

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Can Age-Associated Memory Decline Be Treated?

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Many older adults believe that their memory is not as good as it was when they were younger. An epidemiologic study in Finland documented

that 76% of persons over the age of 60 years reported problems with their memory.¹ Age-associated memory decline has been well studied and refers to changes in the aging brain that affect cognition but have no clear pathologic explanation. Because of the rapid increase in the number of older people in the world's population, the development of treatments for age-associated memory decline must be a high public health priority. Yet no effective, validated treatments currently exist. A recent study by Wang and colleagues,² however, provides hope that discoveries of the biologic mechanisms of the aging process can lay the foundation for clinical interventions.

Wang et al. attempted to remediate age-associated deficits in working memory. Working memory refers to the temporary retention of information that was very recently obtained or that was recently retrieved from long-term memory but no longer exists in the external environment. It is a process that is critically important for a wide range of cognitive functions, such as reasoning, planning, and language comprehension. Almost any daily activity requires the temporary retention of some type of information. More than 40 years of research in animals and humans³ has shown that the neural basis of working memory is persistent neuronal activity within a network of brain regions, with the prefrontal cortex being a critical area. Wang et al. made recordings from neurons in the prefrontal cortex in three pairs of monkeys while they were performing a task involving working memory (Fig. 1A). One pair of monkeys was young (7 and 9 years of age), one pair was middle-aged (12 and 13 years of age), and one pair was old (17 and 21 years of age). The firing rate of the neurons was markedly reduced in the middle-aged and old monkeys as compared with the rate in young monkeys (Fig. 1B), which suggested a neural basis for an age-associated decline in working memory. This age-related physiological change is most likely due to the loss of dendritic spines in layer III of the cortex — the layer where recurrent ex-

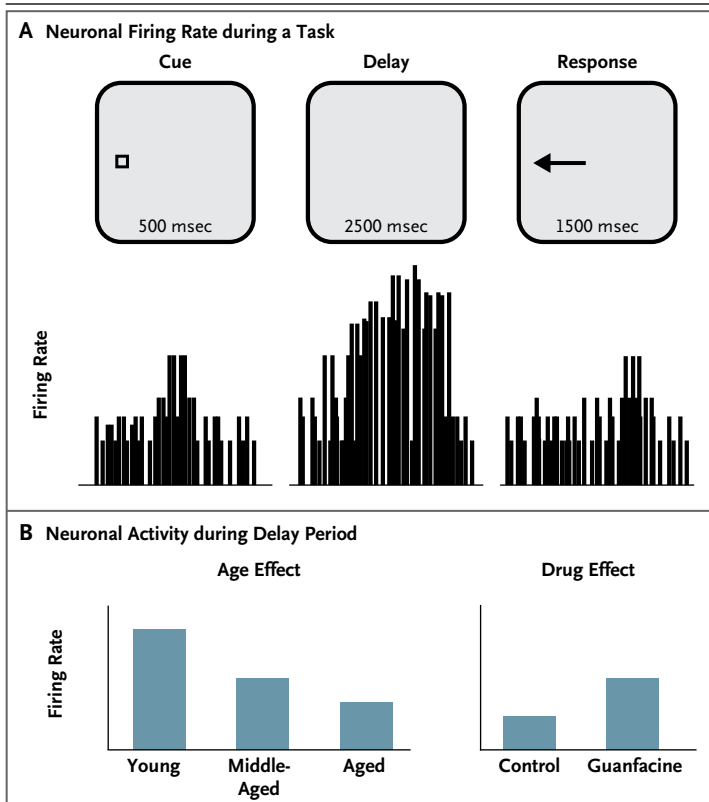


Figure 1. Memory, Neuronal Firing, and the Aging Brain.

Activity in the prefrontal cortex subserves working memory; a recent study by Wang et al.² provides insight into the molecular underpinnings of working memory and how these may change with age. Panel A illustrates a task in which a monkey must remember the spatial location of a stimulus (small square; cue) during a short period without the stimulus (delay) and then must respond with a saccade to the remembered location. A schematic depiction of the firing rate of the neurons in the prefrontal cortex during this task shows that the rate is greatest during the delay period (during which memory is maintained). Panel B illustrates the rate of neuronal firing in the prefrontal cortex during the delay period. The graph on the left shows that middle-aged and aged monkeys have lower neuronal firing rates during the delay period than do young monkeys. The graph on the right shows that, as compared with control conditions, iontophoresis of drugs (e.g., guanfacine) that inhibit cyclic AMP signaling or block potassium channels near the neurons in the prefrontal cortex leads to increased firing rates during the delay period.

citatory networks supporting persistent neuronal activity reside. These spines have a high concentration of cyclic AMP (cAMP)–signaling proteins, and cAMP signaling is increased in the aged prefrontal cortex (because of disinhibition), which weakens the network connectivity of the prefrontal cortex by opening potassium channels. Thus, these investigators measured and attempted to augment persistent neuronal activity in the prefrontal cortex in older monkeys by iontophoresis of drugs (e.g., guanfacine) that either inhibit cAMP signaling or block potassium channels near the neurons. In previous studies, systemic administration of these drugs improved working memory in aged animals. Remarkably, the approach used by Wang et al. was successful — the memory-related rate of neuronal firing in the prefrontal cortex in older monkeys was restored to youthful levels.

As far as we can tell, dementia does not develop in monkeys; therefore, monkeys are an ideal animal model for the study of the neural mechanisms underlying the normal aging process. Moreover, and as illustrated by the study by Wang et al., it is possible to obtain a detailed characterization of interactions between the pharmacologic and physiological properties of neurons in monkeys. This complements the use of functional neuroimaging in humans, which allows for further exploration of higher-level integrative processes, such as an assessment of widespread, distributed neural networks.

Despite substantial progress during the past few decades in the understanding of the neural basis of memory functions and how these functions change with age, this understanding has not been translated into therapeutic interventions to improve cognitive function. The observation linking acetylcholine with episodic memory led to treatments with anticholinesterase inhibitors for patients with Alzheimer's disease. The therapeutic effects of these drugs are moderate, perhaps because Alzheimer's disease affects multiple neurotransmitters. No medication exists for

age-associated memory decline, although guanfacine is currently being tested in a clinical trial (ClinicalTrials.gov number, NCT00935493) for the treatment of deficits in executive function.

Pharmacologic interventions accompanied by cognitive-training interventions may be effective in the remediation of diminishing cognitive abilities. At least two studies have shown that memory can be improved by cognitive training and that detectable brain changes accompany these improvements.^{4,5} However, it remains to be seen whether the pharmacologic and cognitive-training approaches would have a synergistic effect, whether one would substitute for the other, or whether one would eclipse the other. In the meantime, Wang et al. have offered insights into the fundamental physiological changes that occur in normal aging and their underlying molecular correlates. Their detailed characterization of such changes in the prefrontal cortex, perhaps the region of the human brain most vulnerable to age-related changes, is critical to the understanding of the neural basis of cognitive aging and the development of new experimental approaches to the treatment of age-associated memory decline.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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