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These scientists want to redefine Alzheimer's as a 'double-prion' disease

Researchers this week say their work should upturn the conventional narrative of how Alzheimer's disease happens. They argue the progression of Alzheimer's is driven by a very specific form of two proteins that play a crucial role in the disease, and these forms should be considered prions—potentially infectious proteins that self-replicate by turning their brethren into a misfolded version of themselves.

To put it simply, people with Alzheimer's disease have brains that are filled with rigid, clumped-together deposits of the proteins amyloid beta and tau, called plaques and tangles, respectively. It's long been assumed that if we can stop these deposits, particularly plaques, from happening or break them up, we can delay or outright prevent Alzheimer's. But this theory has taken a battering in recent years, as trial after trial of anti-amyloid drug has failed to slow down the disease in human patients.

The researchers behind this latest study, based primarily at the University of California, San Francisco (UCSF), are arguing that it's not the final stages of amyloid beta and tau that are the problem; it's the earlier, prion-like forms of both proteins that are the real culprits. Plaques and tangles, in this theory, are essentially just the “dead,” inactive remains of amyloid and tau prions.

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One of the researchers behind the new argument happens to be neurologist and biochemist Stanley B. Prusiner, whose Nobel prize-winning work first established that prions cause a whole class of rare but universally fatal brain disorders, like Creutzfeldt-Jakob disease in people and scrapie in sheep.

The prions that cause these diseases are actually the mutant, misfolded form of a protein that's naturally produced in many mammal species, also called the prion protein, or PrP. Despite having no genetic material like a virus or bacteria (and being even further removed from the concept of life), this mutant PrP makes more of itself, somehow forcing normal PrP it encounters to misfold in the same exact configuration, destroying the brain along the way.

Scientists have also found proteins in fungi that resemble PrP because they can also shapeshift into different forms that self-replicate, and possibly even other prion-like proteins in sea slugs and mammals. Unlike the bad PrP, these proteins don't seem to cause disease and could even play a beneficial role in the survival of their hosts (in people, they may [help us form long-term memories](#)).

Other research in animals has also shown that amyloid and tau can act and spread like classic prions under certain conditions. And there's even [some evidence](#) of people contracting Alzheimer's through medical procedures, much as some people have gotten classic prion diseases from contaminated surgical equipment or transplants (to be clear, these incidents are

vanishingly rare, and no one's arguing that Alzheimer's is infectious the same way that a flu virus is, just that it can behave like a classic prion disease).

Given all of the above, the team wants to expand the definition of prions to include amyloid, tau, and any other naturally produced proteins that can change into a form that self-replicates.

"It's a very generic definition that can encompass all of these different disease-related proteins capable of propagating through a prion mechanism, but importantly, it also incorporates all of these functional prions we find in yeast and elsewhere," co-lead author Carlo Condello, an assistant professor of neurology at UCSF's Institute for Neurodegenerative Diseases, told Gizmodo.

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Condello and his team also want to reframe how scientists conceptualize Alzheimer's disease and other neurological disorders closely tied to abnormal proteins, such as Parkinson's—to start putting them under the umbrella of prion disease and work from there to better understand the disorder and eventually, finally develop successful treatments.

"It's interesting to think, there's any number of diseases that just have someone's name attached to it—Alzheimer's, Parkinson's—but those names don't infer any meaning to the mechanism behind them... You get stuck with these names and people really cling to them," said Condello. "I don't know, maybe being of a younger generation, I'm more willing to give up a definition."

Other researchers are working to [develop treatments](#) that target amyloid and tau before they clump together into plaques and tangles, even if they don't use the word "prion" when talking about them. Condello said their work doesn't conflict with that research. But he said they've also made an important new contribution to the field in their paper, [published](#) in Science Translational Medicine, by devising a test that can rapidly and specifically detect levels of the prion form of amyloid in people.

Using both their test and an earlier developed test for tau prions, they studied the brains of nearly 100 patients who died with full-blown Alzheimer's or similar dementias and compared them to healthy controls.

In these brains, they found clear evidence of amyloid and tau prions spreading throughout the brain, much like classic prions. Another clear link was seen between those with frontotemporal dementia—a disease associated with only tau, not amyloid—and tau prions. To their surprise, though, they also found that levels of both amyloid and tau prions declined the older someone was when they died. Those over 80 had the lowest prion levels of all, while the opposite was true in the youngest people who died with an inherited form of Alzheimer's passed down in families. With tau in particular, the total amount of tau in the brain increased with age even as levels of prion tau declined.

What that last finding means is unclear at this point, the authors say. We know our genetic make-up can make us more vulnerable to Alzheimer's, particularly when it happens in relatively young people. So maybe, Condello said, those who survived longer had genetics that made their brains better at shoving the toxic prions into plaques and tangles than those who died young. Or maybe, just as there are different strains of a virus or bacteria, there are different prion forms of amyloid and tau that can shape the course of the disease differently.

“This is just the tip of the iceberg, and we naturally want to expand this research to several hundred, thousands of cases. And the beauty is that the assays we developed are rapid and high throughput, so we can get through these samples feasibly fast,” said Condello.

Regardless of the research that's to come, the authors say their findings already suggest that relying on tests or treatments that only take into account a person's total levels of tau and amyloid in the brain may be sending researchers down the wrong path.

“I believe this shows beyond a shadow of a doubt that amyloid beta and tau are both prions, and that Alzheimer's disease is a double-prion disorder in which these two rogue proteins together destroy the brain,” said Stanley Prusiner, now director of the UCSF's Institute for Neurodegenerative Diseases, in a [statement](#). “The fact that prion levels also appear linked to patient longevity should change how we think about the way forward for developing treatments for the disease. We need a sea change in Alzheimer's disease research, and that is what this paper does. This paper might catalyze a major change in Alzheimer's research.”

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