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Featured Article

Objective features of subjective cognitive decline in a US national database

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Abstract

Introduction: Functional and cognitive features of subjective cognitive decline (SCD) were identified in a longitudinal database from the National Alzheimer Coordinating Center.

Methods: Cognitively normal older adults with (SCD+) and without (SCD−) self-reported memory complaints ($N = 3915$) were compared on (1) baseline Functional Assessment Questionnaire ratings, (2) baseline scores and longitudinal rate of change estimates from nine neuropsychological tests, and (3) final clinical diagnoses.

Results: SCD+ had higher baseline ratings of functional impairment, reduced episodic memory practice effects and poorer performance on neuropsychological tests of psychomotor speed and language, and higher frequencies of mild cognitive impairment and dementia diagnoses at the end of follow-up compared with the SCD group.

Discussion: Subtle clinical features of SCD identified in this large cohort are difficult to detect at the individual level. More sensitive tests are needed to identify those with SCD who are vulnerable to cognitive decline and dementia.

Keywords: Alzheimer dementia; Subjective cognitive decline; Subjective cognitive impairment; Memory complaint; SCD; SMC; SMI; Preclinical Alzheimer disease; Prodromal Alzheimer disease; Mild cognitive impairment

1. Background

Approximately one-third of community-dwelling older adults complain of memory or other cognitive difficulties in their daily lives [1]. For some individuals, the self-perception of subjective cognitive decline (SCD) may represent a very early symptom of Alzheimer-type dementia that occurs before the onset of objective cognitive impairment [2]. Indeed, longitudinal reports have suggested that individuals with SCD are at risk for progression to both dementia and its precursor syndrome, mild cognitive impairment (MCI) [3,4]. In addition, studies using both in vivo biomarker tests [5,6] and postmortem brain autopsies [7–10] have identified pathologic evidence of Alzheimer's disease (AD) in those with SCD. Despite these findings, the hypothesis that SCD constitutes a preclinical stage of AD is not consistently supported by the research literature [11,12].

Characterizing the clinical markers of SCD is an important step toward understanding its utility in predicting subsequent development of Alzheimer-type dementia. Although individuals with SCD, by definition, perform in the objective "normal" range on standard clinical assessments [2], they may demonstrate subtle clinical changes. For example, a few studies have identified objective weaknesses in memory [13,14] and executive functioning [15,16] in those with SCD. Another study of community-dwelling older adults found that difficulties in everyday functioning were

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commonly endorsed by participants who had a cognitive complaint [17]. However, these findings have not been consistently replicated, which could partially reflect the insensitivity of standard neuropsychological tests at detecting very subtle changes in individuals who are classified as "normal" for their demographic group.

The goal of the present study was to identify objective functional and cognitive markers of SCD in a large cohort of cognitively normal older adults from the National Alzheimer's Coordinating Center (NACC) database [18]. By harnessing the statistical power of a large data set, we sought to identify very subtle but significant distinctions that may have evaded detection in smaller samples. Prior studies of postmortem cases from the NACC database have reported associations between baseline SCD and subsequent autopsy-confirmed AD pathology [9,10]. We expected that our results would be consistent with these findings and would therefore provide further support for the hypothesis that SCD represents a preclinical stage of AD [2]. Specifically, we hypothesized that SCD would be associated with weakness, albeit subtle, in everyday functional abilities and in longitudinal cognitive performance on tests of episodic memory and psychomotor speed, which are domains affected early in MCI and Alzheimer-type dementia [19]. We also expected that baseline SCD would predict longitudinal progression to clinical diagnoses of MCI and dementia.

2. Methods

2.1. Sample

Data for the present study were obtained from the NACC database, which consists of longitudinal data collected at 34 previous or current National Institute on Aging-funded Alzheimer's Disease Centers (ADCs) in the United States (http://www.alz.washington.edu). The database contains over 35,000 participants who span a broad range of cognitive ability—from normal cognition to MCI and various forms of dementia. Each ADC has its own system for recruiting and enrolling participants. Thus, participants in the NACC database may come from self-referrals, recruitment activities in the community, referrals from clinicians or family members, or word-of-mouth advertising.

Data came from the second version of the Uniform Data Set (UDS 2.0), which is a standardized battery of clinical and cognitive evaluations administered on an annual basis to participants in all ADCs [20]. The research was approved by institutional review boards at each ADC, and written informed consent had been obtained from each participant at enrollment; this included participant agreement to share de-identified data collected at each center with NACC for dissemination to researchers studying various aspects of cognitive aging and dementia.

The present sample included participants in the database who were older than the age of 65 years and classified as "cognitively normal" at baseline based on the judgment of a trained clinician, a Mini–Mental State Examination score of 27 or above [21], and a Clinical Dementia Rating global score of 0 [22]. The sample was further restricted to participants who received longitudinal (i.e., at least two) annual evaluations and genotyping for the apolipoprotein E (APOE) ε4 allele. Participants who endorsed more than seven symptoms on the 15-item Geriatric Depression Scale (GDS-15) at baseline [23] were excluded from the sample, given that some cases of SCD may be an artifact of prominent depression [24,25]. The present analyses included 3915 participants from whom data had been collected between September 2005 and November 2013.

2.2. Determination of SCD

Several methods have been used to investigate the presence of SCD [26]. In the present sample, SCD was assessed within the context of the standardized evaluation protocol used at all ADCs. Specifically, the single yes-no question, "Does the subject report a decline in memory relative to previously attained abilities?" was systematically completed on the large number of individuals included for the current analysis. A trained clinician provides the response to this question after conducting a semistructured interview with the participant. Participants in the present study were classified based on whether SCD was determined to be present (SCD+ group) or absent (SCD− group) at their baseline visit. Although this single item may have failed to detect participants who may have been identified with more comprehensive measures, the proportion of participants with SCD in the sample (19.5%) was generally consistent with prevalence estimates that have been reported in other studies of community-dwelling older adults [1,17].

2.3. Descriptive variables

Demographic factors including age, gender, years of education, race, ethnicity, and primary language were examined in the present study. Family history of dementia and APOE ε4 status were also accounted for, as the relationship between these AD risk factors and SCD is not well understood [27]. Participants who reported having at least one first-degree family member (i.e., a parent, sibling, or child) with dementia at any visit were classified as having a positive family history. Those with one or more APOE ε4 alleles were defined as carriers and those without an ε4 allele were defined as noncarriers.

2.4. Functional Activities Questionnaire

The Functional Activities Questionnaire (FAQ) served as the measure of everyday functional abilities [28]. This 10-item survey captures the level of ability in routine daily activities like paying bills and using the stove. A close informant completes the FAQ based on their observations of the participant over the past 4 weeks. Each item is rated on a