The Primate Hippocampal Formation: Evidence for a Time-Limited Role in Memory Storage

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Clinical and experimental studies have shown that the hippocampal formation and related structures in the medial temporal lobe are important for learning and memory. Retrograde amnesia was studied prospectively in monkeys to understand the contribution of the hippocampal formation to memory function. Monkeys learned to discriminate 100 pairs of objects beginning 16, 12, 8, 4, and 2 weeks before the hippocampal formation was removed (20 different pairs at each time period). Two weeks after surgery, memory was assessed by presenting each of the 100 object pairs again for a single-choice trial. Normal monkeys exhibited forgetting; that is, they remembered recently learned objects better than objects learned many weeks earlier. Monkeys with hippocampal damage were severely impaired at remembering recently learned objects. In addition, they remembered objects learned long ago as well as normal monkeys did and significantly better than they remembered objects learned recently. These results show that the hippocampal formation is required for memory storage for only a limited period of time after learning. As time passes, its role in memory diminishes, and a more permanent memory gradually develops independently of the hippocampal formation, probably in neocortex.

Current understanding of the organization and neural foundations of memory has depended importantly on cognitive studies of memory-impaired patients (1) and on studies of a primate model of human amnesia (2). In humans, neuropathological findings (3, 4), together with high-resolution magnetic resonance imaging (5), have demonstrated that selective, bilateral damage to the hippocampal formation is sufficient to cause significant memory impairment. Similar findings have been obtained in monkeys (6–8) and other mammals (9). On the basis of neuropsychological studies of patients with confirmed hippocampal damage, it appears that the hippocampal formation is necessary for establishing a usable record in long-term memory of previously encountered facts and events (1, 10). One useful source of information about the function of the hippocampal formation is the phenomenon of retrograde amnesia, which is, loss of memories acquired before the onset of amnesia. Retrograde amnesia is often temporally graded; patients lose access to the recent past more readily than to the remote past (11). Further, as measured by objective tests, memory for the very remote past can be intact in patients with hippocampal damage (3, 12), regardless of the difficulty of the test items (13). This finding suggests that the hippocampal formation is not a repository of permanent memory. In addition, the phenomenon of temporally graded retrograde amnesia suggests that the role of the hippocampal formation in memory is time-limited. However, more data are needed to confirm and illuminate these ideas. Indeed, the correct interpretation of temporally graded retrograde amnesia depends on the precise shape of the performance curves, which cannot be determined with certainty with the tests available for assessing remote memory retrospectively in humans (14).

We have assessed retrograde amnesia prospectively in cynomolgus monkeys (Macaca fascicularis) with bilateral lesions of the hippocampal formation (the H+ lesion) (15). Figure 1 shows a cross section from the brain of a monkey in the operated group. Monkeys were trained on five different sets of 20 two-choice object discrimination problems (100 discrimination pairs). Training on each 20-pair set began approximately 16, 12, 8, 4, and 2 weeks before surgery. For training, each object pair was presented for 14 consecutive trials with a 15-s intertrial interval (16). Monkeys were trained on two new object pairs each day so that 10 days were required to train monkeys on each of the five sets of 20 object pairs (17). The ability to learn simple object discrimination problems like the ones used here is known to depend on the integrity of the hippocampal formation (7).

Preoperative performance on the 100 object discrimination problems averaged 54.5% correct (chance, 50%) on the first trial of training and 87.7% correct on trial 14 (average of 18 monkeys and 100 discrimination pairs). The learning curves were numerically very similar for the five training episodes, although some improvement did occur with continuing exposure to discrimination problems (18). Tests given at the end of each training episode, which assessed the level of preoperative learning (17), showed that virtually the same final level of performance was attained on each of the five sets of discrimination problems. Performance on these tests averaged 78.9, 81.9, 79.4, 79.7, and 78.6% for the first to the last training episode, respectively. A two-way analysis of variance (training episode × group) revealed no significant differences (F < 2.0, P > 0.10).

Two weeks after surgery, we assessed memory for the preoperatively learned object pairs by presenting a single trial of each of the 100 pairs in a mixed order. This retention test consisted of 50 trials present-
gery. cortex (area TE). This damage was moderate, was completely spared. On the left side of the campal formation, including the dentate gyrus, was nearly total bilateral ablation of the hippocampal formation. Also, nearly all of the parahippocampal cortex was damaged bilaterally. Overall, the damage was very probably the result of an infarction during surgery.

Monkeys with $H^+$ lesions remembered remote information significantly better than recently acquired information. Specifically, the score for object pairs learned 12 weeks before surgery (72.3% correct) was significantly higher than the score for object pairs learned either 2 weeks before surgery (62.3%) or 4 weeks before surgery (64.1%) ($P < 0.05$). Moreover, the scores of the $H^+$ group for object pairs learned from 2 weeks to 12 weeks before surgery increased monotonically (20) and improved significantly across this portion of the performance curve (trend analysis, $P < 0.01$). Only one operated monkey obtained a lower score for object pairs learned 12 weeks before surgery than for object pairs learned 2 weeks before surgery.

There have been two different ways to explain temporally graded retrograde amnesia in patients with hippocampal lesions. Both views propose that the hippocampal formation has a temporary role in memory. In the first view, the role of the hippocampal formation is temporary because the particular kinds of memory that depend on the hippocampal formation are ordinarily short-lived. No transformation or reorganization occurs in memory; across time there is simply differential attrition of memory by type. As a result, recent memory is always more vulnerable to hippocampal damage than remote memory, and temporally graded retrograde amnesia will occur. However, according to this view, the ability to recall the recent past can never be poorer than the ability to recall the remote past (21).

In the second view, the hippocampal formation has a temporary role in memory because information that initially depends on the hippocampal formation can eventually become independent of this structure. As time passes after learning, a process of reorganization and consolidation (22) occurs such that temporary storage in the hippocampal formation is eventually replaced by a more permanent memory elsewhere. This view uniquely explains how monkeys with hippocampal lesions can remember the remote past better than the recent past, precisely the result observed in the present study. Accordingly, our findings favor the second of the two explanations; namely, that information in remote memory is unaffected by hippocampal lesions because of a change in the organization of memory storage (from hippocampal-dependent to independent) that occurs gradually with the passage of time after learning (23).

It has been proposed that the hippocampus is initially the storage site for a simple memory, a conjunction, or an index (24). This storage site is established in the hippocampus at the time of learning through convergent anatomical projections from distributed sites in neocortex, where simultaneous and coordinated neural activity is thought to underlie perception and the capacity for immediate (short-term) memory (10, 23). The hippocampus might serve temporarily as a way of binding the distributed neocortical sites that together comprise the record of a whole event so that subsequently a complete memory can be revived even in the absence of a partial cue. The characteristics of retrograde amnesia demonstrated here require in addition a gradual transformation or consolidation process in the organization of memory storage whereby the contribution of the hippocampus gradually diminishes and a more permanent memory gradually develops, probably in neocortex.

Although the neural events underlying consolidation remain to be identified, it seems likely that slow changes in synaptic connectivity are involved. The hippocampus is needed at the time of learning and during consolidation,

Fig. 1. A thionin-stained coronal brain section midway through the lateral geniculate from one monkey in the operated group. This animal sustained nearly total bilateral ablation of the hippocampal formation, including the dentate gyrus, the subicular complex, and entorhinal cortex. Also, nearly all of the parahippocampal cortex was damaged bilaterally. Overall, the damage was very probably the result of an infarction during surgery.

Fig. 2. Retention of 100 object discrimination problems learned approximately 2, 4, 8, 12, and 16 weeks before hippocampal surgery (20 pairs per time period). Retention was assessed 2 weeks after surgery in monkeys with lesions ($H^+$) (C) (n = 11) or after an equivalent interval in unoperated animals (N) (●) (n = 7). Brackets show standard error of the mean.

Fig. 2. Retention of 100 object discrimination problems learned approximately 2, 4, 8, 12, and 16 weeks before hippocampal surgery (20 pairs per time period). Retention was assessed 2 weeks after surgery in monkeys with lesions ($H^+$) (C) (n = 11) or after an equivalent interval in unoperated animals (N) (●) (n = 7). Brackets show standard error of the mean.

**REFERENCES AND NOTES**


21. Assume that some acquired information will be short-lived, then what survives in memory after damage of the hippocampus? What are the conditions, and it will be at least as abundant in recent time periods as in more remote time periods. According- ingly, after hippocampal damage, performance scores should always be at least as good for the most recent time period (that is, for the period just before the time of damage), as for any more remote time period. The limiting case would have performed as if scores equal across all time periods. The present finding, that retention was significantly poorer for recent time periods than for more remote time periods, rules out this account of temporally graded retrograde amnesia.

22. For earlier versions of the consolidation concept, see G. E. Müller and A. Pitcher, Z. Psychol. 1, 1 (1900); J. L. McGaugh and M. Herz, Behav. Neurosci. 98, 345 (1984). However, results with rats trained on four trials might be directly related to neuroanatomy or to hippocampal function. Recently, this same kind of temporal gradient of retrograde amnesia was described in rats with hippocampal lesions; in this case, the gradient extended 2 to 5 days (G. Winocur, Behav. Brain Res. 38, 145 (1990); also see R. Sutherland et al., Soc. Neurosci. Abstr. 13, 1066 (1987)).

23. Gradients of retrograde amnesia have been obtained previously, in which the remote past was remembered better than the recent past; with psychiatric patients prescribed electroconvulsive therapy [L. R. Squire, P. C. Slater, P. M. Chace, Science 187, 77 (1975)] and in prospective tests of mice given electroconvulsive shock [L. R. Squire and C. W. Spanis, Behav. Neurosci. 98, 345 (1984)]. However, results with rats trained on four trials could be directly related to neuroanatomy or to hippocampal function.

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Widespread Expression of BDNF But Not NT3 by Target Areas of Basal Forebrain Cholinergic Neurons

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Brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT3) are homologs of the well-known neurotrophic factor nerve growth factor. The three members of this family display distinct patterns of target specificity. To examine the distribution in brain of messenger RNA for these molecules, in situ hybridization was performed. Cells hybridizing intensely to antisense BDNF probe were located throughout the major targets of the rat basolateral cholinergic system, that is, the hippocampus, amygdala, and neocortex. Strongly hybridizing cells were also observed in structures associated with the olfactory system. The distribution of NT3 mRNA in forebrain was much more limited. Within the hippocampus, labeled cells were restricted to CA1, the most mediolateral portion of CA1, and the dentate gyrus. In human hippocampus, cells expressing BDNF mRNA are distributed in a fashion similar to that observed in the rat. These findings point to both basal forebrain cholinergic cells and olfactory pathways as potential central targets for BDNF.

The prototypic neurotrophic factor nerve growth factor (NGF) has recently gained much attention as a potential therapeutic agent for Alzheimer’s disease by virtue of its apparent trophic action on cholinergic forebrain neurons. Although the more recently described neurotrophic factors BDNF and NT3 are present in the central nervous system (2–4), little is known about the sources or targets for these molecules in the brain. To localize mRNA for BDNF and NT3 in rat brain, we performed in situ hybridization at high stringency (5) with 35S-labeled RNA probes (6). An initial survey of the brain revealed a striking pattern of BDNF hybridization in several forebrain regions. Significant labeling for BDNF mRNA was also observed in

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