Neurodegeneration study reveals targets of destruction

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William W. Seeley, MD, is an assistant professor of neurology at the UCSF Memory and Aging Center. Credit: UCSF

Scientists are reporting the strongest evidence to date that neurodegenerative diseases target and progress along distinct neural networks that normally support healthy brain function. The discovery could lead to earlier diagnoses, novel treatment-monitoring strategies, and, possibly, recognition of a common disease process among all forms of neurodegeneration.

The study, reported in the April 16 issue of the journal "*Neuron,*" was conducted by scientists at the University of California, San Francisco and the Stanford University School of Medicine, who characterized their finding as "an important new framework for understanding

neurodegenerative disease."

The finding inspired the image for the cover of the issue of the journal.

Researchers have known that neurodegenerative diseases are associated with misfolded proteins that aggregate within specific populations of neurons in the brain. Alzheimer's disease, for instance, results from misfolding events involving beta-amyloid and tau proteins, which result in neuritic plaque and neurofibrillary tangle formation in medial temporal memory structures. In all neurodegenerative diseases, synapses between nerve cells falter, and damage spreads to new regions, accompanied by worsening clinical deficits.

In most cases, however, scientists have not known what determines the specific brain regions affected by a disease. The current neuroimaging study, which examined patients with five forms of early age-of-onset dementia -- Alzheimer's disease, behavioral variant frontotemporal dementia, semantic dementia, progressive nonfluent aphasia, and corticobasal syndrome - as well as two groups of healthy controls, showed that each disease targets a different neural network.

"The study suggests that these diseases don't spread across the brain like a wave but instead travel along established neural network pathways," says the lead author of the study, William W. Seeley, MD, assistant professor of neurology at the UCSF Memory and Aging Center.

Earlier work performed by Michael Greicius, MD, senior author and assistant professor of neurology and neurological sciences at Stanford, provided Seeley with the inspiration for the present study, which extended Greicius' work on Alzheimer's disease to a host of additional dementias. The findings suggest that network degeneration represents a class-wide neurodegenerative disease phenomenon.

"Something about a network's architecture or biology is either bringing the disease to networked regions or propagating disease between network nodes," says Seeley.

At this point, the scientists have shown that the diseases cause atrophy in networked regions. "We still need to determine how the diseases impact connectivity, and we don't yet know how, at the molecular level, disease spreads between networked areas," says Seeley.

Greicius further commented, "These results suggest that brain imaging measures of network strength should be sensitive enough to detect these diseases at an early stage and, as importantly, specific enough to reliably distinguish one disease from the others."

If all forms of neurodegenerative disease are propagated along synaptic connections, says Seeley, "the framework would have major mechanistic significance, predicting that the spatial patterning of disease relates to some structural, metabolic or physiological aspect of neural network biology."

"We hope our finding will stimulate basic researchers to try to understand the molecular mechanisms for network-based neurodegeneration," he says.

Meanwhile, Seeley, Greicius, and their colleagues plan to test neural network-based diagnostic and disease-monitoring studies in younger people with genetic predispositions to Alzheimer's disease and frontotemporal dementia. The goal is to try to track incipient changes in neural network connectivity and, ultimately, to track how well new experimental drugs can repair or maintain connectivity once an individual begins to show signs of dysfunction.

"Our hope is to develop tools that can detect these diseases even before

symptoms emerge, so that disease-modifying therapies can get started before it is too late," Seeley concludes.

Source: University of California - San Francisco