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Brain Activity in Youth May Presage Alzheimer's Pathology

Researchers who used five different medical imaging techniques to study the brain activity of 764 people, including those with Alzheimer's disease, those on the brink of dementia, and healthy individuals, have found that the areas of the brain that young, healthy people use when daydreaming are the same areas that fail in people who have Alzheimer's disease.

On the basis of their data, the researchers are proposing a new hypothesis that suggests that Alzheimer's disease may be due to abnormalities in the regions of the brain that operate the "default state." This is the term used to describe the cognitive state people defer to when musing, daydreaming, or thinking to themselves.

Writing in the August 24, 2005, issue of the *Journal of Neuroscience*, the researchers state that "the default activity patterns of the brain may, over many years, augment a metabolic- or activity-dependent cascade that participates in Alzheimer's disease pathology."

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"The regions of the brain we tend to use in our default state when we are young are very similar to the regions where plaques form in older people with Alzheimer's disease," said the lead author of the study, Randy L. Buckner, a Howard Hughes Medical Institute (HHMI) investigator at Washington University in St. Louis. "This is quite a remarkable convergence that we did not expect," Buckner adds.

The new findings are important because they could help scientists and clinicians identify and understand the beginnings of what is probably a

cascade of events that ultimately leads to Alzheimer's.

The most common form of dementia among older people, Alzheimer's is characterized outwardly by the erosion of language, thought and memory. Within the brains of people with Alzheimer's disease, abnormal clumps of plaque and tangled bundles of fibers form and characterize the physical manifestation of the disease, which may affect as many as 4.5 million Americans. The causes of the disease are unknown.

The availability of powerful imaging techniques and the ability to merge different sets of imaging data through new bioinformatics and statistical methods enabled Buckner and his team to construct a picture of Alzheimer's from molecular changes to the structural and functional manifestations of the disease. In the process, the team unexpectedly observed that the regions of the brain that light up when we slip into comfortable patterns of thought are the same as those that, later in life, exhibit the disabling clumps of plaque characteristic of Alzheimer's, a disease that most frequently manifests itself after age 60.

That remarkable correlation, said Buckner, suggests that dementia may be a consequence of the everyday function of the brain.

“It may be the normal cognitive function of the brain that leads to Alzheimer's later in life,” said Buckner. “This was not a relationship that we had even considered. The hypothesis is that the cascade of events that leads to Alzheimer's begins at young adulthood.”

Scientists have long known that when the mind is not concentrated on a task—reading, engaging in conversation or solving a math problem, for example—it switches to a default mode, a state of mind where we may muse, daydream or retrieve pleasant memories. When a young person is asked to concentrate on a specific task, they are easily able to shut off the default mode—and the corresponding regions of the brain that run this mode. With the help of powerful imaging technologies such as positron emission tomography (PET) and magnetic resonance imaging (MRI), scientists, including Buckner's HHMI team, have begun to map the activity of the brain in its different states, including the default state. Among the observations they are making is that when a person who has clinical Alzheimer's disease is asked to concentrate on a specific task, the default mode actually becomes more active—rather than showing less activity, as it would in a young, healthy adult.

The default state, according to Buckner, is characterized by metabolic activity in specific regions of the brain, notably the posterior and cortical regions. “These regions were active in the default states in young adults and also showed amyloid (plaque) deposition in older adults with Alzheimer's disease,” the researchers write in the new *Journal of Neuroscience* paper.

“The key insight is that brain activity and metabolism are not uniform across the brain,” Buckner said. “When we looked at people on the cusp of dementia, we saw a loss of brain tissue in the regions we predicted it would occur,” based on our observations of metabolism.

Insight from the new study may help explain why the memory systems of the human brain are vulnerable. “We appear to use memory systems often in our default states. This may help us to plan and solve problems. Maybe it helps us be creative. But it may also have metabolic consequences,” Buckner explained.

The newfound correlation may also have future clinical implications as Alzheimer's is typically diagnosed when it is too late to intervene. To develop and administer effective treatments, clinicians will need to figure out ways to detect the disease in its earliest stages, said William Klunk, associate professor of psychiatry at the University of Pittsburgh and a co-author of the *Journal of Neuroscience* paper.

“You have to get to this pathology before it has its biggest effect, before it has done its damage,” said Klunk, who has developed techniques for imaging the amyloid plaques in Alzheimer's patients.

The findings reported in the new study, he said, suggest that there is now the potential to begin to trace the patterns of the disease and develop methods to detect it before the clinical symptoms set in.

Buckner emphasized that the notion of a causative relationship between everyday metabolic functions of the brain and Alzheimer's remains a hypothesis. However, new studies may help “show if amyloid (plaque) deposition is really dependent on metabolism. Can we find a biologically plausible reason for how metabolism causes Alzheimer's disease?”

Moreover, looking to see if the phenomenon varies or is the same among many individuals will be required to firm up the link between brain metabolism in early life and Alzheimer's pathology later in life. Understanding variation may also help us to explain why some people are at high risk for Alzheimer's disease.

“We are very interested in exploring these new observations to understand who is at risk and who is protected from Alzheimer's,” said Buckner.

In addition to Buckner and Klunk, authors of the *Journal of Neuroscience* article include Abraham Z. Snyder, Benjamin J. Shannon, Gina LaRossa, Rimmon Sachs, Anthony F. Fatenos, Yvette I. Sheline, John C. Morris and Mark A. Mintun, all of Washington University; and Chester Mathis of the University of Pittsburgh.

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