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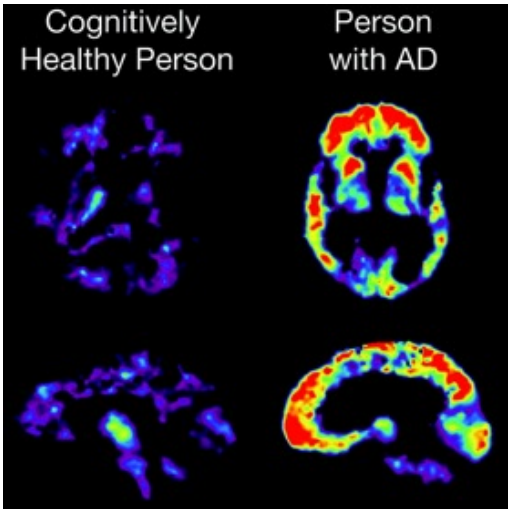
Cracks in the Plaques: Mysteries of Alzheimer's Slowly Yielding to New Research

By Daisy Yuhas | February 6, 2012



A PET scan's bright areas reveal the concentration of amyloid beta, a protein that forms a plaque in Alzheimer's patients. The scan compares the brains of a healthy patient [*left*] and a patient suffering from Alzheimer's [*right*]. Image: Alzheimer's Disease Education and Referral Center, NIH

Science is bringing some understanding of the heritability, prevalence and inner workings of one of the most devastating diseases

This has been a big week in Alzheimer's news as scientists put together a clearer picture than ever before of how the disease affects the brain. Three recently published studies have detected the disease with new technologies, hinted at its prevalence, and described at last how it makes its lethal progress through the brain.

The existence of two forms of Alzheimer's—early- and late-onset—has long baffled scientists. Of the estimated five million Americans who suffer from Alzheimer's, only a few thousand are diagnosed with an early-onset form of the affliction, which affects people before the age of 65. This rare early-onset form is thought to be hereditary and scientists have associated multiple genetic mutations contributing to its occurrence. Late-onset Alzheimer's, although more common, has been the bigger mystery. One variant of the APOE gene-—sometimes known as the Alzheimer's gene—is linked to the late-onset disease. But the APOE gene, unlike dominant early-onset genes, does not determine whether a person will ultimately have dementia.

Now there's evidence that late-onset Alzheimer's has a genetic basis similar to that of early-onset Alzheimer's. By sequencing select genes associated with the latter, along with frontotemporal dementia, researchers at Washington University in Saint Louis and other institutions found that patients with late-onset Alzheimer's carry some of the same genetic mutations as those with the early-onset form. The evidence, published on Wednesday in *PLoS ONE*, bolsters the argument that the forms of Alzheimer's that appear at different life stages should be classified as the same disease. As to why the disease appears earlier in some cases, the scientists speculated that those patients diagnosed relatively early in life carry more genetic risk factors for the disease.

This study's use of rapid genetic sequencing, the authors noted, may provide a model for more precise identification of dementias. Within the study, the researchers identified patients who may have been misdiagnosed as having Alzheimer's; the genes of these patients suggested that they had another type of dementia. Given the heritable component, patients with a family history could be screened to detect and diagnose Alzheimer's early.

Other genetic research unveiled in the past week or so has shed light on the biological processes that underlie how Alzheimer's affects the brain. Certain mutations may lead to an increased production of a protein called amyloid beta in the region of the brain that creates memory. This excess amyloid beta, naturally secreted by brain cells, then becomes a complex called an oligomer. These oligomers may interrupt the signals transmitted between neurons. As in other neurodegenerative diseases like Parkinson's or Huntington's, the spread of oligomers appears to be driving the disease process.

Oligomer-linked diseases are relatively common, in part because oligomers can also play an essential biological role in the brain. A recent investigation using fruit flies reveals that the **presence of a specific oligomer is actually required for the flies to form long-term memories.**

In an early stage of Alzheimer's, the naturally secreted amyloid beta protein builds up as oligomers in the brain, which then go on to form larger aggregates called plaques. Later in the disease, another aberrant form of a protein called tau starts to build up, in the entorhinal cortex. Normally, tau helps provide structure crucial to neuron functioning. The buildup of tau, however, causes the protein to tangle and eventually kill brain cells. What was unknown until recently, however, was how the tau protein spreads through different brain regions.

Two studies—one to be published in *Neuron* and the other published in *PLoS ONE* on Wednesday—have answered this question using brain samples from mice genetically engineered to express tau as it occurs in the human brain. Using a staining technique to highlight tau's distribution in the brain, they compared samples from mice of different ages to analyze how tau moved through brain cells over time. They found the protein spread from neuron to neighboring neuron, traveling along synapses.

Understanding how this protein moves may allow scientists to stop tau in its tracks. "This opens up a whole new world of biology," says Columbia University's Karen Duff, an author on the study published in *PLoS ONE*. Tau is implicated in 30 different forms of dementia. In addition, the movement of tau may be similar to the spread of oligomers associated with Parkinson's and Huntington's. Nonetheless, we are still a long way from a therapeutic solution and stopping tau, which comes at a relatively late stage of Alzheimer's, might be a very limited therapy.

As the world's population continues to age, Alzheimer's becomes a threat to more of us with every passing day. Although we may not yet have new treatments from this work, the take-away on these findings is clear: If we really are going to win the war, or even a battle, against Alzheimer's, we need basic research that can delve into the complex biology that contorts proteins and kills brain cells to find treatments for this disease.