

UC San Diego

UC San Diego Previously Published Works

Title

Who Are the Seniors with Subjective but Not Objective Cognitive Impairment?

Permalink

<https://escholarship.org/uc/item/2t01z41c>

Journal

American Journal of Geriatric Psychiatry, 25(5)

ISSN

1064-7481

Authors

Jeste, Dilip V
Eglit, Graham ML

Publication Date

2017-05-01

DOI

10.1016/j.jagp.2017.02.005

Peer reviewed

Who Are the Seniors with Subjective but Not Objective Cognitive Impairment?

Dilip V. Jeste, M.D., Graham M.L. Eglit, Ph.D.

In recent years there has been growing interest in early detection of late-life major neurocognitive disorders (i.e., dementias). This new emphasis has been spurred largely by a recognitions of two facts. First, the pathology underlying Alzheimer disease (AD) begins decades before the emergence of clinical symptoms warranting a diagnosis of AD. Second, in a number of recent trials, initially promising putative cognitive enhancers and so-called disease-modifying pharmacologic agents have failed to halt the progression of dementia after AD is diagnosed. There is now emerging consensus that new treatments for AD will need to target individuals at risk of developing the disease long before a dementia syndrome manifests. Mild cognitive impairment (MCI; renamed as mild neurocognitive disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*)¹ has emerged as a critical diagnostic construct to identify such individuals.

Several classification algorithms for MCI have been proposed. These algorithms involve combinations of three primary criteria: subjective cognitive complaints, objective cognitive impairment, and absence of significant functional impairment (that would warrant a diagnosis of major neurocognitive disorder or dementia). However, there is currently no agreed on operationalization of these three criteria. Brodaty et al.² explored the accuracy of a variety of algorithms for MCI based on different operationalizations of these three criteria in predicting incident dementia. Eight hundred seventy-three community-dwelling, dementia-free older adults (ages 70–90) were followed for 6 years. Measures of objective cognitive impairment—defined as either two test scores 1 standard deviation below the mean or one test score 1.5 standard deviations below the mean—emerged as the single best predictor of progression to dementia at the 6-year follow-up. Both subjective cognitive

complaints and subtle functional impairments were poor individual predictors of incident dementia. Construction of MCI algorithms through a combination of objective cognitive impairment with subjective cognitive complaints and/or subtle functional impairment did not meaningfully improve predictive accuracy over and above that resulting from objective cognitive impairment alone. The authors concluded that objective cognitive impairment per se, and not MCI, is the best predictor of progression to dementia in a community sample.

This article makes a major contribution to the literature on MCI and AD and has a number of strengths. The study, conducted by a distinguished group of scientists, includes a large, well-characterized sample and uses several measures of subjective cognitive complaints, objective cognitive deficits, and functional impairment from which a multitude of MCI algorithms were constructed. The authors have been thoughtful in discussing the implications and limitations of their results. We expect that the study will generate considerable research in this important arena.

One related but slightly different question we want to discuss is this: Who are the older adults that have subjective cognitive complaints but do not progress to dementia, at least within a 6-year follow-up period? In other words, what is the basis for these cognitive complaints if they are not an indication of a neurocognitive disorder? Findings from our previous research may shed some light on this issue.³ We examined a cross-sectional association of subjective cognitive complaints with objective cognitive performance and depressive symptoms in the Successful Aging Evaluation study, a community-based study of adults in San Diego County, without a diagnosis of dementia who were chosen using random-digit dialing, with oversampling of individuals older than 75 years. In this sample, after controlling for relevant

From the Department of Psychiatry (DVJ, GMLE); and the Sam and Rose Stein Institute for Research on Aging (DVJ, GMLE), University of California San Diego, La Jolla, CA. Send correspondence and reprint requests to Dr. Dilip V. Jeste, Sam and Rose Stein Institute for Research on Aging, University of California, San Diego, 9500 Gilman Drive #0664, San Diego, CA 92093. e-mail: djeste@ucsd.edu

Published by Elsevier Inc. on behalf of American Association for Geriatric Psychiatry.

<http://dx.doi.org/10.1016/j.jagp.2017.02.005>

demographic, physical, and psychosocial variables, subjective cognitive complaints were significantly associated not with objective cognitive performance but with severity of depressive symptoms across all middle and older adult age groups. This suggests that subjective cognitive complaints may indicate depression rather than a neurocognitive disorder.

At the same time, depression is related to dementia in several ways. Earlier-life depression (occurring before age 60) may be a risk factor for late-life dementia. Several longitudinal studies have demonstrated an increased risk of dementia among individuals with onset of depression before age 60.⁴ There may be a dose-dependent relationship between depression and dementia, with dementia risk increasing with greater number of earlier-life depressive episodes.⁵ Given that these depressive episodes occurred several decades before a diagnosis of a major neurocognitive disorder was made, earlier-life depression represents a risk factor for dementia rather than an early prodrome. Mechanisms contributing to the association between depression and dementia are likely multifactorial, including cardiovascular disease, frontostriatal dysfunction, increased glucocorticoid levels, hippocampal atrophy, β -amyloid plaque formation, neuroinflammation, and nerve growth factor abnormalities.^{4,6}

Other research suggests that late-onset depression is common among individuals who subsequently develop dementia. A meta-analysis of 23 population-based prospective cohort studies (total sample size: 44,496) found that late-onset depression significantly increased the risk of all-cause dementia, AD, and vascular dementia.⁷ Ad-

ditionally, in some cases cognitive impairment may co-occur with late-onset depression but is reversible with treatment and remission of depressive symptoms. These cases, often referred to as depressive pseudo-dementia, may place individuals at heightened risk for dementia. For instance, a prior episode of depressive pseudo-dementia has been reported to impart a nearly fourfold increase in the incidence of dementia after 5–7 years, relative to depressed older individuals who were cognitively intact at baseline.⁸ This finding supports a suggestion we made many years ago, that pseudo-dementia is a misnomer—a pseudo-entity.⁹

Taking into consideration the findings of Brodaty et al.,² it is possible to suggest that the average time lag between late-onset depression, starting out as subjective cognitive complaints only, and later onset of dementia might be longer than 6 years. In older adults, late-onset depression, manifesting with cognitive symptoms without objective signs of cognitive impairment, might be viewed as a very early prodrome of the underlying neuropathologic processes leading to subsequent cognitive decline.¹⁰ Indeed, some studies have shown that depression and other behavioral changes may precede MCI.¹¹ Thus, older adults with subjective cognitive complaints but no manifest cognitive deficits are an important population for longer-term follow-up investigations.

Supported, in part, by the National Institute of Mental Health (grant R01 MH094151), the National Institute on Aging (grant R01 AG028827), and the Sam and Rose Stein Institute for Research on Aging, University of California, San Diego.

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Publishing, 2013
2. Brodaty H, Aerts L, Crawford JD, et al: Operationalizing the diagnostic criteria for mild cognitive impairment: the salience of objective measures in predicting incident dementia. *Am J Geriatr Psychiatry* 2017; 25:485–497
3. Zlatar ZZ, Moore RC, Palmer BW, et al: Cognitive complaints correlate with depression rather than concurrent objective cognitive impairment in the Successful Aging Evaluation Baseline sample. *J Geriatr Psychiatry Neurol* 2014; 27:181–187
4. Byers AL, Yaffe K: Depression and risk of developing dementia. *Nat Rev Neurol* 2011; 7:323–331
5. Dotson VM, Beydoun MA, Zonderman AB: Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology* 2010; 75:27–34
6. Taylor WD, Aizenstein HJ, Alexopoulos GS: The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry* 2013; 18:963–974
7. Diniz BS, Butters MA, Albert SM, et al: Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry* 2013; 202:329–335
8. Saez-Fonseca JA, Lee L, Walker Z: Long-term outcome of depressive pseudodementia in the elderly. *J Affect Disord* 2007; 101:23–129
9. Jeste DV, Harris MJ, Rockwell E: Is pseudodementia a pseudo entity? *Bull Clin Neurosci* 1988; 53:20–24
10. Panza F, Frisardi V, Capurso C, et al: Late-life depression, mild cognitive impairment, and dementia: possible continuum? *Am J Geriatr Psychiatry* 2010; 18:98–116
11. Ismail Z, Smith EE, Geda Y, et al: Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement* 2016; 12:195–202