

Irritability, agitation and anxiety in Alzheimer's patients caused by brain inflammation, study says

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Common neuropsychiatric symptoms that doctors see in Alzheimer's disease patients originate from brain inflammation rather than amyloid

and tau proteins, report University of Pittsburgh School of Medicine researchers in [JAMA Network Open](#).

The finding strengthens mounting evidence for the role of [neuroinflammation](#) in Alzheimer's progression and suggests new pathways for the development of therapies targeting neurological symptoms of the disease.

"Neuropsychiatric symptoms such as irritability, agitation, anxiety and depression are among the most difficult symptoms to treat in patients with Alzheimer's. They are difficult to control, have no clear cause and make it difficult for families to care for their loved one without lots of support," said first author Cristiano Aguzzoli, M.D., postdoctoral associate at Pitt. "Here, we show for the first time that [brain inflammation](#) may be to blame for these symptoms."

Earlier in 2023, Pitt scientists [discovered](#) that excessive brain inflammation is critical for disease initiation and can predict whether cognitively unimpaired elderly are at a higher risk of developing Alzheimer's symptoms. Their [earlier research](#) hinted at the importance of neuroinflammation in the pathological cascade involving other key players in Alzheimer's pathology including [amyloid beta](#) and tau.

The new findings provide the first strong evidence that brain inflammation is also a direct cause of [neuropsychiatric symptoms](#) that often accompany Alzheimer's-associated dementias.

In the new study, the researchers worked with 109 [elderly individuals](#), the majority of whom had no cognitive impairments. Most of those individuals were, however, positive for amyloid and tau.

By measuring levels of neuroinflammation, amyloid beta and tau via brain imaging and comparing the results with clinical assessments of

neuropsychiatric symptom severity, the scientists discovered that microglial activation was strongly associated with a variety of neuropsychiatric symptoms, including disturbed sleep and agitation. While levels of amyloid and tau alone were predictive of neuropsychiatric symptoms, neuroinflammation seemed to have an added effect.

Neuroinflammation was most strongly associated with caregivers or family members reporting their loved one's rapid mood swings from calm to tears or anger, one of the common symptoms of the disease. Individuals whose caregivers showed higher levels of distress when caring for them had greater levels of brain inflammation.

Taken together, the study adds to the growing evidence of the role of brain [inflammation](#) in the early stages of the disease progression, when symptoms like excess irritability tend to emerge. It also suggests that clinical trials targeting neuroinflammation as a preventive therapy for Alzheimer's could track neuropsychiatric symptoms as one way of measuring the treatment's effectiveness.

Conversely, drugs specifically targeting neuroinflammation could potentially help reduce neuropsychiatric symptom severity and alleviate some of the psychological burden experienced by caregivers, thus improving patient support.

"Since both neuroinflammation and neuropsychological abnormalities are found in several other types of dementia, including Parkinson's dementia, we are collaborating with scientists around the world to expand these findings to these other diseases," said senior author Tharick Pascoal, M.D., Ph.D., associate professor of psychiatry and neurology at Pitt.

More information: Neuropsychiatric Symptoms and Microglial

Activation in Patients with Alzheimer Disease, *JAMA Network Open* (2023). DOI: [10.1001/jamanetworkopen.2023.45175](https://doi.org/10.1001/jamanetworkopen.2023.45175).
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