

# Alzheimer's pathology, not cognitive decline, drives neuropsychiatric symptoms

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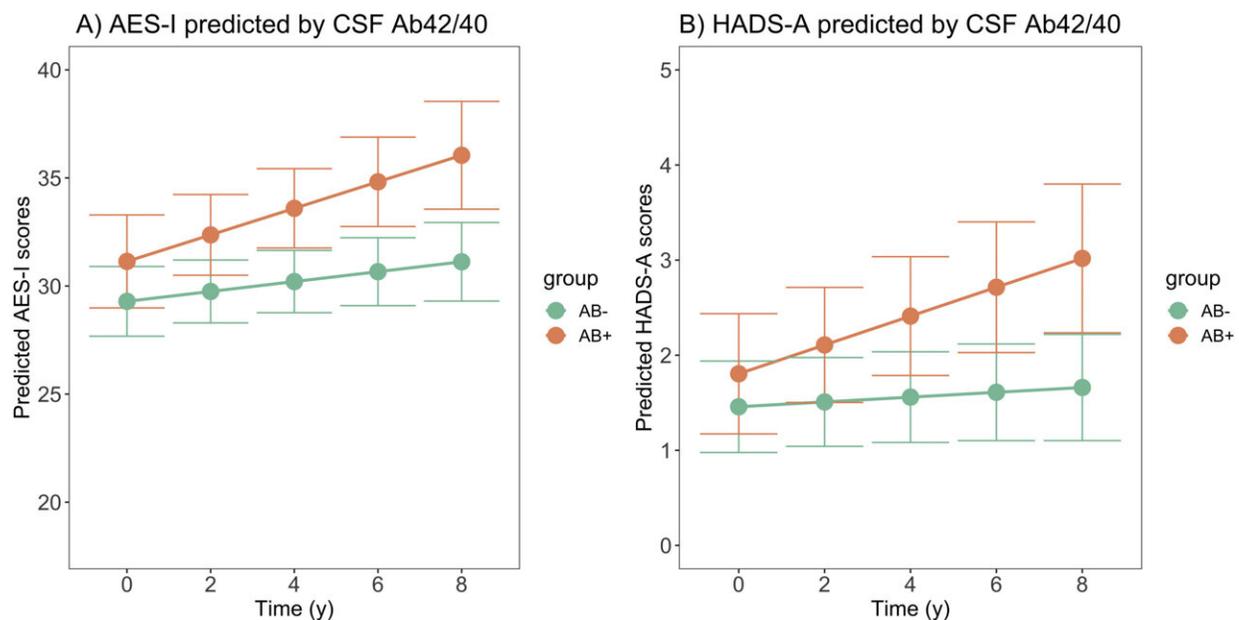


Figure 1. Linear Mixed Effect Models displaying effects of pathology at baseline over time on the development of neuropsychiatric symptoms. Plots of estimated marginal means and 95% CI of the means obtained from linear mixed effect models displaying significant effects (also after adjustment for multiple comparisons) by pathology over time on the longitudinal measures of neuropsychiatric symptoms found in table 1. Longitudinal measures of informant-rated apathy (panel A) (274 participants) and self-rated anxiety (panel B) (321 participants) were separately entered as the dependent variable. Interaction terms between time and A $\beta$ 42/40 were entered as a zero-centered fixed effect. Models were corrected for age, sex, and education and included random slopes and intercepts. Participants were grouped according to a CSF A $\beta$ 42/40 cut point of 0.066 obtained by mixture modeling. Models initially displaying significant

effects, but notwithstanding adjustment for multiple comparisons are found in the supplement. Abbreviations: A $\beta$ 42/40 = amyloid- $\beta$  42/40, AES-I = Apathy Evaluation Scale - Informant-rated version, CU = Cognitively Unimpaired, CSF = Cerebrospinal fluid, HADS-A = Hospital Anxiety and Depression Scale – Anxiety, T = tertial, y = year. Credit: *Biological Psychiatry* (2022). DOI: 10.1016/j.biopsych.2022.01.012

Alzheimer's disease (AD) eventually leads to severe cognitive decline, but most affected individuals also develop distressing neuropsychiatric symptoms. These earlier effects may be more subtle and are not well understood; it remains unclear whether they arise directly from AD pathology or secondarily as psychological reactions due to the cognitive deficits. Now, a new study examines the connections between biomarkers of AD's hallmark neuropathology, cognition, and other neuropsychiatric symptoms. The study appears in *Biological Psychiatry*, published by Elsevier.

The researchers, led by Oskar Hansson, MD, at Lund University in Sweden, tested [cerebrospinal fluid](#) or [blood plasma](#) from 356 cognitively unimpaired older adults for levels of the proteins amyloid-beta (Ab) and tau, which are thought to contribute to AD neurotoxicity, as well as markers of neurodegeneration.

Strikingly, the presence of Ab was associated with increased anxiety and apathy. Higher levels of apathy were also related to a more rapid cognitive decline.

"Most importantly, this study signals that certain neuropsychiatric symptoms such as apathy and anxiety develop predominantly due to underlying AD-related pathology and not due to the concomitant [cognitive impairment](#)," said Maurits Johansson, MD, lead author of the

study. "It seems reasonable that neuropsychiatric symptoms would arise from neuropathology just as cognitive deficits do, especially because AD ultimately affects large areas of the brain," he added.

The study did not exclude a role for cognitive impairment altogether. For example, in one of the statistical analyses, cognitive decline slightly but significantly mediated the effect of amyloid pathology on the development of apathy.

"Combined with earlier studies, our findings strengthen the proposed idea that cognitive deficits and neuropsychiatric symptoms can develop independently, yet in parallel to one another. They have a common underlying neuropathology, but to some extent they can also reinforce one another," said Professor Hansson.

"These findings could ultimately lead to more efficient study design of clinical trials for AD in that they point to [neuropsychiatric symptoms](#) as potential alternative outcome measures," concluded Professor Hansson.

John Krystal, MD, editor of *Biological Psychiatry*, said of the new findings, "We are used to thinking about Alzheimer's disease from the perspective of memory impairments. This new study highlights that the earliest signs of amyloid-related pathology may be changes in mood and behavior, particularly apathy and anxiety."

**More information:** Maurits Johansson et al, Development of apathy, anxiety, and depression in cognitively unimpaired older adults: effects of Alzheimer's disease pathology and cognitive decline, *Biological Psychiatry* (2022). [DOI: 10.1016/j.biopsych.2022.01.012](https://doi.org/10.1016/j.biopsych.2022.01.012)

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