Tau protein load in the brain impairs memory functions only when amyloid burden is high

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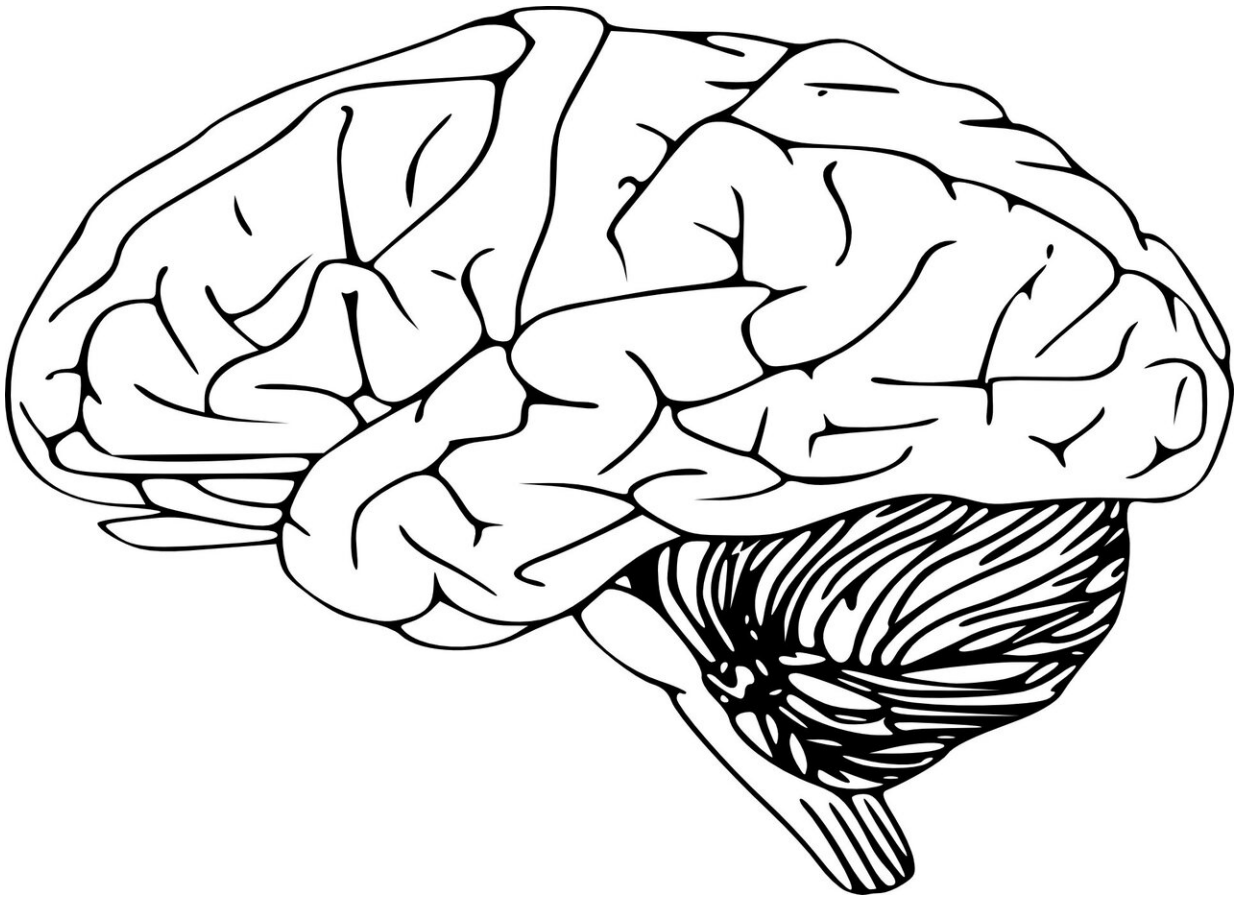

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In the course of Alzheimer's disease, two proteins called amyloid and tau accumulate in the brain. A DZNE study with more than 200 participants now provides insights into the interaction of these pathological phenomena. The data suggest that tau load in the brain impairs memory functions only when amyloid burden is also high. These findings therefore support therapeutic approaches aimed at removing amyloid from the brain in the early stages of Alzheimer's disease. A research team led by Prof. Emrah Düzel reports on this in the journal *Brain*.

"It has long been known that deposits of tau proteins in the so-called hippocampus and in neighboring brain areas impair memory. In the case of amyloid, on the other hand, no clear relationship to memory performance has been found to date. For this reason, among others, it is debated whether it makes sense at all to target amyloid therapeutically. Our current results suggest that this could indeed be helpful for memory function in the early stages of the disease," says brain researcher Emrah Düzel, speaker of the DZNE's Magdeburg site and director of the Institute of Cognitive Neurology and Dementia Research of Otto-von-Guericke University Magdeburg. "The crucial aspect is that you don't look at tau in isolation, but together with amyloid pathology. This is where a link becomes apparent when you study a larger number of individuals and accordingly have solid statistics."

Data acquisition at several sites

The data now evaluated come from a DZNE long-term study (DELCODE) in collaboration with university hospitals in which 10 study centers across Germany are participating. The current investigations included data from 235 subjects over 60 years of age. This group included not only cognitively normal adults, but also individuals with memory problems that were either mild ("mild cognitive impairment") or only subjectively perceived—i.e., common testing methods could not detect memory impairment. Data from individuals with dementia were

not considered, because the focus was on early stages of Alzheimer's disease. Düzel's team analyzed the cerebrospinal fluid (CSF) of the study subjects and examined their memory and brain activity using functional magnetic resonance imaging (fMRI).

Levels of amyloid and tau proteins in CSF are commonly used indicators for assessing the burden of these proteins on the brain. Since amyloid and tau proteins also occur in the CSF of cognitively healthy individuals, the study participants were grouped according to established thresholds into those with pathological (i.e., abnormal) readings and those with levels in the normal range. To assess memory by fMRI, study participants were given the task of memorizing photographic images while brain activity in the hippocampus—the switchboard for memory—was simultaneously registered.

"Using this task fMRI, we found that hippocampal activation to new images decreased with increasing tau load, and so did memory performance, only when amyloid load was high. In other words, high load by both proteins was the likely cause of memory impairment," Düzel says. "This relationship has not been demonstrated in previous studies. The necessary technical harmonization across all study sites is very complex. Such studies require the kind of infrastructure that DZNE has established over the years."

Backing for anti-amyloid therapies

"Our data show several relevant associations. If amyloid levels are beyond the pathological threshold, and only then, we see that the higher the tau levels in the CSF, the worse the memory performance and the more pronounced the reduction in hippocampal activation," Düzel says. "And we also see that if you compare study participants with similar tau data, memory performance is more impaired in those with abnormal amyloid levels than in those with amyloid levels in the normal range."

The causes of the interaction of amyloid and tau pathology are still largely unclear, Düzel acknowledges, but concludes: "Our data show that it might be useful to reduce tau load if amyloid burden is also high. However, our findings also suggest that it might help to reduce or keep amyloid burden low in the early stages of the disease, even if tau load remains the same. One can infer from our results that memory could benefit from this."

This is where anti-amyloid therapies using "monoclonal antibodies" come in that are currently undergoing clinical trials and of which the drug "Aducanumab" (brand name: Aduhelm) is the first to have been approved in the U.S.. However, the approval is controversial. Düzel: "Regardless of how well this particular drug is clinically effective, our study results provide additional support for the general concept of targeting amyloid. This approach should continue to be considered in therapy development."

More information: Emrah Düzel et al, Amyloid pathology but not APOE ε4 status is permissive for tau-related hippocampal dysfunction, *Brain* (2021). DOI: 10.1093/brain/awab405

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