

The Biology of Recognition Memory

by John J. Medina, PhD



Last month I examined emotions and their surprising impact on the formation of memories. Nor-epinephrine arriving at certain memory-related tissues near the moment of learning turned out to play a critical role. There has been great progress in attempting to explain the interaction between emotions and memory formation at the molecular level.

There was an issue I left out of that article, however, that is appropriate to address in this column. If you did not read my text closely, you might have been left with the impression that memory was a unitarily described, monolithic cognitive talent upon whose various underlying substrates everyone agrees. Nothing could be further from the truth. In fact, I was only describing a single category of memory in the text, a type usually called declarative memory (ie, something you can declare, such as “Thomas Jefferson was the third president of the United States”)—the star player of medial temporal lobe-mediated learning.

It turns out that there are many types of memory, categories of which are actively debated at this very moment, and many involving far-flung regions beyond the medial temporal lobe. Currently, we have very little idea how even the major categories relate to each other, let alone how their originating neurological substrates produce observed behaviors.

In this article, I will illustrate how fluid things can be in this line of work by investigating one subtype of declarative memory, a category usually called recognition memory. I will start with some basic definitions of recognition memory, review a few older ways of describing such memory formation at the tissue level, and then show how newer data cast some suspicion on these older descriptions. Patient recognition and recall is extraordinarily important in the field of psychiatry and, given its centrality, you may be surprised at how little is known about it.

Some basics

As mentioned, a subcategory of declarative memory is called recognition memory. Classically, recognition memory has been defined as the ability to assess accurately that a stimulus has been encountered before. There can be direct recall, which is the ability to remember a stimulus in the ab-

sence of that stimulus. There can also be discrimination components in which the learner may be able to distinguish between a stimulus that had been previously presented and a new stimulus, without any further knowledge of either one.

Many cognitive neuroscientists believe that these characteristics split recognition memory into 2 interlocking components that have been assigned to unique neurological substrates. One is formally termed recollection. This involves remembering discrete details about an experience to which the learner has been previously exposed. Several years ago a group of researchers proposed that these behaviors were centered in the hippocampus. Their ideas were largely based on neuroimaging case studies involving individual patients with amnesia. Such assignments became the investigational womb from which a great deal of research—and subsequent data—emerged.

The second component, formally termed familiarity, is a stripped-down version of the first. This involves the conscious awareness that some object has been encountered before, but without an ability to recall anything further about it. The group of researchers mentioned previously proposed that these behaviors originated in the perirhinal cortex, a region next to the hippocampus. Both regions are part of the medial temporal lobe memory system, whose full complement includes the parahippocampal gyrus; carrying parahrinal, entorhinal, and perirhinal cortices, as well as the hippocampus, subiculum, and dentate gyrus. All are involved in various aspects of declarative memory formation.

Life in the brain, however, is hardly this clear-cut or this simple, and the ideas that recollection stems from the hippocampus and that familiarity stems from the perirhinal cortex have been challenged. To understand the details of this turbulence, I will need to turn to some of the tests that re-

searchers use in attempting to understand recognition memory. As you shall see, the sum total may paint a very different, much more complex picture of interactions within the medial temporal lobe.

Testing recognition

The first set of tests is called remember-know assessments, which appeared to confirm the hypothesis of recollection events occurring in the hippocampus. Learners who undergo these tests are presented with a collection of objects that, ideally, their brains will record. They are then asked to review another collection of objects that contain previously encountered objects (“old” objects) and objects not previously encountered in the initial exposure (“new” objects). As the learners are being exposed to this second collection of items they are asked 2 questions. Question A is “Do you remember this particular item?” Question B is “Do you simply remember that the item had been presented before?” Question A (the remember part) attempts to measure recall. Question B (the know part) attempts to measure familiarity.

When remember-know tests were administered to learners with hippocampal lesions, an extraordinary result was obtained. Patients appeared to be deficient in their ability to recollect objects but had less trouble (and in some cases, no trouble) with familiarity. Research just like this caused some investigators to conclude that this was due to a division of labor within the brain.

The second set of tests is often called delayed nonmatching-to-sample tests. These examinations involve the presentation of an object followed by a delay that can last from 1 to 2 seconds to several minutes. After that period the learner is simultaneously reexposed to the test object and an object he or she has never before observed. In the case of animal studies, the choice of the novel, previously unexposed object is rewarded.

The third set of tests is called novel object recognition tests. In these protocols the learner is exposed to a pair of identical objects. This is followed by a delay that can range from a few seconds to a few hours. The learner is then exposed to another pair of objects consisting of a previously seen object and a novel object. Because humans and animals

attend to the novel object, indicating a memory of the previous object, the test is useful for assessing recognition.

In laboratory animals, hippocampal lesion studies showed that the region was critically involved in the ability to detect both new and familiar stimuli—at least most of the time. The problem was that some studies showed no impairment in behavior, even with well-characterized lesions. This has been explained several ways, from variability in lesion size to individual behavioral differences among animals.

When larger groups of patients with hippocampal damage were examined using recognition tests, the individual assignments originally proposed for recognition memory (recollection and familiarity) were not observed. Findings from a study that involved a group of 6 patients indicate that the hippocampus was involved in both recollection and familiarity. Findings from another study that involved 56 patients show the same thing. Because they all had larger sample sizes, these data were in obvious contradiction to the previous case studies. What, then, were the researchers who advocated for this dichotomy actually studying?

Close analysis of data derived from these tests eventually led some researchers to become skeptical of the hippocampal-perirhinal recognition assignments. They concluded that researchers who were attempting to isolate the recollection/familiarity substrate dichotomy were actually just measuring memory strength.

This conclusion was based on another test—described below—which is based on a notion called signal-detection theory. This theory combines old items called the target with new items called the foils in the context of memory strength. Memory strength is a probabilistic judgment on the part of the learner that an item did or did not appear on a list previously given to the learner. It is measuring the degree of certainty the learner is exhibiting about an item. In general, items with greater memory strength (usually above some numerical threshold) are judged to be old,

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or targets. Any items with weaker memory strength (usually below that threshold) are judged to be new, or foils.

Curves that are generated from these tasks are called receiver operating characteristic (ROC) curves. In general, an ROC curve contrasts the rate at which the learner really does identify old items correctly with the rate at which the learner is inaccurate. By inaccurate I mean “false alarm” rates, which are the rates at which foils are incorrectly tagged as targets.

These analyses tend to fit better with the real-world situations of the brain, according to some researchers. In this model, recollection and familiarity are both continuous processes that are capable of combining to allow the researcher to examine the memory strength of an item on a test list. This way of looking at retrieval makes some sense. Many factors can influence memory strength, including prior experience and the events that occur at the time of encoding. It would be hard to make an argument that these factors could not influence recollection and familiarity.

Some researchers studying data

from ROC curves smelled a rat and actively faulted the remember-know findings by challenging the assumption that remember and know mean recollection and familiarity in any objective sense and that such distinctions actually reflect a division of labor in the brain.

In their view, the data seem to point to a much less complex interpretation—that what is being measured is simple memory strength; scientists who are trying to study recollection versus familiarity are actually studying the differences between strong memories and weak memories. They believe that the dichotomy,

if taken at face value, leads to a near contradiction (Figure).

Even the brain lesion experiments that purport to show a division of labor have been questioned. Most stroke patients do not have neatly bordered areas of damage that affect only one well-defined neuroanatomical structure and not another. Indeed, it is often not possible in real-world research laboratories to show the exact-to-the-cell extent of the damage even when there are clear behavioral deficits—and remember, the hippocampus and perirhinal cortex lie adjacent to each other in the brain. Maybe there is no such thing as recollection and familiarity. Maybe there are only strong memories and weak memories.

Obviously, the neuroanatomical issues could be resolved with direct recording of neuronal activity, noninvasive imaging experiments, or both. The most robust results would be obtained using such technologies in a direct comparison of recollection with recognition assays in patients who have damaged hippocampi. Functional assignments could be achieved even in patients in whom the lesions are “messy” or ill-defined.

When such rigor was brought to bear on the question of the roles of the hippocampus and perirhinal cortex in recognition memory, a clearer, more nuanced picture emerged. While it is beyond the scope of this article to fully explain all these data, 2 very specific findings emerged.

First, single-unit studies of recollection showed that both the hippocampus and perirhinal cortex were involved in recollection and familiarity. Single-unit recordings are technologies that can measure the activity of individual neural cells in conscious animals. It can provide both temporal and spatial information about the functions of a remarkably small number of neurons. The use of this technology directly refuted the notion that recollection and familiarity occurred in separable neuroanatomical substrates.

Second, more finely tuned resolution showed that while the distinction in recognition memory was blurred, the 2 regions were hardly identical functionally. Neurons that lie in the perirhinal cortex are more reactive to novel stimuli, at least for a short while, but quickly revert to baseline levels upon subsequent reexposure. Neurons in the hippocampus were found to be more reactive to previously exposed stimuli and showed active depression or excitation above baseline for a period.

Another difference between the

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Figure

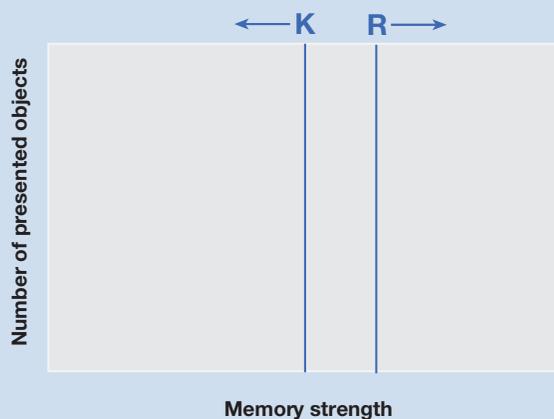
Receiver operating characteristic (ROC) graphs

Shown below are typical graphs that illustrate ROCs in memory recognition tasks. The graphs show an analysis of signal-detection ideas such as in the context of remember-know experiments (see text). Some researchers believe that the simplest interpretation of data like these involves the formation of strong vs weak memories as opposed to separable “recollection” vs “familiarity” memory subsystems in the medial temporal lobe.

A

Interpreting this graph

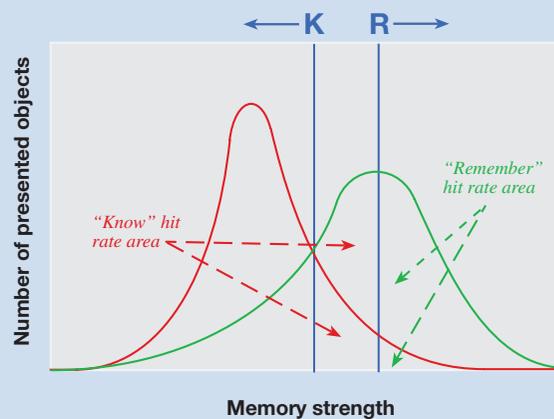
“Remember” events (R) are said to occur when scores exceed a high memory-strength threshold. “Know” assessments (K) are said to occur when scores fall below the R value but above the K value. Scores that fall below the K value are judged to be new events, never previously encountered.



B

Strong memory condition

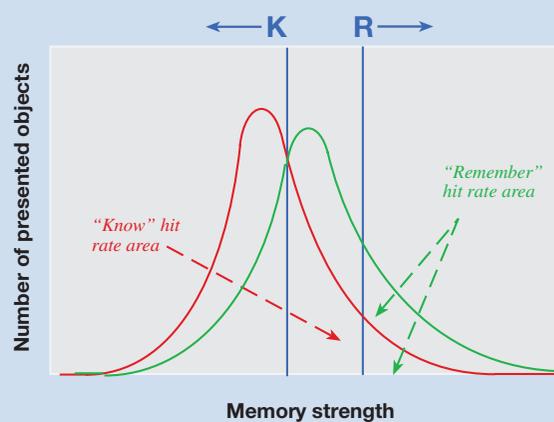
Shown here are typical profiles obtained when memory conditions are said to be “strong.” The red curve represents the “target,” which involves objects the learner has encountered before. The green curve represents the “foil,” which involves objects the learner has not encountered before. The “remember” hit rate area (which could be called the “recollection score”) is the proportion of the targets that exceed the R threshold. The “know” hit rate area (which could be called the “familiarity score”) is the proportion of the targets between the K and R.



C

Weak memory condition

Shown here are typical profiles obtained when memory conditions are said to be “weak.” Note that both K and R criteria are left-shifted. The consequence here is that the “remember” hit rate goes down and the “remember” false-alarm rate goes up. Recollection and familiarity scores are often assessed from graphs such as these, which can lead to an odd conclusion: recollection is greatly reduced under weak memory conditions, the same conditions that leave familiarity relatively unaffected. Some researchers suggest that a simpler explanation is that memory is generally weaker under these conditions.



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2 regions emerged as studies progressed. Perirhinal neurons turned out to be quite finicky about the type of stimulus to which they would respond, requiring very specific inputs before reacting. Hippocampal cells turned out to be much less particular. They were more likely to alter their firing rates if a stimulus had been previously encountered, regardless of the type of input supplied.

Conclusion

These conclusions seem to point to a different, less sharply defined role for the hippocampus and perirhinal cortex in recognition memory. The distinctions between recollection and familiarity may actually have more to do with historical attempts to organize memory behavior than with describing neuroanatomical reality. The brain's recognition features seemed more distributed among a variety of medial temporal lobe structures acting in complementary, cooperative ways and are not easily pigeonholed into 1 or 2 categories.

And that is the whole point of this article. The understanding of many of the human behaviors important to psychiatrists—even ones as simple as “remember that?”—is currently in a near-constant state of flux in the research laboratory. As the physical tools of neuroscience become ever more sophisticated, older ways of thinking about cognition give rise to new ones. Generally, the view gets more complex. Occasionally, the ground shifts from underneath one's feet and, in this example, may actually be disappearing altogether!

Dr Medina is a developmental molecular biologist and private consultant, with research interests in the genetics of psychiatric disorders. □