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New insights could result in changes to the therapeutic strategy to combat Alzheimer's

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A typical characteristic of the brain of an Alzheimer sufferer is the presence of insoluble Tau protein aggregates. Scientists at VIB, KU Leuven and Janssen Pharmaceutica have demonstrated that the distribution of these aggregates through the brain is facilitated by synaptic connections between brain cells. This news is highly significant because the focus is increasingly on repairing synaptic connections as a therapeutic strategy in neurodegenerative diseases such as Alzheimer's. In fact, it is generally accepted that a loss of synaptic connections leads to a loss in cognitive skills.

Dieder Moechars (Janssen Pharmaceutica): "Looking at our results, we would advise caution regarding the therapeutic approach to the repair of synapses. Our research suggests that synapses also promote the distribution of Tau aggregates, which could counteract the positive effects of a repaired synapse. It is also important to take this into account when developing new therapeutic strategies, for example by combining a synapse restoring approach with one that would remove the Tau aggregate at the synapse."

Patrik Verstreken (VIB/KU Leuven): "We have set up a new in vitro system specifically for this research, to enable us to study the distribution throughout the brain of aggregate proteins that are typical of neurodegenerative diseases. We also want to use this system to explore which substances could counteract the progress of neurodegeneration in the brain without having to use animal models at this early stage. This could become an important tool in the search for potential drugs against,

for example, Alzheimer's disease.'

Synapses

Brain cells communicate via synapses. Successful synaptic connections are vital in order to function properly. Synaptic degeneration is a prime symptom in neurodegenerative diseases such as Alzheimer's. With Alzheimer's, the loss of synapses results in a decline in cognitive skills. That is why a lot of research is being carried out into treatments focused on the repair of synapses.

Together with colleagues at VIB, KU Leuven and Janssen Pharmaceutica, Sara Calafate, Patrik Verstreken and Dieder Moechars discovered that this approach is not straightforward.

Sara Calafate: "We noticed that the spread of Tau aggregates, a typical characteristic of Alzheimer's, proceeded much more effectively via interconnecting brain cells. But it was not clear what role the synapses played in this process. We have now managed to demonstrate that synapses facilitate this distribution and can probably promote neurodegeneration in this way."

A new in vitro model

Scientists developed a new research tool for this study that enabled them to monitor the spread of Tau aggregates whilst changing the synaptic connections between brain cells. They grew brain cells in microscopically small chambers that made it possible to separate synaptic connections from the rest of the cells. When synaptic connections were made, researchers observed that the distribution of Tau was 50 % more efficient than in the absence of synaptic connections.

Patrik Verstreken: "Our research into brain diseases is not possible

without animal models. Nevertheless, we are constantly looking for ways in which we can minimize the number of animal tests. This new tool could help us achieve this."

More information: "Synaptic contacts enhance cell-to-cell Tau pathology propagation," Calafate et al., *Cell Reports* 2015. www.ncbi.nlm.nih.gov/pubmed/25981034

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