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Self-rated and informant-rated everyday function in comparison to objective markers of Alzheimer's disease

Alicia D. Rueda[a], Karen M. Lau[b], Naomi Saito[c], Danielle Harvey[c], Shannon L. Risacher[d], Paul S. Aisen[e], Ronald C. Petersen[f], Andrew J. Saykin[d], Sarah Tomaszewski Farias[b,*], Alzheimer's Disease Neuroimaging Initiative[1]

[a]*Veterans Affairs, Northern California Health Care System, Sacramento, CA, USA*
[b]*Department of Neurology, University of California, Davis, Sacramento, CA*
[c]*Department of Public Health Sciences, University of California, Davis, Davis, CA, USA*
[d]*Indiana University School of Medicine, Indianapolis, IN, USA*
[e]*Department of Neuroscience, University of California, San Diego, La Jolla, CA, USA*
[f]*Department of Neurology and the Mayo Alzheimer Disease Research Center, Mayo Clinic College of Medicine, Rochester, MN, USA*

Abstract It is recognized that individuals with mild cognitive impairment (MCI) already demonstrate difficulty in aspects of daily functioning, which predicts disease progression. This study examined the relationship between self- versus informant-report of functional ability, and how those reports relate to objective disease measures across the disease spectrum (i.e. cognitively normal, MCI, Alzheimer's disease). A total of 1080 subjects with self- and/or informant-rated Everyday Cognition questionnaires were included. Objective measures included cognitive functioning, structural brain atrophy, cerebrospinal fluid abnormalities, and a marker of amyloid deposition using positron emission tomography with [^{18}F]AV45 (florbetapir). Overall, informant-report was consistently more associated with objective markers of disease than self-report although self-reported functional status may still have some utility in early disease.
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*Corresponding author. Tel.: +1-916-734-6442; Fax: +1-916-703-5290.
E-mail address: sarah.farias@ucdmc.ucdavis.edu

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1. Introduction

There is considerable interest in identifying the prodromal clinical signs of Alzheimer's disease (AD). While loss of independence in everyday functional abilities is a core feature of AD dementia, there is increasing recognition that mild functional changes occur early in the disease, including within Mild Cognitive Impairment (MCI) [1–3]. New evidence suggests subtle functional changes may be detected in individuals who are still considered cognitively normal [4]. Early detection of functional decline has prognostic value in predicting future disease progression [5].

Past research on functional changes in preclinical AD has been hindered by a lack of instruments sensitive to early and subtle functional problems. The Everyday Cognition (ECog) is a newer instrument designed to assess functional abilities linked to specific cognitive abilities and it has been shown to be sensitive to early disease [2,6]. While the utility of *self*-report on the ECog has not yet been specifically evaluated, previous studies have suggested that early self-reported changes in everyday functioning may be associated with development of MCI or dementia [7,8].

Approaches to assessing the validity of self-report include comparing self- and informant-reports, and evaluating associations between self-report and objective measures of disease. In general, the degree to which individuals with early disease, such as MCI, can accurately report cognitive and functional problems remains unclear. Some studies report a lack of difference between self- and informant-ratings in MCI [3,9,10], suggesting that individuals may retain the ability to accurately report functional status. Other studies, however, have questioned the usefulness of self-reported functional change in MCI due to its discrepancy with informant-ratings [11,12]. In dementia, self-reported functional status is often inaccurate due to loss of awareness/insight [10,13].

Self- and informant-ratings of everyday functioning in MCI and prodromal AD have been compared with objective cognitive tests. The correspondence between self-reported everyday function and cognition is inconsistent; some studies show no relationship [14,15] while others have found that subjective everyday cognitive complaints among elderly individuals are associated with cognitive performances [16,17]. More consistent associations have been reported between *informant*-ratings of reduced everyday function and cognition [1,5,18–20]. When self- and informant-ratings were concurrently compared with neuropsychological performance, the latter ratings have been more strongly associated with objective cognitive testing [10,21].

Ratings of everyday functioning have also been compared with other biomarkers of disease. For instance, informant-reports of functional decline have been associated with structural abnormalities on imaging, including decreased cortical gray matter [22] and smaller hippocampal volume [1], and neuropathological abnormalities in MCI, such as elevated concentrations of total tau (t-tau) [23], reduced Aβ 1–42 in CSF [23], and increased amyloid deposition on Pittsburgh compound B positron tomography (PiB-PET) [24]. Considerably less work has examined *self*-reported functional decline and associated disease biomarkers. There is some evidence that elderly individuals with subjective cognitive complaints and normal cognitive test performances exhibit reduced medial temporal and frontotemporal gray matter volumes similar to individuals with MCI [14] and increased amyloid-β deposition on PiB-PET imaging [7,25]. Such findings suggest self-appraisals may be sensitive to underlying early neuropathologic changes when objective cognitive impairments are be less apparent.

In sum, informant-reported everyday function has been previously associated with a number of disease related outcomes in MCI and dementia. The validity of self-reported functional decline across the full disease spectrum, particularly among older adults with normal cognition or MCI, is less clear. The present study used a variety of approaches to examine the relative validity of self- and informant-reported functional status among individuals defined as Normals, early MCI (EMCI), late MCI (LMCI), or AD. Specifically, we investigated [1] the degree of agreement between informant- and self-reported everyday functioning at different disease stages [2], the utility of informant- and self-reported functional status in discriminating between diagnostic groups, and [3] the relationships between informant- and self-reported functional ability and multiple objective markers of disease. Generally, we hypothesized that while informant-reported functional status would be superior to self-report in all of these regards, self-report would have some demonstrable validity particularly in early disease.

2. Methods

2.1. Participants

Data was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a consortium of university and medical centers in the United States and Canada aimed to study changes in cognition, function, brain structure, and biomarkers in cognitively normal and subjects with MCI and AD [26]. The present study included 1080 subjects with self-rated and/or an informant-rated ECog (see Table 1).

Subjects were diagnosed based on the following criteria: MCI was diagnosed based on subjective memory complaints, objective memory impairment measured by education-adjusted scores falling at least 1.5 standard deviations below the normative mean on delayed recall of the Logical Memory test (Story A), essentially independent for activities of daily living, global score of 0.5 on the Clinical Dementia Rating scale (CDR), and Mini-Mental State