

# Dementia spreads via connected brain networks

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In a new study, UC San Francisco scientists used maps of brain connections to predict how brain atrophy would spread in individual patients with frontotemporal dementia (FTD), adding to growing evidence that the loss of brain cells associated with dementia spreads via the synaptic connections between established brain networks. The results advance scientists' knowledge of how neurodegeneration spreads and

could lead to new clinical tools to evaluate how well novel treatments slow or block the predicted trajectory of these diseases.

"Knowing how dementia spreads opens a window onto the biological mechanisms of the disease—what parts of our cells or neural circuits are most vulnerable," said study lead author Jesse Brown, Ph.D., an assistant professor of neurology at the UCSF Memory and Aging Center and UCSF Weill Institute for Neurosciences. "You can't really design a treatment until you know what you're treating."

FTD, the most common form of dementia in people under the age of 60, comprises a group of neurodegenerative conditions with diverse linguistic and behavioral symptoms. As in Alzheimer's disease, the diversity of FTD symptoms reflects significant differences in how the neurodegenerative disease spreads through patients' brains. This variability makes it difficult for scientists searching for cures to pin down the biological drivers of [brain](#) atrophy and for clinical trials to evaluate whether a novel treatment is making a difference in the progression of a patient's disease.

[Previous research](#) by the study's senior author, William Seeley, MD, a professor of neurology and pathology at the Memory and Aging Center and Weill Institute, set off a sea change in dementia research by showing that patterns of brain atrophy in many forms of dementia map closely onto well-known [brain networks](#)—groups of functionally related brain regions that work cooperatively via their synaptic connections, sometimes over long distances. In other words, Seeley's work proposed that neurodegenerative diseases don't spread evenly in all directions like a tumor, but can jump from one part of the brain to another along the anatomical circuits that wire these networks together.

In their new study—published October 14 in *Neuron*—Brown, Seeley and colleagues provided further evidence supporting this idea by

examining how well neural network maps based on brain scans in healthy individuals could predict the spread of brain atrophy in FTD patients over the course of a year.

The researchers recruited 42 patients at the UCSF Memory and Aging Center with behavioral variant fronto-temporal dementia (bvFTD), a form of FTD that causes patients to exhibit inappropriate social behaviors, and 30 patients with semantic variant primary progressive aphasia (svPPA), a form of FTD that mainly impacts patients' language abilities. In their first visits to UCSF, each of these patients underwent a "baseline" MRI scan to assess the extent of existing brain degeneration and then had a follow-up scan about a year later to measure how their disease had progressed.

The researchers first estimated where the brain atrophy seen in each patient's baseline scans had begun, based on the hypothesis that brain degeneration begins in some particularly vulnerable location, then spreads out to anatomically connected brain regions. To do this, the researchers built standardized maps of the main functional partners of 175 different [brain regions](#) based on functional MRI (fMRI) scans of 75 healthy adults. They then identified which of these networks best matched the pattern of brain atrophy seen in a given FTD patient's baseline brain scans, and defined that network's central hub as the likely epicenter of the patient's degeneration.

They then used the same standardized connectivity maps to predict where the patient's brain atrophy was most likely to have spread in the follow-up scans done one year later, and compared the accuracy of these predictions to others that didn't take functional network connectivity into account.

They found that two particular connectivity measures significantly improved their predictions of a given brain region's chances of

developing brain atrophy between the baseline and follow-up brain scans. One, called "shortest path to the epicenter," captured the number of synaptic "steps" that region was from the estimated disease epicenter—essentially the number of links in the neural chain connecting the two areas—while the other, called "nodal hazard," represented how many regions connected to a given region were already experiencing significant atrophy.

"It's like with an infectious disease, where your chances of becoming infected can be predicted by how many degrees of separation you have from 'Patient Zero' but also by how many people in your immediate social network are already sick," Brown said.

The researchers showed that on average these two measures of network connectivity did better at predicting the spread of disease to a new brain region than its simple straight-line distance from a patient's existing atrophy. In many cases the disease completely bypassed brain areas that were adjacent but not anatomically connected to already-atrophied regions, instead jumping to more functionally linked regions.

Although this method shows great promise, the researchers emphasize that it is not yet ready for clinical use. They hope to improve the accuracy of their predictions by—among other approaches—using individualized network maps for each patient rather than using average connectivity maps, and by developing more specialized prediction models for particular subtypes of FTD.

In addition to the biological insights the discovery provides about the mechanisms of spreading [brain atrophy](#) in FTD, which will inform ongoing efforts to develop treatments, the researchers also hope the findings will lead to improved metrics for evaluating therapies already entering clinical trials—for instance by giving trial scientists early insights into whether the treatment is altering a predicted course of

disease progression. Researchers could also use better predictions of how atrophy will spread through the brain to help prepare patients and their families for the symptoms they are likely to experience as their disease progresses.

"We are excited about this result because it represents an important first step toward a more precision medicine type of approach to predicting progression and measuring treatment effects in neurodegenerative disease," Seeley said.

In the future, Brown said, scientists might be able to develop therapies that specifically target the likely next site of disease and perhaps prevent [atrophy](#) from spreading from one region to another.

"Just like epidemiologists rely on models of how infectious diseases spread to develop interventions targeted to key hubs or choke points," Brown said. "Neurologists need to understand the underlying biological mechanisms of neurodegeneration to develop ways of slowing or halting the spread of the disease."

**More information:** *Neuron* (2019).  
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