# Lack of a Role for Alzheimer's Disease Pathology in Late-Life Depression, or Just No Relationship With Amyloid?

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This issue of the *Journal* includes an important study (1) relevant for our understanding of aging and geriatric psychiatric syndromes, titled "No Association of Lower Hippocampal Volume With Alzheimer's Disease Pathology in Late-Life Depression." The study, by De Winter and colleagues, focuses on the potential relationship between Alzheimer's pathology and late-life depression by exploring how amyloid pathology is related to neuroimaging and clinical features of late-life depression. The authors prospectively examined 48 depressed older adults and 52 age- and sex-matched comparison subjects. Participants in this cross-sectional study underwent [$^{18}$F]flutemetamol amyloid positron emission tomography (PET), structural MRI for measurement of hippocampal volume, apolipoprotein E genotyping, and neuropsychological assessments. In the study's primary results, despite finding that the depressed cohort exhibited smaller hippocampal volumes, hippocampal volume was related neither to increased amyloid binding nor to APOE ε4 genotype, a primary genetic risk factor for Alzheimer's disease. The authors additionally report no differences in amyloid binding between the depressed and nondepressed groups. Notably, although the depressed group performed more poorly on tests of episodic memory, their performance was not associated with either hippocampal volume or amyloid binding. This is thus a negative study, finding no relationship between amyloidosis and occurrence of depression or hippocampal volume.

This study is highly relevant, as there is a substantial literature associating late-life depression with an almost twofold higher risk of all-cause dementia, although the relationship with Alzheimer's dementia specifically is slightly lower (2, 3). While the data are not always consistent, this increased risk is observed both in older adults with early-life-onset depression (an initial depressive episode occurring in adolescence, early adulthood, or midlife) and in those with late-onset depression (a first depressive episode occurring in later life) (2, 4). These observations have led to distinct yet complementary theories explaining the relationship between depression and cognitive decline. Most relevant to early-onset depression, the stress hypothesis proposes that stress-related physiological mechanisms occurring in repeated depressive episodes across one's lifetime result in pathological brain aging and vulnerability to cognitive decline (5). More relevant to late-onset depression is the neuropathology or neuropsychiatric model, wherein many individuals with an initial depressive episode later

in life may in fact have neurodegenerative processes and preclinical Alzheimer's disease (6). In this model, underlying neuropathology initially contributes to depressive behavior and later results in cognitive decline.

Considered in context of these theories, the De Winter et al. study clearly provides evidence contrary to the neuropathology/neuropsychiatric model. This is highlighted by the study's secondary analyses, in which no difference was observed in amyloid binding between patients with early-onset and late-onset depression (1). Supporting these findings, some previous studies in both cognitively impaired and cognitively intact older adults have similarly failed to associate amyloid burden with depressive symptoms (7, 8). Even more compellingly, a large longitudinal neuropathological study found that the occurrence of depression was not related to a specific underlying neuropathology, and the effect of depressive symptoms on cognitive decline was unrelated to and independent of underlying neuropathology (9).

> **Although the depressed group performed more poorly on tests of episodic memory, their performance was not associated with either hippocampal volume or amyloid binding.**

These findings do not necessarily refute the neuropathology/neuropsychiatric model, and amyloid could still be a factor influencing depression in some older adults. Other studies in late-life depression have observed altered CSF amyloid metabolite levels and increased amyloid binding (10–12), although those studies did not attempt to link amyloid status with hippocampal morphology. It is also important to remember that the development of Alzheimer's disease and Alzheimer's pathology is a dynamic process, in which changes at the cellular level predate morphological changes on MRI, which in turn predate clinical symptoms (13). In this model, it is possible that amyloid status is less related to cross-sectional snapshots of hippocampal volume and still be related to longitudinal hippocampal atrophy. This could be quite relevant, as greater longitudinal hippocampal atrophy is related to poorer clinical course of late-life depression (14).

Importantly, a role for amyloid is not required for a neuropathology/neuropsychiatric model of late-life depression. As mentioned by the study's authors, the observed differences between diagnostic groups in hippocampal morphology may

be related to a recently described condition called "suspected non-Alzheimer's disease pathophysiology," or SNAP. SNAP is a recently developed and somewhat controversial biomarker-based concept wherein older individuals with normal levels of brain amyloid markers exhibit other abnormal biomarkers of neurodegeneration, including high CSF tau levels, FDG-PET patterns of regional hypometabolism concordant with Alzheimer's disease, and atrophy on MRI (15). SNAP does not appear to be related to either Lewy body disease or subclinical vascular disease and is common in older populations, occurring in approximately 23% of cognitively normal older adults (15, 16). Perhaps unsurprisingly, SNAP is more common in mildly impaired individuals and is associated with increased rates of cognitive decline and progression to dementia. Although SNAP's underlying pathology is unclear, it is possible that medial temporal lobe tau pathology is a major constituent, given that such tau pathology shares some clinical features with SNAP (15, 17). It is unclear whether meeting criteria for SNAP or the presence of significant medial temporal lobe tau pathology is related to the occurrence or outcomes of late-life depression.

Although detailed studies examining the questions raised here may lead to the identification of clinically relevant subpopulations, such work is unlikely to characterize the entirety of late-life depression. The population of depressed older adults exhibits substantial heterogeneity, ranging from differences in age at onset, influence of genetic factors, presence of various medical morbidities, socioeconomic differences, and variability in longer-term cognitive outcomes. As previously proposed (18), individual factors that negatively influence emotional or cognitive neural circuit function can cumulatively increase the risk of depressive episode or negatively affect clinical outcomes of depression. In this model, amyloid or tau deposition in the medial temporal lobe alone may be insufficient to cause depression. But in conjunction with other factors that negatively influence neural circuit function, such as proinflammatory processes, genetic differences, and subclinical cerebrovascular disease, neurodegenerative processes may "tip the scales," and the cumulative burden on neural circuits may then contribute to depressive symptoms or negatively affect the success of antidepressant treatments.

In the end, the De Winter et al. study clearly supports the hypothesis that hippocampal volume differences and cognitive decline in late-life depression are not related to underlying Alzheimer's pathology, or at least amyloid pathology. Clearly we need more research, likely in longitudinal studies, examining what factors influence medial temporal lobe atrophy in late-life depression and how depression contributes to cognitive decline independently of underlying pathology (9). Such work should consider the role of stress-related mechanisms, a factor not examined in the present study.

## AUTHOR AND ARTICLE INFORMATION

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