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Alzheimers Disease Is Not Accelerated Aging

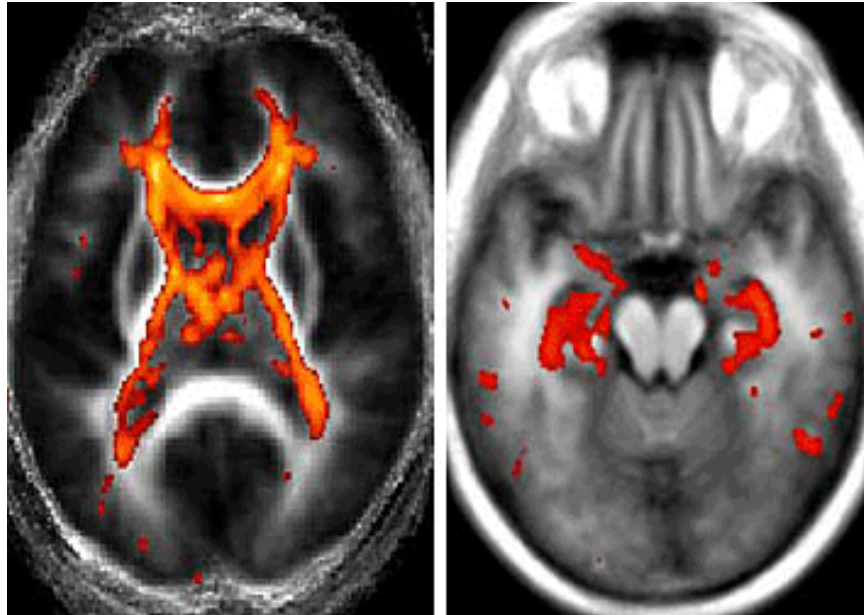


Image Title: Distinct MRI methods reveal changes associated with normal aging, which occur in frontal regions, and those prominent in Alzheimer's disease, which affect the hippocampus. Areas of color show regions of change for aging (left image) and Alzheimer's disease (right image). - Courtesy of Randy L. Buckner and Denise Head, HHMI at Washington

Certain brain changes that are common in normal aging are not the beginnings of Alzheimer's disease. Recent research by cognitive aging experts suggests that changes related to Alzheimer's disease appear in distinct regions of the brain and reflect unique pathology compared with changes that occur in older adults without dementia.

"We're getting a better understanding of the complex constellation of factors that change [in the brain] with aging," said Howard Hughes Medical Institute researcher Randy L. Buckner of Washington University in St. Louis. "When you start to look across the literature, lots of data points converge suggesting there are certain changes that take place in aging that are not what cause

Alzheimer's disease."

Buckner is the author of a review article published in the September 30, 2004, issue of *Neuron*, that points out recurring distinctions between factors that influence what he calls executive function, which more commonly falters with normal aging, and the decline in long-term memory typical of Alzheimer's. Executive function involves the cognitive processes used to complete complex, goal-oriented tasks. Elderly individuals with no symptoms of dementia may have difficulty attending to one thing when distractions are present, for example, or they may experience difficulties in complex, novel situations.

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- **Randy L. Buckner**

Buckner says the data suggest that changes in executive function are due to age-associated influences on frontal-striatal circuits of the brain, including an area called the corpus callosum □ a tract of white matter that connects the two cerebral hemispheres. The accelerated memory loss of Alzheimer's disease is more likely due to changes in the medial temporal lobe memory system, which includes the hippocampus.

For brain changes in non-demented aging, Buckner reviews studies that use structural magnetic resonance imaging (MRI) images to link white matter lesions in the anterior part of the brain with the severity of cognitive dysfunction. Hypertension and accompanying vascular compromise is a salient predictor of white-matter damage. Other studies directly implicate dopamine as an important neurotransmitter that participates in frontal executive function and declines with age. Researchers are still unclear as to how anatomical deterioration and neurotransmitter depletion relate to each other and to executive impairment.

The review includes data from traditional pathological and volumetric analyses, studies of rare genetic mutations, and functional imaging methods such as positron emission tomography (PET) and functional MRI in healthy adults and individuals with Alzheimer's disease, as well as new techniques that enable imaging of amyloid plaques in people living with Alzheimer's. Together, these point toward a disrupted network in the brains of patients with Alzheimer's disease, which includes the medial temporal lobe and other regions of the brain that undergo atrophy and reduced glucose metabolism, and appear to be involved in memory impairment. "We see profound disturbances in the medial temporal lobe memory system across methods—in

studies of volume, function, and now showing what we think is the pathology in Alzheimer's disease," Buckner said.

A paper published in the September 15, 2004, issue of *Cerebral Cortex* by Buckner and colleagues adds more evidence to the argument that some age-associated causes of memory impairment are not the initial stages of Alzheimer's disease. "Our goal was to examine whether typical aging and Alzheimer's disease are on a continuum or distinct," explained lead author and HHMI research associate Denise Head. The researchers used MRI to measure the volume of two regions of the brain previously linked with age-associated changes: the corpus callosum, and the medial temporal lobe.

Comparing volume in young adults, older adults without dementia, and individuals with mild dementia of the Alzheimer type, they found clear differences between the effects of normal aging and Alzheimer's disease. According to Head, the corpus callosum was smaller in older adults, regardless of whether they had dementia. In contrast, volume reductions in the hippocampus were markedly accelerated and larger in people with Alzheimer's disease.

"What we call aging is actually a conjunction of disruption of two different brain systems," said William Jagust at the University of California, Berkeley. "Randy has done a very nice job of showing how these two systems produce different behavioral changes and are probably related to different pathological processes. I think it's probably going to be the way many people start to think of cognitive aging."

Buckner said he hopes the review will help researchers consider the aging condition as the outcome of multiple factors. "We need to look at them as potential separate causes that interact with each other." He added that the field is moving toward integrating divergent research methods to relate underlying molecular events to behavioral changes.

"I'm very interested in learning what these multiple factors are—those that affect executive function in non-demented aging and those that affect core memory systems that are severely disturbed in AD," he continued. "We're trying to understand these things on a mechanistic level. With new methods to image amyloid deposition, we can look within the context of how the deposits change structure and function of the brain. Are there antecedent causes? Are some individuals more at risk? Are some areas of the brain more vulnerable and is that why memory is more affected?"