NEUROSCIENCE:
Remembrance of Things Past

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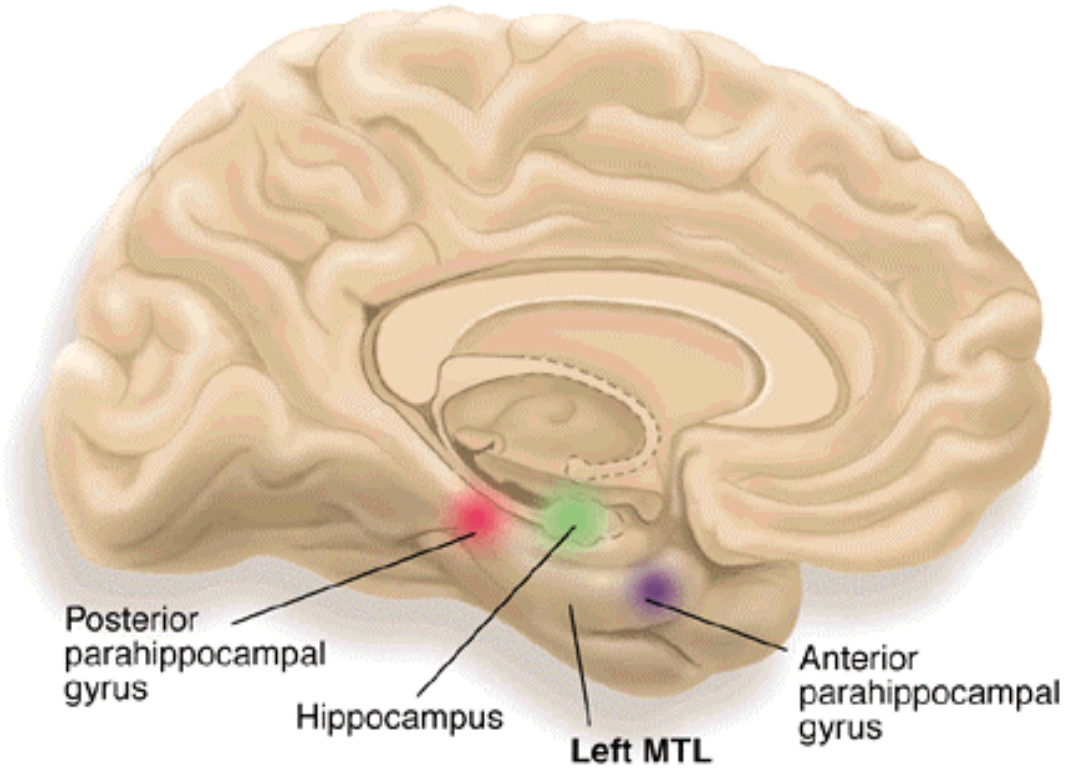
In a typical day, people experience myriad events and see innumerable objects, yet only some of these experiences are converted into enduring memories (1). Progress in understanding the neural pathways that encode these memories has been rather modest thus far. Typical studies of brain-injured amnesic patients (2) cannot cleanly distinguish between the effects of brain damage on the encoding of memories and their retrieval from storage (3). Although neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), detect activity in specific brain regions as people carry out various kinds of memory tests (4), their time resolution is not fine enough to determine the precise sequence in which different brain regions influence the encoding and formation of memories. Now, Fernandez et al. (5) track the serial encoding of memories within the medial temporal lobe (MTL) of the brain (a region beneath the temporal lobe surface that includes the parahippocampal gyrus and hippocampus) using a real-time electrophysiological technique (see the figure). They report on page 1582 an attempt to answer the fundamental question: Where and when are memories formed in the brain?



Memories are made of this. Lateral view of the brain highlighting three regions of the medial temporal lobe (MTL) that are involved in memory formation: the anterior parahippocampal gyrus (purple) and hippocampus (green) in the anterior MTL, and the posterior parahippocampal gyrus (red) in the posterior MTL.

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Previous studies (6) have used event-related fMRI (7) or electrophysiological techniques (8) to look at areas of brain activity during encoding of specific experiences that were subsequently forgotten or remembered. Study participants (6)--scanned by fMRI as they viewed a series of words and then tried to recognize them from a new list--showed increased brain activity during information encoding in the posterior region of the left MTL (also called the left parahippocampal gyrus) and in the left frontal lobe for words that were subsequently remembered compared to words that were subsequently forgotten. Comparable results were reported in subjects scanned as they studied pictures of everyday scenes, and later tried to remember them. But here, the increased fMRI signal during encoding for recalled pictures was located in both the left and right posterior MTL and in the right frontal lobe.

The Fernandez study now shows that two parts of the left MTL--the anterior MTL in the rhinal cortex and the hippocampus proper--contribute to the memory encoding of words and their subsequent recall. The investigators conclude that the timing of the contributions of the two regions is staggered such that encoding activity in the hippocampus follows encoding activity in the anterior MTL. Fernandez et al. recorded electrical activity with long electrodes inserted into the MTL of 12 epilepsy patients in whom the MTL was unaffected. The event-related potentials (ERPs) measured by these depth electrodes provide fine-grained spatial resolution of brain activity (also available with fMRI) and real-time temporal resolution (which is not possible with fMRI). During electrical recording the patients were asked to memorize 12 words that were presented on a computer monitor. After a brief period of distraction, patients attempted to recall the words they had just read. In the anterior MTL, ERPs recorded for list words that were remembered versus those that were forgotten began to differ approximately 310 ms after stimulus presentation (that is, the negative potential was greater for remembered than for forgotten words). In the hippocampus, by contrast, ERPs for remembered and forgotten words did not begin to differ until approximately 500 ms after stimulus onset (in this case, there was a greater positive potential for recalled than for nonrecalled words).

These results are broadly consistent with the earlier fMRI studies (6) in that both the fMRI and ERP data directly implicate MTL structures in memory encoding associated with both subsequent remembering and forgetting. The two avenues of research appear to differ, however, in that the fMRI studies demonstrate that activity in the posterior MTL (posterior parahippocampal gyrus) is associated with subsequent retention of memory, whereas the ERP results indicate that activity in the anterior MTL (anterior parahippocampal gyrus and hippocampus) is associated with memory retention. Fernandez et al. did not record from the posterior MTL and it may be that if ERPs had been recorded from this region then an association between activity during encoding and memory formation would have been found. The fMRI and ERP data suggest that there may be at least three distinct regions of the MTL involved in memory encoding.

Why did the earlier fMRI studies fail to find an association between activity during encoding and subsequent memory in anterior MTL regions? Meta-analyses of neuroimaging data indicate that, whereas PET studies reveal activation during encoding in both anterior and posterior MTL, fMRI experiments demonstrate activation almost exclusively in the posterior MTL (9). These contrasting results could reflect differences in experimental protocols between the studies, or could be attributable to loss of fMRI signal (susceptibility artifact) in the anterior MTL. Further experiments comparing PET, fMRI, and electrophysiological techniques will be required to settle these apparently conflicting findings.

The Fernandez study brings into bold relief a critical and as yet unanswered question: exactly what computations do each of the MTL regions perform, and how is the later encoding activity in the hippocampus influenced by, or dependent on, earlier activity in the MTL? Consistent with the observation of temporally staggered encoding events within these structures, the MTL is the principal cortical input pathway to the hippocampal region. However, additional evidence is necessary to determine whether these structures support encoding of the same or similar types of information, or whether they support the encoding of fundamentally different kinds of information. This distinction bears on a current debate about the architecture of memory and the specific roles of MTL structures in memory formation (10). One theory proposes that parahippocampal and hippocampal regions support the encoding of the same type of declarative information, which supports later recall and recognition of facts and events. An alternative theory postulates that the parahippocampal gyrus contributes mainly to the encoding of information about the occurrence of an item (required for subsequent recognition) whereas the hippocampus supports encoding of relations between an item and its context (primarily useful for subsequent recall) (10). Although the Fernandez findings do not settle this debate, they will provoke future studies melding electrophysiological and fMRI techniques with behavioral observations. Such studies should help to elucidate how the parahippocampal and hippocampal MTL structures encode and form memories of items and their connections to other objects and, more broadly, how memories are organized (11).

References and Notes

1.F. I. M. Craik and R. S. Lockhart, J. Verb. Learn. Verb. Behav.11, 671 (1972).
2.W. B. Scoville and B. Milner, J. Neurol. Neurosurg. Psychiatry 20, 11 (1957); L. R. Squire, Psychol. Rev. 99, 195 (1992) [Medline].
3.D. L. Schacter and E. Tulving in Human Memory and Amnesia, L. S. Cermak, Ed. (Erlbaum, Hillsdale, NJ, 1982), pp. 1-32.
4.R. L. Buckner, W. H. Kelley, S. E. Petersen, Nature Neurosci. 2, 311 (1999) [Medline]; A. D. Wagner, W. Koutstaal, D. L. Schacter, Philos. Trans. R. Soc. London B 354, 1283 (1999).
5.G. Fernandez et al., Science 285, 1582 (1999).
6.J. B. Brewer, Z. Zhao, J. E. Desmond, G. H. Glover, J. D. E. Gabrieli, Science 281, 1185 (1998); A. D. Wagner et al., ibid., p. 1188.
7.A. M. Dale and R. L. Buckner, Hum. Brain Mapp. 5, 329 (1997).
8.H. J. Neville, M. Kutas, G. Chesney, A. L. Schmidt, J. Mem. Lang. 25, 75 (1986); K. A. Paller, M. Kutas, A. R. Mayes, Electroencephalogr. Clin. Neurophysiol. 67, 360 (1987) [Medline].
9.M. Lepage, R. Habib, E.Tulving, Hippocampus 8, 313 (1998) [Medline]; D. L. Schacter and A. D. Wagner, ibid. 9, 7 (1999) [Medline].
10.F. Vargha-Kadem et al., Science 277, 376 (1997); L. R. Squire and S. M. Zola, Hippocampus 8, 205 (1998) [Medline]; J. P. Aggleton and M. W. Brown, Behav. Brain Sci., in press.
11.B. Bontempi et al., Nature 400, 671 (1999) [Medline]; E. Teng and L. R. Squire, ibid., p. 675 [Medline].
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