# Study shows Alzheimer's disease may spread by 'jumping' from one brain region to another

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For decades, researchers have debated whether Alzheimer's disease starts independently in vulnerable brain regions at different times, or if it begins in one region and then spreads to neuroanatomically connected areas. A new study by Columbia University Medical Center (CUMC) researchers strongly supports the latter, demonstrating that abnormal tau protein, a key feature of the neurofibrillary tangles seen in the brains of those with Alzheimer's, propagates along linked brain circuits, "jumping" from neuron to neuron.

The findings, published today in the online journal PloS One, open new opportunities for gaining a greater understanding of Alzheimer's disease and other neurological diseases and for developing therapies to halt its progression, according to senior author Karen E. Duff, PhD, professor of pathology (in psychiatry and in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain) at CUMC and at the New York State Psychiatric Institute.

Alzheimer's disease, the most common form of dementia, is characterized by the accumulation of plaques (composed of amyloid-beta protein) and fibrous tangles (composed of abnormal tau) in brain cells called neurons. Postmortem studies of human brains and neuroimaging studies have suggested that the disease, especially the neurofibrillary tangle pathology, begins in the entorhinal cortex, which plays a key role in memory. Then as Alzheimer's progresses, the disease appears in anatomically linked higher brain regions.

"Earlier research, including functional MRI studies in humans, have also supported this pattern of spread," said study coauthor Scott A. Small, MD, professor of neurology in the Sergievsky Center and in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at CUMC. "But these various findings do not definitively show that Alzheimer's spreads directly from one brain region to another."

To look further into this issue, the CUMC researchers developed a novel transgenic mouse in which the gene for abnormal human tau is expressed predominantly in the entorhinal cortex. The brains of the mice were analyzed at different time points over 22 months to map the spread of abnormal tau protein.

The researchers found that as the mice aged, the abnormal human tau spread along a linked anatomical pathway, from the entorhinal cortex to the hippocampus to the neocortex. "This pattern very much follows the staging that we see at the earliest stages of human Alzheimer's disease," said Dr. Duff.

The researchers also found evidence suggesting that the abnormal tau protein was moving from neuron to neuron across synapses, the junctions that these cells use to communicate with each other.

The findings of the study have important implications for therapy.

"If, as our data suggest, tau pathology starts in the entorhinal cortex and emanates from there, the most effective approach may be to treat Alzheimer's the way we treat cancer-through early detection and treatment, before it has a chance to spread," said Dr. Small. "The best way to cure Alzheimer's may be to identify and treat it when it is just beginning, to halt progression. It is during this early stage that the disease will be most amenable to treatment. That is the exciting clinical promise

down the road."

Treatments could conceivably target tau during it extracellular phase, as it moves from cell to cell, added Dr. Duff. "If we can find the mechanism by which tau spreads from one cell to another, we could potentially stop it from jumping across the synapses - perhaps using some type of immunotherapy. This would prevent the disease from spreading to other regions of the brain, which is associated with more severe dementia."

**More information:** The paper is titled, "Trans-synaptic Spread of Tau Pathology in vivo."

Provided by Columbia University Medical Center

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