The authors mention that fosmidomycin and FR900098 had to be given three times a day owing to their short half-life in mouse plasma. A half-life of just a few hours in humans would mean multiple dosing over many days. This would significantly limit the use of these compounds as antimalarials in the clinic as it would be difficult to ensure compliance with such treatment regimens and so prevent reappearance of the parasites in blood (recrudescence). But, even if these two compounds do have a very short half-life in human plasma, they could conceivably be used in combination with other therapies. More significantly, given their low toxicity, these compounds could serve as valuable leads for the design of candidate antimalarial compounds with improved pharmacokinetic properties.

In the longer term, the validation of the DOXP pathway as a source of antimalarial drug targets opens up the possibility of screening large libraries of compounds for new chemical leads against DOXP reductoisomerase and other enzymes in the pathway. It is worth noting that antimalarial drugs that target a single enzyme, such as pyrimethamine (which inhibits dihydrofolate reductase) and atovaquone (which inhibits the mitochondrial cytochrome b/c1 complex) have ultimately found clinical application in synergistic drug combinations. Identifying inhibitors of several enzymes in the DOXP pathway might also result in synergistic drug combinations of increased therapeutic value.

Finally, it is worth acknowledging that sequence data from the malaria genome project have facilitated this work and will continue to be of benefit to future drug discovery efforts. As more data are generated from the malaria genome project, our understanding of the metabolic pathways in the malaria parasite will improve. As the genome sequence nears completion, one worthy goal is the generation of a complete *P. falciparum* metabolic map (metabolome) based on predicted gene products.

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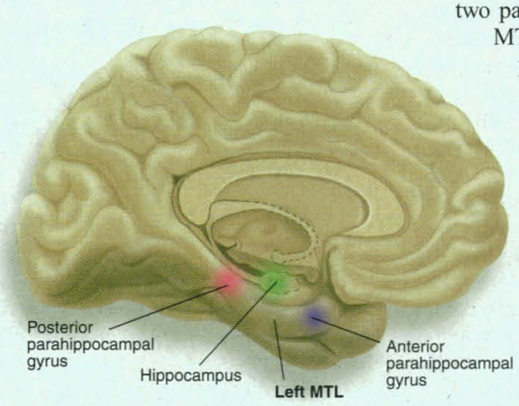
PERSPECTIVES: NEUROSCIENCE

Remembrance of Things Past

Daniel L. Schacter and Anthony D. Wagner

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?

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.



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.

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

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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*).

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NOTA BENE: NEUROSCIENCE

For Time Is the Longest Distance Between Two Places

TENNESSEE WILLIAMS, *THE GLASS MENAGERIE*

Imagine that you can vividly describe the neighborhood in which you grew up 60 years ago but are unable to remember anything about the area in which you now live. This is the plight of a 76-year-old amnesic man who suffered damage to the hippocampus and other structures in the medial temporal lobe (MTL) of the brain (see the figure, previous page) after encephalitis. His misfortune has proved providential for neuroscientists studying how the brain forms memories, a process known to involve the hippocampus.

Teng and Squire, the University of California researchers who studied the amnesic patient, report in a recent issue of *Nature* (*1*) that he could recall as readily as several of his old schoolmates how to navigate from his boyhood home to school and gave comparable responses to a series of questions about the neighborhood in which he grew up. But, he could give no directions at all from his current residence to particular locations in his new neighborhood (to which he moved after becoming amnesic). The investigators conclude that the hippocampus is essential for forming new memories of places but that these memories are stored for long-term retrieval in other parts of the brain.

A neuroimaging study in mice, reported in a companion paper (*2*), supports that conclusion and identifies regions of the neocortex where place memories are eventually stored. Bontempi *et al.* (University of Bordeaux) taught their mice to discriminate between eight arms of a radial maze (three arms contained food, the other five did not). Five or 25 days after learning the task, the mice (injected with a radioactive tracer) were again presented with the maze, and changes in metabolic activity in different brain regions were visualized by neuroimaging. Mice negotiating the maze after a 25-day hiatus showed decreased metabolic activity in the hippocampus but increased activity in several neocortical structures compared with mice that had traversed the maze just 5 days previously. But presenting mice with a new maze (in which food appeared in different arms), 25 days after they had memorized the original version, reactivated hippocampal activity as new memories were formed. Although the hippocampus is active in the early formation of spatial memories, it appears that they are gradually consolidated and stored outside of the MTL in the neocortex. With the finding that other regions of the MTL (within the parahippocampal gyrus) are important for the initial step in memory encoding (see page 1503), the intricate skeins of memory's web are slowly becoming untangled.

–ORLA SMITH

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