of apathy. Apathy syndrome has cognitive, affective, and behavioral dimensions that persist longer than 4 weeks and cause significant impairment in personal, social, occupational, and other key areas of functioning (4). Motivation and goal-directed behaviors and cognitive activity are lost, and emotional blunting is found in patients with apathy (5). Daytime sleepiness and inattention are not symptoms of apathy syndrome. In fact, when diagnosing apathy syndrome during cognitive impairment, depression and other medical conditions are ruled out (4, 5).

The authors provide an important reminder that obstructive sleep apnea can be mistaken as apathy, and vice versa, in cognitively impaired older adults. Obviously, incorrect diagnosis could render treatment of either problem and of cognitive impairment less effective and could render the testing of new treatments uninterpretable. We feel strongly that management of apathy is essential to individual health. For example, preliminary studies have shown that resolution of apathy leads to improved functioning and self-care and has the potential to improve distal outcomes for comorbidities such as diabetes (6). Thus, future research into the ability for treatment of apathy and obstructive sleep apnea to empower individuals to optimally self-manage cognitive decline and other health conditions during aging will be exciting and has potential for great impact.

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**Prasad R. Padala, M.D., M.S.**
**Richard A. Dennis, Ph.D.**
**Kalpana P. Padala, M.D., M.S.**

*From the Geriatric Research Education and Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock; and the Departments of Psychiatry and Geriatrics, University of Arkansas for Medical Sciences, Little Rock.*

*Address correspondence to Dr. Prasad Padala (prasad.padala@va.gov).*


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## The Temporal Relationship Between Alzheimer's Disease and Depressive Symptoms: Variable Matters

TO THE EDITOR: In their recent comprehensive analysis, published in the June 2018 issue of the *Journal*, Donovan et al. (1) present convincing support of the hypothesis that emerging neuropsychiatric symptoms represent an early manifestation of preclinical Alzheimer's disease. Donovan et al. appropriately viewed their analysis as a first step toward understanding the temporal relationship between Alzheimer's disease and depressive symptoms in cognitively normal older adults, with the initial aim to examine association rather than causation.

Physiological aging is accompanied by a chronic low-grade proinflammatory state, which has been named "inflammaging" (2). Inflammaging likely acts as a prodromal cofactor in the subclinical course of Alzheimer's disease (3). Neuroinflammation can also be associated with amyloid beta burden independently of inflammaging (4). In addition, several lines of evidence also associate inflammation with depressive symptoms (5). This makes the relationship between Alzheimer's disease and depressive symptoms more complex. If Alzheimer's disease causes inflammation that leads to depression, inflammation can be considered a mediating variable in the relationship between Alzheimer's disease and depressive symptoms. Alternatively, if the strength of the relationship between Alzheimer's disease and depressive symptoms is changing across levels of inflammation, then inflammation is a moderating variable. Eventually, inflammation could also be a confounding variable if it causes both Alzheimer's disease and depressive symptoms independently.

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**Didier Wion, Ph.D.**

*From INSERM UMR1205, Brain Tech Lab, Université Grenoble Alpes, La Tronche, France.*

*Address correspondence to Dr. Wion (didier.wion@univ-grenoble-alpes.fr).*


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