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Subjective cognitive decline: Self and informant comparisons

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Abstract

Background: It is unclear whether self- or informant-based subjective cognition better distinguishes emotional factors from early-stage Alzheimer's disease (AD).

Methods: Healthy members (n = 447) of the Arizona apolipoprotein E (*APOE*) cohort and their informants completed the self and informant paired Multidimensional Assessment of Neurodegenerative Symptoms questionnaire (MANS).

Results: Decline on the MANS was endorsed by 30.6% of members and 26.2% of informants. Self- and informant-based decliners had higher scores of psychological distress and slightly lower cognitive scores than nondecliners. Over the next 6.7 years, 20 developed mild cognitive impairment (MCI). Converters were older at entry than nonconverters (63.8 [7.0] vs 58.8 [7.3] years, $P = .003$), 85% were *APOE* ε4 carriers ($P < .0001$), and they self-endorsed decline earlier than informants (58.9 [39.2] vs 28.0 [40.4] months before MCI; P = .002).

Conclusions: Self- and informant-based subjective decline correlated with greater psychological distress and slightly lower cognitive performance. Those with incident MCI generally self-endorsed decline earlier than informants.

Keywords: Subjective cognition; Preclinical Alzheimer's disease; Mild cognitive impairment; Cognitive aging

1. Introduction

Subjective cognitive complaints are common, but their clinical significance is not always clear. Stage two of the 1982 Global Deterioration Scale for Primary Degenerative Dementia defines "very mild cognitive decline" as a disease phase in which patients complain of memory loss but have no clinical, psychometric, or functional evidence of decline [1,2]. Nonetheless, whether subjective memory complaints represent early-stage Alzheimer's disease (AD) or not has remained highly controversial. Clinical [3] as well as large population-based cross sectional [4] and longitudinal [5] studies have found memory complaints to correlate more closely with psychological factors such as anxiety and depression than with psychometrically objective impairment. However, more recently, a longitudinal study of 2415 German primary care patients age 75 years and older reported greater rates of incident mild cognitive impairment (MCI) and AD at 1 and 3 years of follow-up among those expressing concern about their memory [6]. Reisberg and colleagues reported similar results in a cohort of 213 cognitively normal individuals followed for at least 7 years, although the baseline characteristics of those with subjective memory complaints revealed them to be older and with lower baseline cognitive performance compared with those without such complaints [7].

By the time individuals with subjective complaints reach a clinical setting, informant reports are often used to validate the patient's concern, but in the setting of minimal to no objective patient impairment, it is unclear whether the patient or the informant is able to provide the more medically salient history. Therefore, we sought to compare the responses of individuals and their informants on the Multidimensional Assessment of Neurodegenerative Symptoms (MANS) questionnaires [8], which are paired self- and informant-based questionnaires

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sensitive to the cognitive-, behavioral-, and movement-related problems that are prevalent among patients with early-stage AD and related disorders.

2. Methods

2.1. Study participants and enrollment

Cognitively normal residents of Maricopa County age 45 to 79 years with a family history of dementia were recruited through local media ads into the Arizona apolipoprotein E (*APOE*) cohort, a longitudinal study of cognitive aging [9]. Demographic, family, and medical history data were obtained on each individual undergoing *APOE* genotyping, and a study assistant coded identity. All individuals gave their written, informed consent, approved by the institutional review boards of the Mayo Clinic and the Banner Alzheimer Institute, and they agreed to have the results of the *APOE* test withheld from them as a precondition for their participation in this study. Genetic determination of *APOE* allelic status was performed using a polymerase chain reaction (PCR)-based assay [10].

Screening tests included a medical history, neurologic examination, the Folstein Mini-Mental Status Exam (MMSE [11]), the Hamilton Depression Rating Scale (Ham-D [12]), the Functional Activities Questionnaire (FAQ), Instrumental Activities of Daily Living (IADL), and Structured Psychiatric Interview [13]. There were no potentially confounding medical, neurological, or psychiatric problems (such as prior stroke, traumatic brain injury, memory or other form of cognitive impairment, parkinsonism, major depression, or substance abuse). None met the published criteria for MCI [14], AD [15], or any other form of dementia [13] or major depressive disorder [13]. On the MMSE, participants had to score at least 27 on the basis of published age and education-based norms (and must have scored at least 1 of 3 on the recall subtest) [11]. On the Ham-D, participants had to score 10 or less [12] at the time of their first visit. All FAQ and IADL questions had to indicate no loss of function.

2.2. Neuropsychological testing

Those fulfilling these requirements were administered an extensive standardized battery of neuropsychological tests that was repeated every 2 years. The neuropsychological tests within our battery are detailed in reference 16 and encompass four broadly defined cognitive domains. The scores used were as follows.

2.2.1. Memory

Auditory Verbal Learning Test Long-Term Memory Score (LTM; 30-minute delayed recall of a 15-word list, maximum possible is 15), Buschke Free and Cued Selective Reminding Test Total Free (SRT-free) Recall (maximum is 112), Rey-Osterrieth Complex Figure Test Absolute Recall (CFT-recall; maximum possible is 36), the Wechsler Memory Scale-Revised Paragraph Recall (one story, total 30-minute delayed recall), and the Benton Visual Retention Test total number correct (VRT; maximum possible is 10).

2.2.2. Executive

Wisconsin Card Sorting Test Total Errors (WCST-errors; lower scores are better); Paced Auditory Serial Attention Task 3 and 2 second versions total correct (PASAT-3, PASAT-2; mental arithmetic tests in which problems are presented 3 and 2 seconds apart; maximum possible for each is 60); Controlled Oral Word Association Test total words (COWAT; word generation over 1 minute for each of three letters; no upper limit, higher is better); Category fluency task (total vegetables named in one minute); Trail Making Test parts A (easier) and B (more difficult) total time to connect the alternating numbers and letters; and Age Scaled Scores (a score of 10 is 50th percentile) of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) subtests including Digit Span (DigSp), Mental Arithmetic (WAIS-arithmetic), and Digit Symbol Substitution Age Scaled Score (DSS).

2.2.3. Language

Boston Naming Test (BNT; 60 item) and Token Test total correct (maximum is 44).

2.2.4. Visuospatial

Judgment of Line Orientation total correct (JLO; maximum is 30), Facial Recognition Test Short Form corrected long-form score (FRT; 27 matches), WAIS-R Block Design Age Scaled Score (BD), and the CFT copy score (maximum score is 36).

2.3. Behavioral testing

As noted above, the Ham-D is an examiner-based depression measure [12] used to screen out those with potentially clinically significant depression. Participants also complete the Beck Depression Inventory [17], a generally applicable self-scored depression measure, and the Geriatric Depression Scale [18], most appropriate for older age groups. Finally, participants completed the Personality Assessment Inventory [19], which surveys a wide variety of behavioral domains including somatization and anxiety in addition to depression (scores are reported as t scores).

2.4. Subjective cognitive assessment

All participants and their informants (typically a spouse) completed the paired MANS [9]. The MANS are paired self- and informant-based questionnaires composed of 87 questions that assess changes over the preceding year in daily habits, personality, and motor functioning. It uses a quantitative scale for rating the frequency of a symptom from zero (never) to four (routinely), with intermediate values of one (once), two (occasionally), and three (more than monthly); scores can range from 0 to 348 with higher scores indicating