal gradient. Moreover, in one of the studies, in which rats were tested on a water maze [58], performance of the animals with hippocampal lesions was at chance at both time periods for one measure, and performance was at chance at the remote period for a second measure. Accordingly, these floor effects might have precluded observing a gradient of retrograde amnesia. In the other study, in which three monkeys were tested on visual discrimination learning [59], the recent and remote training regimens were not equivalent. The material to be remembered from each time period (recent and remote) involved different numbers of stimulus items that had been trained with different schedules and for different numbers of trials. In addition, a retention test for both sets of items was given just before surgery, so that the items tested postoperatively did not belong exclusively to either remote or recent memory.

Memory consolidation

As documented in the preceding sections, temporally-graded retrograde amnesia can cover months or years. In addition, extensive temporally-graded retrograde amnesia can result from damage limited to the hippocampal formation (patients L.M. and W.H.). Apparently, as time passes after learning, there is gradual reorganization within long-term memory storage whereby the importance of the hippocampal formation gradually diminishes and a more permanent memory system develops that is independent of this region. This gradual process of reorganization is usually termed memory consolidation. Memory consolidation was first proposed in 1900 to account for the phenomenon of retroactive interference in human subjects, that is, the fact that material that is learned remains vulnerable to interference from presentation of similar material for a period of time after learning [60]. Almost immediately, support for consolidation was found in the facts of human retrograde amnesia [61,62], and these ideas were eventually developed in some detail through studies of temporally-graded retrograde amnesia in experimental animals and humans [52,63,64]. The key concept is that memory consolidation is the process by which memory becomes independent of the hippocampal region.

Although this concept describes one important tradition of work on memory consolidation, it is important to note that the term 'consolidation' has other contemporary usages that derive from the same historical sources. For example, the term has been used to refer generally to time-dependent processes during which memory becomes fixed, regardless of what brain system is involved [65]. In addition, the term 'consolidation' is often used to describe the molecular cascades and morphological changes whereby synaptic modifications gradually become stable after learning [66,67]. There should be no confusion among these usages, if one keeps in mind the distinction between the level of analysis that describes the gradual stabilization of synaptic modifications and

the level of analysis that describes how different brain systems participate in memory as time passes after learning [37].

The nature of memory consolidation: hippocampal–cortical interaction

If one begins with the idea that the neocortex is the permanent repository of memory [37,68,69], then memory formation must involve some kind of interaction between the neocortex and the hippocampal region or other components of the medial temporal lobe memory system [34]. Several proposals have been developed about how the medial temporal lobe might interact with neocortex to establish representations in memory [70–75], but most of these do not address directly the notion of consolidation and gradual change.

Other proposals have considered consolidation specifically and how the hippocampal region might be involved [36,76–79,80•,81,82••]. Researchers have employed various anatomical terms to discuss consolidation (e.g. hippocampus, hippocampal system, medial temporal lobe). Below, we generally employ the terms used by each author.

A key difference between these accounts is in the role played by medial temporal lobe structures. One early idea was that the hippocampus does not itself store information, but sends an arousal signal to neocortex that enables the formation of new 'chunks' of information [36]. Others have suggested that the hippocampus stores 'indexes' [78] or 'pointers' that support the retrieval of specific patterns of cortical activation, or that the medial temporal lobe links together the different cortical sites that together represent a whole memory [77]. A third idea is that initial storage takes place within the medial temporal lobe or the hippocampus itself [76,80•,82••]. An important concept in several of these proposals is that information contained within the medial temporal lobe directs consolidation by gradually changing the organization of cortical representations, for example, by strengthening connections between the cortical sites that participate in representing a memory.

More recent approaches have made a basic distinction between the operating principles of the hippocampal system and neocortex [79,82••,83••]. The hippocampal system is able to serve as a temporary memory store because hippocampal synapses can change quickly. Neocortical synapses change slowly. Consolidation occurs when the hippocampal system repeatedly reactivates representations in neocortex, leading eventually to strong interconnections among cortical sites, which can support memory independently of the hippocampal system.

Computational considerations led McClelland, McNaughton and O'Reilly [82••] to suggest that consolidation is important precisely because it enables the neocortex to change in a gradual way, slowly incorporating into its representations the regularities of the environment, such as facts about the world. Rapid modification of cortical representations would lead to instability. Temporary storage of information, during the consolidation period, is accomplished by rapidly established and short-lived modifications within the hippocampal system. Facts and events that are to be stored permanently are then gradually incorporated through the consolidation process into an already existing framework in neocortex.

It has been pointed out repeatedly that the phenomenon of long-term potentiation (LTP) is well-suited for the kind of associative, rapid learning for which the hippocampal system is specialized [71,76–79,80•,84]. Further consideration of the neuroanatomy and neurophysiology of the hippocampus led to the proposal that the hippocampus stores memory rapidly within the CA3 field (which operates as an auto-associative network) [80•,84]; later, when a partial cue is presented, the hippocampus can reconstruct memory in neocortex by reactivating neocortical sites [80•]. Across time, and as a result of repeated reactivation, memories are fully established in neocortex.

A simple neural network model of consolidation has recently been constructed that captures many of the ideas just reviewed, and produces behavior like that observed in studies of retrograde amnesia [83••] (Fig. 1). Information is initially established rapidly as short-lived modifications in the reciprocal connections between neocortex and the medial temporal lobe. The role of the medial temporal lobe is to store sufficient information to point to and activate the relevant sites in neocortex, rather than to store the entire memory representation itself. These changes allow the medial temporal lobe to bind together the multiple neocortical sites that store the representation of a whole event. Consolidation occurs when the neocortical representations are repeatedly co-activated by the medial temporal lobe. When this occurs, gradual and long-lasting changes occur in the connections between the cortical areas. Eventually, these cortico-cortical connections become strong enough that the medial temporal lobe is not needed to recreate the original representation.

The model suffers from several limitations because of its small size and simple structure, but it behaves in a way that is consistent with experimental data and provides a useful hypothesis to guide further investigation. The remaining sections consider two features of memory consolidation that are crucial to several of the recent proposals and that neurobiological studies are beginning to address: first, the idea that consolidation is driven by reactivating representations within the medial temporal lobe; and second, the idea that consolidation is embodied in long-term, gradual changes in connections within and between neocortical areas.

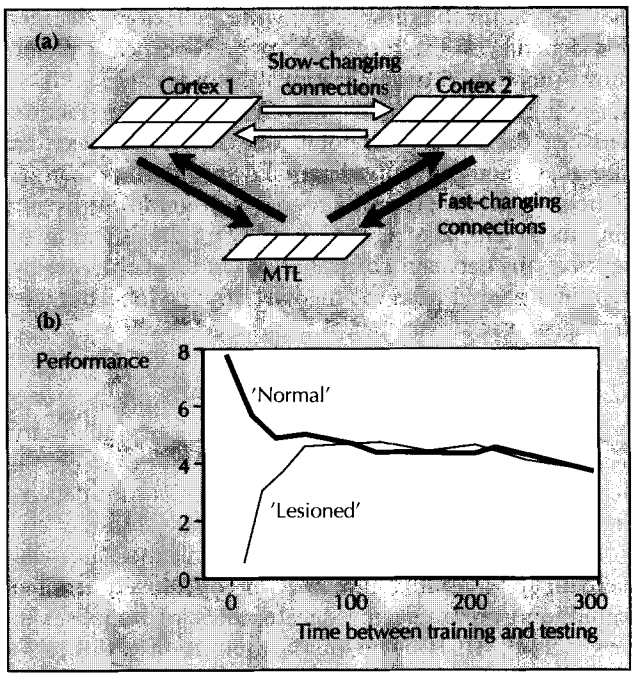

Fig. 1. A neural network model of memory consolidation. **(a)** Schematic diagram of the neural network model. Areas cortex 1 and cortex 2 represent association neocortex, and area MTL represents the medial temporal lobe memory system. Each unit in each of the areas is reciprocally connected to all units in all other areas. Connection strengths change with experience according to a Hebb-like competitive learning rule. A key feature of the model is that changes in the connections to and from the MTL area are fast and short-lasting, whereas changes in the connections between the neocortical areas are slow and long-lasting. Consolidation occurs when random activity in the MTL co-activates the stored patterns in cortex 1 and cortex 2, which results in strengthening of the cortico-cortical connections. **(b)** Performance of this model in a 'retrograde amnesia' experiment. The network learned two different patterns concurrently, and was tested on how well it was able to reproduce these patterns after varying amounts of time, given presentation of a part of each pattern. The X-axis shows a measure, in arbitrary units, of the time allowed for consolidation and forgetting. The Y-axis shows a measure of the network's performance, in arbitrary units, where high values indicate good recall of the learned information. The 'normal' curve (thick line) shows the performance of the intact network. The 'lesioned' curve shows the performance of the network when the MTL area was inactivated immediately prior to testing. The performance of this model is similar to the results of animal experiments: damage to the MTL produces temporally-graded retrograde amnesia, and remote memories are remembered better than recent memories. Reprinted with permission from [83••].

When and how are representations in the medial temporal lobe reactivated?

If consolidation is occurring constantly, that is, if stored memories are continually being revived as a part of normal brain activity, an explanation is needed for why this process does not regularly intrude into consciousness. Alternatively, consolidation might occur in a particular brain state, such as rapid eye movement (REM) sleep or slow-wave sleep. Recent findings identify some interesting properties of slow-wave sleep that would appear to make it useful for consolidation. First, the effectiveness of neural transmission within the hippocampal circuitry is greater during slow-wave sleep than during REM sleep or waking states [85,86]. Yet, plasticity within the same circuitry is reduced during slow-wave sleep [87]. Thus, if reactivation of stored representations in the hippocampus occurred during slow-wave sleep, excitation might be transmitted readily through the hippocampus without modifying the stored representations. Also, during slow-wave sleep, CA3 and CA1 cells discharge in synchronous, high-frequency, population bursts that lead to increased activity in deep-layer neurons of hippocampal target structures (the subicular complex and entorhinal cortex) [88,89••]. Chrobak and Buzsaki [89••] suggested that such a mechanism provides a way to drive synaptic changes within hippocampal–entorhinal circuitry and a way, ultimately, to influence representations in neocortex.

In another study [90], CA1 pyramidal neurons in rat hippocampus fired during the waking state when the animal entered appropriate spatial locations (place fields) in a test apparatus. During subsequent REM sleep or slow-wave sleep, the same neurons were more active than neurons not activated during the waking state. In a more recent study by Wilson and McNaughton [91••], simultaneous recordings were made from 50 to 100 CA1 neurons of rat hippocampus. Neurons that tended to fire together during exploratory behavior, because they were co-activated when the animal entered overlapping place fields, had an increased probability of firing together during a subsequent episode of slow-wave sleep. (Data from REM sleep episodes were not reported.) Thus, a distributed ensemble of neurons in the hippocampus that is active during behavior persists after the behavior has ceased and then exhibits increased coherence during slow-wave sleep. These studies provide suggestive evidence for the reactivation of memory representations during sleep as part of an endogenous, gradual process by which memory is consolidated in neocortex.

Evidence for changes in neocortical connections

The facts of temporally-graded retrograde amnesia, and virtually all accounts of this phenomenon that involve the concept of memory consolidation, suggest that memory storage and retrieval come eventually to be supported by neocortex as the result of gradual changes in connectivity within neocortex. Recent studies show how changes in cortical connectivity can occur as the result of behavioral experience and give some hints about how memory consolidation in neocortex might occur. One well-known finding is that exposure of rats to an enriched environment leads to an increase in dendritic length and to an approximately 22% increase in the number of synapses per neuron in layers I–IV of occipital cortex (for review, see [92]). The changes in dendritic

length have been detected after only four days [93]. In a preliminary study, changes in total dendritic length were reduced by damaging the hippocampal formation prior to the environmental manipulation (RJ Sutherland, BE Kolb, R Gibb, Soc Neurosci Abstr 1993, 19:362).

Further evidence that behavioral experience can induce substantial morphological growth and change in neocortex has come from a demonstration in rats that learning to traverse a difficult, elevated path increased by 25% the number of synapses per Purkinje cell in the paramedian lobule of the cerebellum [94], and that training rats to reach for food with one forelimb increased total dendritic length in layer V pyramidal cells [95].

In adult monkeys, changes in the size and organization of somatosensory or auditory cortical maps can be induced by behavioral training (for review, see [96•]; for possibly related observations after sensory deprivation in adult humans, see [97•]). For example, when owl monkeys learned to discriminate vibration frequencies with a single digit of one hand, the somatosensory cortical maps of the trained digit (and, to a lesser extent, adjacent digits) reorganized and expanded, and the timing of neural responses within the maps became sharper and more coherent. The temporal changes occurred in parallel with and correlated highly with progressive improvement in discrimination ability [98,99].

Direct evidence for structural changes in neocortex in response to a specific manipulation of visual experience was observed in adult cats with small, binocular retinal lesions [100••]. Immediately after the lesions, unit activity could not be driven by visual stimuli along a 7.5 mm length of visual cortex (area V1); that is, there was a scotoma covering about 15 degrees of the visual field. After about nine months, about 5 mm of the cortical scotoma had recovered visually driven activity. Quantitative, anatomical studies showed that horizontally projecting intracortical neurons, within the reorganized portion of cortex, had increased their fiber density by 57–88%. The structural changes appeared to be gradual, implying a slow-developing and eventually substantial increase in the number of synaptic connections. Presumably, the neuronal targets of this axonal sprouting were innervated originally by input from the area of the scotoma. New connections permit these neurons to become newly responsive to retinal loci just outside the scotoma, thereby reducing its effective size. It seems likely that the observed changes depend on continuous visual experience, but this point has not been addressed experimentally.

The examples of modified cortical connectivity just described lead to the following generalizations: the changes can occur gradually across weeks and months; the changes are limited to expansion of the original axonal and dendritic fields or arborizations within these fields; and the changes probably depend on continuing input into the reorganized area.

Although these examples are somewhat remote from the concept of memory consolidation under discussion (e.g. they do not for the most part involve behavioral changes that depends on the medial temporal lobe), each of the above-mentioned generalizations is compatible with, if not required by, current views of the kind of interaction between the medial temporal lobe and neocortex that underlies memory consolidation. Specifically, changes in neocortex are proposed to develop gradually over a long time period, to involve modifying the strengths of connections between cortical areas, and to be driven by continuing input from the medial temporal lobe, perhaps during slow-wave sleep.

A recent preliminary report (Y Miyashita *et al.*, Soc Neurosci Abstr 1994, 20:428) suggests the possibility of studying memory consolidation even more directly by recording in the awake, behaving monkey from cortical neurons that are part of memory representations dependent on the hippocampal system. Ibotenate lesions of entorhinal and perirhinal cortices abolished experience-dependent single-unit responses to preoperatively learned stimuli and prevented the development of responses to new stimuli [101]. The implication is that the sampled neurons are part of memory representations and that the normal input to neocortex from the medial temporal lobe is required to maintain recently acquired representations in memory as well as to establish new ones. When it becomes feasible to observe directly within single cells the development of cortical plasticity dependent on the hippocampal system, one can expect the entire discussion of memory and memory consolidation to rise to a new level.

Conclusions

In studies of both humans and experimental animals with damage to medial temporal structures, retrograde amnesia is often temporally graded within very long-term memory, supporting the idea of a memory consolidation process that occurs gradually across an extended time period. The sparing of remote memory (but not recent memory) after medial temporal lobe damage shows that, as time passes after learning, the importance of medial temporal lobe structures for memory gradually diminishes. Recent theoretical accounts of memory consolidation propose that medial temporal lobe structures direct consolidation in neocortex by gradually binding together the multiple, geographically separate cortical regions that together store memory for a whole event. Recent physiological data demonstrate the activation of hippocampal–entorhinal circuitry and the apparent replaying of recent experiences during slow-wave sleep, suggesting a mechanism for driving consolidation in neocortex. Recent anatomical data demonstrate gradual, experience-dependent reorganization of cortico-cortical connectivity. It should soon be possible to study consolidation directly at different times after learning by sampling neurons in neocortex that are part of memory representations dependent on the medial temporal lobe.

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