Brain aging and memory: New findings help differentiate forgetfulness and dementia

Mark D’Esposito, MD • Marc E. Weksler, MD

Many older patients complain about memory loss, yet others never detect a change in memory function. To understand the types of complaints older individuals have about their memories, it is important to know how to classify memory loss. It is also important to understand the differences between forgetfulness and dementia and be familiar with pharmacologic approaches to managing memory loss.

Mark D’Esposito, MD, professor of neuroscience and psychology and director of the Brain Imaging Center, University of California, Berkeley, is increasing the understanding of memory loss through the use of functional MRI (fMRI). Dr. D’Esposito received the AFAR-sponsored Paul Beeson Physician Faculty Scholars in Aging Research award and the Norman Geschwind Prize in Behavioral Neurology from the American Academy of Neurology. Dr. D’Esposito, who serves as a section editor for the Journal of Cognitive Neuroscience, was interviewed for this article by Marc E. Weksler, MD, past president of the American Federation for Aging Research (AFAR).

How do older adults perceive memory loss?

Most older individuals believe that their memory is not as good as it was when they were younger. Others never detect a change. In an epidemiologic study conducted in Finland a few years ago, 3 three-quarters of individuals over the age of 60 had subjective memory complaints, and one-half of these individuals showed evidence of objective memory impairment.

To understand the types of complaints that older individuals have about their memory, it is important to know that there are many types of memory ability (figure 1). Episodic memory includes memories of specific personal experiences. Semantic memory includes memories of facts, principles, and rules that make up our general knowledge of the world. Procedural memory includes memory for motor skills or mental processes such as performing complex arithmetic. These types of memory are referred to as long-term memory, because they are for information learned in the past. In contrast, short-term memory (or working memory) refers to information that is temporarily stored (e.g., remembering a telephone number until it can be written down).

Examples illustrating the different types of memory are: recalling when you last rode your bicycle (episodic memory), knowing what a bicycle is (semantic memory), or knowing how to ride a bicycle (procedural memory). Older individuals with memory complaints have difficulty with episodic memory, whereas semantic memory and procedural memory do not decline with age. Moreover, older individuals who complain of memory difficulties have a specific type of episodic memory problem. They have
difficulty remembering what happened the day before, or even that morning (anterograde memory) but do not have any difficulty remembering events that took place many years earlier (retrograde or remote memory). In addition, the memory that has been forgotten is often on the tip of their tongue and quickly returns if the person is reminded of the event.

Q What is the difference between age-associated memory loss and dementia?

There are two common outcomes in older individuals with complaints of forgetfulness. The first possibility is that their forgetfulness will worsen over time, although usually only minimally, but they will not develop other cognitive impairments. This scenario is called age-associated memory impairment; an older, less accurate term is “benign senescent forgetfulness.” Age-associated memory impairment is an impairment in episodic memory that occurs in older persons. In 1986, criteria for age-associated memory impairment were proposed by the National Institute of Mental Health Work Group on Aging and Memory. These included subjective complaints of gradual memory loss in persons over age 50 and objective evidence of an impairment on a standardized memory test (specifically on episodic memory measures) without evidence of dementia or medical conditions that could cause cognitive impairments (table).

The second scenario for individu-
**Table: Criteria for age-associated memory impairment versus dementia**

<table>
<thead>
<tr>
<th>Age-associated memory impairment</th>
<th>Dementia</th>
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<tbody>
<tr>
<td>Occurs over age 50</td>
<td>Occurs at any age</td>
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<tr>
<td>Subjective complaint of gradual memory loss</td>
<td>Acquired persistent impairment in intellectual function</td>
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<tr>
<td>Objective evidence of impairment on standardized memory tests</td>
<td>Impairment in at least three cognitive domains such as memory, language, visuospatial skills, or executive function</td>
</tr>
<tr>
<td>Absence of dementia or medical condition that could cause memory impairments</td>
<td>Impairment in activities of daily living</td>
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This increase in the concentration of deoxygenated to oxygenated hemoglobin in a brain region (due to greater blood flow) changes the local magnetic field detectable on fMRI. With data processing methods, areas of the brain that are active during the performance of a memory task can be identified. For example, fMRI reveals that moving one's finger increases blood flow to the motor areas of the brain.

This brain mapping technique has gradually replaced its predecessor, positron emission tomography (PET), because fMRI has several clear advantages. Functional MRI does not require injection of a radiisotope into the patient, is otherwise noninvasive, has better spatial and temporal resolution, and is less expensive than PET. Functional MRI is still a relatively new method and is not performed in many university medical centers. Because MRI scanners are readily available, however, the number of institutions that have the capability to perform fMRI far exceeds the number of PET centers.

Using fMRI, researchers have been able to map the brain regions that are involved in memory. In my laboratory, we are specifically interested in short-term, or working memory. The performance of tasks that stimulate working memory during fMRI scanning has shown that the frontal lobes are a criti-
Ical brain region for this cognitive process.

We are now using fMRI to localize the area of the brain affected in healthy older persons with impaired working memory, a common patient complaint. We have hypothesized that a decline in frontal lobe function accompanying normal aging is the source of such difficulties. Using fMRI, we are comparing brain activity in young and older subjects during the performance of working memory tasks. Our results thus far suggest that during the performance of a working memory task, older persons do not use their frontal lobes to the same extent as younger individuals (figure 3). However, other areas of the brain that are not used by younger individuals may be used by older persons. These areas may be used by older persons as a means of compensating for impairments in memory function caused by frontal lobe dysfunction.

**Q Is fMRI a clinical tool? Can it distinguish age-associated memory impairment from dementia?**

At present, because fMRI is a new technique, it has only a few clinical applications. It is being used in presurgical work-up of epilepsy patients to determine the cerebral hemisphere in which language is localized. It is also being used to collect information for presurgical planning from patients who require the removal of arteriovenous malformations or tumors from their brains. At the present time, however, fMRI studies cannot be used to distinguish between individuals with age-associated memory impairment that will not worsen and those individuals who will go on to develop dementia. Yet making this distinction is an important goal. Early diagnosis of dementia is a significant area of research right now, because new medications are being developed that may slow the course of progressive memory disorders. These medications are likely to be more effective if used early in the course of the disease.

**Q Can fMRI be used to determine the effect of medications on cognitive function?**

Using fMRI to understand the effect of medications on brain function is a reasonable goal. In my laboratory, we have recently been performing studies in which young volunteers who have taken a medication or placebo are scanned with fMRI while performing a working memory task. The agent we are studying is bromocriptine, a common medication used in Parkinson's disease that stimulates dopamine activity in the brain. We chose this medication based on results from animal research that showed a relationship between dopamine levels and working memory. Thus far, we have found that in some brain regions, bromocriptine increases activity and in other regions it decreases activity.

Studies that combine pharmacologic intervention and imaging have the potential to reveal the interaction of brain neurotransmitters with brain activity during cognitive function. At present, however, we are not able to use fMRI as a clinical tool to determine which medications compromise and which enhance brain function.

**Q What is the consensus concerning various therapies recommended to improve or maintain memory in older persons?**

Although no medication has been marketed for age-associated memory impairment, three cholinesterase inhibitors have been approved by the FDA for the treatment of cognitive impairment in AD. These drugs—tacrine (Cognex), donepezil (Aricept), and rivastigmine tartrate (Exelon)—increase the amount of the neurotransmitter acetylcholine in the brain.

Tacrine is of limited usefulness, because it must be given four times per day and can cause severe liver toxicity. Donepezil can be taken once per day and has minimal side effects. Clinical
trials with donepezil have shown modest cognitive improvement in some patients taking this medication. More than 80% of patients showed no decline in cognitive skills during 6 months of therapy. Experience is limited with rivastigmine, which was recently approved for the treatment of mild to moderate dementia of the Alzheimer's type.

Vitamin E has also been recommended for patients with AD. In one study, vitamin E appeared to slow the progression of the disease during a 2-year period. In a separate study of a small number of patients with AD and multi-infarct dementia, patients taking the tree-leaf extract Gingko biloba showed mild improvement in cognitive abilities compared with patients taking placebo. Future studies with larger numbers of patients will be necessary to provide recommendations regarding this therapy.

Summary
Understanding the classifications of memory and the neural basis of memory function can help the clinician determine the appropriate course of therapy for patients who complain of forgetfulness. Distinguishing between age-associated memory loss and the early stages of AD is clinically difficult, but fMRI may pave the way to improved diagnosis and treatment.

References