The effect of age on memory and the brain has been the focus of many studies. Results have identified critical questions that need to be addressed to further our understanding of age-related memory decline: Is cognitive decline diffuse or selective? Where does memory decline localize to anatomically? Does decline represent an abnormal state? What are the causes of memory decline? What level of analysis is needed to investigate age-related cortical changes? These questions are reviewed herein, and attempts at early answers are discussed.

The neuroscience community has increasingly focused on age-related changes in higher cortical function. The drive behind this interest extends beyond the influence aging baby boomers have on policy-makers or arouse in the pharmaceutical industry. Bench researchers have come to appreciate that age-related memory decline offers insight into the neurobiological underpinnings of normal mnemonic function. Clinical investigators, emboldened by successes in diagnosing neurological diseases with high morbidity, have been inclined to tackle subtle entities such as mild memory deficits.

Beyond expanding our knowledge base, the accumulation of new findings has served to identify important questions critical in understanding age-related changes in higher cortical function. These questions, and attempts at providing answers, are reviewed herein.

IS COGNITIVE DECLINE DIFFUSE OR SELECTIVE?

Do age-related changes occur equally across all cognitive domains, or is memory function uniquely sensitive to the effects of aging? Age-related processes, some which underlie cognitive decline, do not target cortical regions equally. Insofar as different cognitive domains involve independent cortical topographies, a starting assumption is that the effect of aging will not be cognitively diffuse.

Neuropsychologic studies1-6 have attempted to address this question using cross-sectional or longitudinal designs. Both approaches, however, have inherent limitations. Cross-sectional findings are limited by the sensitivity of cognitive tests to demographic differences.7 Although an attempt can be made to control for some differences among cohorts of varying ages, the effect of generational differences—such as unequal levels of education and exposure to different environmental stimuli—cannot be accounted for. This cohort effect is most effectively addressed by following up a group of subjects prospectively and observing how performance changes with time. Administering a cognitive test repeatedly, however, results in improving performance,8 and this learning effect can obscure an underlying cognitive decline. Furthermore, longitudinal effects often necessitate long follow-up, which results in greater subject attrition, and this could minimize the change over time because attrition might occur differentially among subjects with greater cognitive decline.9

Thus, cross-sectional studies may overestimate cognitive decline because of the cohort effect, whereas longitudinal studies may underestimate decline because of the learning effect—or if the learn-
ing effect is controlled, then because of selective subject attrition.

Recent studies9,10 have addressed these limitations by using a mixed experimental design. By following separate cohorts prospectively, a cross-sectional × longitudinal analysis can be performed that controls for the limitations of each. Results of these studies show that across cognitive domains, memory performance undergoes conspicuous decline with increasing age. Future studies using complicated designs are needed to further establish the precise profile of age-related cognitive decline and to determine which aspects of cognition are preserved throughout the life span.

WHERE DOES MEMORY DECLINE LOCALIZE TO ANATOMICALLY?

One of the fundamental findings to emerge from cognitive science in the past half century is that memory is a fractionated process and that memory subtypes localize to different anatomical sites.11 Aging has a salient effect on declarative memories—conscious, explicit recollections of episodes and events, as well as semantic information. Although the neuroanatomic mapping of any complex cognitive function oversimplifies, the basic scheme of declarative memory is illustrated in Figure 1. The long-term storage of memory resides in the same associational neocortical sites accessed during perception and activated during memory acquisition.12 The consolidation of long-term memories requires an interplay between the neocortical sites and components of the medial temporal lobes, including the hippocampus. This consolidation phase likely lasts weeks to months, and maybe longer.13 Finally, a successful memory system requires the ability to retrieve information on demand, and retrieval strategies involve the prefrontal cortices.14

Where does memory decline localize to within this functional circuit? Neuropsychologic, physiological,15 and brain imaging16-18 studies suggest that the prefrontal cortex, where memories are consolidated and activated during memory acquisition,12 the medial temporal lobes, including the hippocampus. This consolidation phase likely lasts weeks to months, and might show bimodality, compared with the young age group. Studies9,10 with humans and animals have shown that the variance of memory performance in aging samples increases with age, and some studies have found clear bimodal distributions. These findings suggest that memory decline is not inevitable with increasing age and therefore should be considered a clinical entity.

A more ecological approach to defining abnormal memory decline has less to do with population statistics and more to do with whether the decline has a negative impact on functional ability. The number and proportion of aging individuals in the population is increasing. These aging individuals expect to lead intellectually challenging lives in an environment rich with information and reliant on rapidly changing technologies. The ability to negotiate this environment depends on cognitive skills that include the specific types of memory systems most vulnerable to age-associated changes. Memory decline interferes with an aging individual’s activities of daily living, without necessarily progressing to amnesia or extending into dementia.25-27 Thus, even if memory decline were quantitatively normal, it would still qualify as an entity that warrants clinical attention.

WHAT ARE THE CAUSES OF MEMORY DECLINE?

Nondegenerative disorders causing dementia—metabolic, toxic, infectious, and structural—can present with isolated memory deficits,28-30 but such causes account for only a small percentage of elderly people with isolated cognitive decline.

Because Alzheimer disease (AD) is relatively common in individuals older than 65 years, and because AD pathological processes target the hippocampal formation early in its course,31 early AD is a major contributor to memory decline in otherwise healthy and nonde-
mented older people. Still, not every older individual with memory deficits progresses to AD dementia, and there is evidence from postmortem studies supporting other—non-AD—causes of memory decline. These studies have shown that among brains free of AD pathology, cell loss occurs in select subfields of the hippocampal formation in an age-dependent fashion.

Indirect support of non-AD causes of memory decline is provided by animal studies: all nonhuman mammalian species demonstrate some form of hippocampal-based memory decline with age. None develop the pathognomonic features associated with AD, and the memory decline therefore is caused by non-AD processes. It is unlikely that a non-AD process pervasive across all mammalian species would spare our own.

The exact cause of non-AD memory decline is still a matter of debate and is the focus of ongoing investigations. As shown in Figure 2, likely causes include age-related changes in adrenal and gestational hormonal levels, changes in cerebrovascular supply, and age-related accrual of oxidative stress. Non-AD memory decline does not necessarily have to be a secondary effect of these processes; rather, it might reflect time-dependent alterations inherent to particular sets of neuronal populations.

There is indirect evidence suggesting that age-related memory decline might have a genetic component. Twin studies show an association between genes and cognition—including language, visuospatial ability, and memory function. Memory function is unique, however, because its genetic association seems to increase in an age-related fashion. A gene, or a set of genes, that increases the vulnerability of strategic brain regions, such as the hippocampal formation, to age-related injury might account for this intriguing finding. Although all individuals in a population might be equally exposed to pathological processes that target the hippocampal formation, individuals expressing the “vulnerability” gene would be at greater risk to sustain hippocampal lesions as they age. With time, therefore, this subpopulation would be more likely to undergo memory decline, and in late life those with and without the gene would segregate along memory performance scores. There are, in fact, genes that might act in this manner. The APOE gene is one candidate because it is expressed with relative selectivity in hippocampal neurons, and its products are involved in mechanisms of neuronal repair, and its expression is up-regulated in the setting of hippocampal injury. Consistent with this, the APOE4 genotype is associated not only with AD but also with cognitive deficits associated with head trauma, open heart surgery, mesiotemporal sclerosis, and stroke.

**FUTURE INVESTIGATIONS OF MEMORY DECLINE**

What variable should be measured in assessing cortical abnormalities associated with memory decline? An important observation to emerge from recent studies is that age-related memory decline need not be associated with clear structural lesions. This corresponds to the fact that many age-related processes result in physiological dysfunc-

![Figure 2](image-url)
Because hippocampal subregions are interconnected to form a circuit, a lesion at any subregion may be equipotent in disrupting the global hippocampal network. Thus, techniques that measure global hippocampal function—such as neuropsychologic testing and most functional imaging modalities—cannot resolve lesions to different subregions and have difficulty in honing a differential diagnosis among multiple causes of memory decline. An example of this diagnostic ambiguity is provided by the current clinical goal of detecting AD in its earliest stages, when it primarily affects the hippocampal formation and presents with isolated memory impairment. Measures of global hippocampal function will be sensitive in detecting early AD. However, a global measurement will not be specific in disassociating early AD from other age-related processes that disrupt hippocampal function.

An optimum technique for evaluating the neuroanatomic characteristics of memory decline, therefore, is sensitive to neuronal physiological processes and has sufficient spatial resolution to differentially evaluate neuronal populations.

Among the techniques that evaluate brain function in humans, functional magnetic resonance imaging provides the best spatial resolution, and a few studies have used this technique to evaluate select subregions. Nevertheless, most functional magnetic resonance imaging protocols have difficulty resolving all hippocampal subregions. Because neuronal populations are usually a few millimeters in dimension, the ideal technique for localizing memory decline will be one that can assess neuronal function at the submillimeter range. This is the goal of the next generation of imaging techniques.

**CONCLUSIONS**

There is little question that memory declines with age. Although there is continued debate as to whether memory decline is normal, epidemiological data suggest that components of memory decline are not inevitable and, at the very least, that memory decline impacts day-to-day function.

Numerous physiological processes change in an age-dependent manner, changes that target brain regions involved in memory function. Organizing these causes according to functional neuroanatomic characteristics provides an effective classification scheme for age-related memory decline. Currently available techniques that assess brain function can localize memory decline at the gross anatomical level. Newer techniques are required to localize memory decline to specific neuronal populations within a brain region.

Identifying the source of memory decline at the level of a neuronal population will offer a more precise nosologic classification of memory decline and will aid in developing effective treatments.

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