

Uncovering one of the driving forces of Alzheimer's disease

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Alzheimer's disease, the most common form of dementia, currently has no cure or effective therapy, in part due to gaps in our understanding of how the progressive neurodegenerative disorder arises in the brain.

Now, a Flinders University study has shown how a protein called tau, a critical factor in the development of Alzheimer's disease, turns from normal to a disease state—and demonstrates how this discovery could deliver a [therapeutic target](#).

Published in the journal *Science Advances*, the team's findings provide hope for preventing the tau transformation process from happening, thereby keeping tau in a healthy state and avoiding [toxic effects](#) on [brain cells](#).

"Alongside a small peptide called amyloid-beta, the [tau protein](#) is a central factor in Alzheimer's disease. Tau is necessary for the toxic effects on brain cells that then result in impaired memory function," says senior study author Dr. Arne Ittner, Senior Research Fellow in Neuroscience in the Flinders Health and Medical Research Institute.

In the course of Alzheimer's disease development, tau accumulates in deposits inside brain cells. During this process, tau gets heavily modified, with various deposits made up of tau carrying multiple small changes at many different positions within the tau molecule.

While such changes to tau have been known to neuropathologists for decades, it remained unclear how tau arrives at this multi-modified stage. The new study has solved part of this mystery and provides a new mechanism to explain how tau gets progressively modified.

The study set out to answer whether one change at one specific spot in tau would make it easier for another spot to be modified. The team focussed on the relationship between tau and [protein kinases](#), which are enzymes that introduce changes in tau.

"Usually, protein kinases target specific spots, called phosphorylation sites, in tau and other proteins, and introduce changes only at these

specific spots," says study lead author Dr. Kristie Stefanoska, Research Fellow in Dementia at Flinders University.

"However, we suspected that some of these enzymes are able to target several spots in tau and would do so even more efficiently if tau were already modified at one spot to begin with."

The researchers conducted a large experiment that included up to 20 different changes in tau and 12 enzymes, focusing on the most abundant type of change seen in tau from the brains of Alzheimer's patients.

While the study did discover that one change in tau does make it easier for another change to be introduced, it was also able to identify "master sites" in tau, being specific spots that govern subsequent modifications at most of the other sites.

"By modifying these master sites, we were able to drive modification at multiple other spots within tau, leading to a similar state seen in the brains of Alzheimer's patients," says Dr. Ittner.

The next step for the team was to see whether master sites could be targeted to reduce the toxic properties of tau in Alzheimer's, in a bid to improve [memory function](#).

The current study employed mice that have both amyloid and tau and developed Alzheimer's-like symptoms, including memory deficits. The researchers found that mice did not develop memory deficits when they had a version of tau that lacked one of the identified master sites, compared with mice that had the usual version of tau.

The team will now investigate how its findings can be translated into a treatment.

"We have shown that this new concept has therapeutic potential, but future work is needed to understand the role of these master sites in health and disease," says Dr. Stefanoska.

"Tau modification in Alzheimer's disease is a complicated process. Ours is the first study to link an initial change in tau with multi-site modification along the entire protein."

The authors say the new mechanism and the master sites at its center could apply to a range of neurological disorders in which tau is involved, including Parkinson's disease, concussion-induced chronic brain injury and stroke.

"Slowing down the changes at master sites of tau in these diseases may put the brakes on tau toxicity and dementia," says Dr. Ittner.

"This new mechanism helps us understand why there is extensive tau modification in Alzheimer's disease in the first place. This will assist researchers and clinicians in designing means for better and earlier diagnosis."

The paper, "Alzheimer's disease: Ablating single master site abolishes tau hyperphosphorylation" by Kristie Stefanoska, Mehul Gajwani, Amanda R. P. Tan, Holly I. Ahel, Prita Riana Asih, Alexander Volkerling, Anne Poljak and Arne Ittner, is published in *Science Advances*.

More information: Kristie Stefanoska et al, Alzheimer's disease: Ablating single master site abolishes tau hyperphosphorylation, *Science Advances* (2022). [DOI: 10.1126/sciadv.abl8809](https://doi.org/10.1126/sciadv.abl8809).
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