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Objective features of subjective cognitive decline in a U.S. 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 (FAQ) 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 to 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.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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 prior to 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 post-mortem brain autopsies [7-10] have identified pathologic evidence of Alzheimer disease in those with SCD. Despite these findings, the hypothesis that SCD constitutes a preclinical stage of Alzheimer disease is not consistently supported by the research literature [11,12].

Characterizing the clinical markers of SCD is an important step towards understanding its utility in predicting subsequent development of Alzheimer-type dementia. Even though 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 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 dataset, we sought to identify very subtle but significant distinctions that may have evaded detection in smaller samples. Prior studies of post-mortem cases from the NACC database have reported associations between baseline SCD and subsequent autopsy-confirmed Alzheimer disease 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 Alzheimer disease [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 over age 65 and classified as "Cognitively Normal" at baseline based on the judgement of a trained clinician, a Mini-Mental State Examination (MMSE) 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 Subjective Cognitive Decline

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 semi-structured 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 Alzheimer disease 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 non-carriers.

2.4. Functional Activities Questionnaire

The Functional Activities Questionnaire (FAQ) served as the measure of everyday functional abilities [28]. This ten-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 four weeks. Each item is rated on a three-point scale where 0 = normal, 1 = has difficulty, but does by self, 2 = requires assistance, and 3 = dependent. The ratings from the baseline visit were averaged together, yielding a single score that ranged from zero to three points, where a score of three points would indicate maximum impairment.

2.5. Neuropsychological Tests

Nine standardized paper-and-pencil tests from the UDS 2.0 neuropsychological battery were used to measure objective cognitive abilities in the present study. As previously described [29], these tests capture domains sensitive to cognitive aging and the early stages of Alzheimer disease. The present study included measures of auditory attention span (Wechsler Memory Scale - Revised (WMS-R) Digit Span Forward and Backward), auditory episodic memory for a short story (WMS-R Logical Memory (Story 1) Immediate and Delayed Recall), object naming (30-item version of the Boston Naming Test), semantic fluency (60-second list generation tasks), and psychomotor speed (Wechsler Adult Intelligence Scale - Revised (WAIS-R) Digit Symbol Coding and Parts A and B of the Trail Making Test).

2.6. Final Clinical Status

The clinical status from each participant’s final visit was used to examine the hypothesis that SCD represents an early stage in the development of Alzheimer-type dementia [2]. Specifically, the frequencies of participants who were designated as “Cognitively Normal” or diagnosed with either MCI or dementia at that visit were examined in the present study. One or more trained clinicians had made these determinations in accordance with published research diagnostic criteria and procedures standardized across all ADCs [30,31].

2.7. Analyses

Independent sample t-tests and Chi-square procedures were used to compare the SCD- and SCD+ groups on descriptive variables, baseline FAQ rating, and final clinical status. To compare baseline neuropsychological scores, a linear mixed model was used with fixed effects for SCD group and APOE ε4 status and a random intercept for clinical center in

order to account for potential variability in test administration and performance across ADCs. To compare longitudinal changes in neuropsychological test scores over the follow-up period, an annualized rate of change [32] was calculated using a method described previously [33], by estimating the random slope of the relationship between test score and visit for each participant, assuming a linear trend over the follow-up period. Unlike annualized change estimates based on scores obtained only at the baseline and final visits, these slopes use all available longitudinal data from every participant. This slope was then analyzed as described in the linear mixed model above, with the slope replacing the baseline score. Nine neuropsychological tests were analyzed in this manner. Bonferroni-adjusted significance levels were applied to correct for nine multiple comparisons ($p = 0.0055$).

3. Results

3.1. Descriptive Features

Of 3915 participants in the present sample, 763 (19.5%) had SCD at baseline and 3152 (80.5%) did not. The average age at baseline was 75.6 ± 7.3 years. The sample consisted predominantly of non-Hispanic, White women with college-level educational attainment. As shown in Table 1, the SCD- and SCD+ groups did not differ significantly from each other on any demographic variable, APOE ε4 allele status, or family history of dementia (all $p > 0.10$). The proportion of APOE ε4 allele carriers in the sample was 27%, which is similar to prevalence estimates that have been reported in other healthy adult samples [34]. As expected, no evidence of cognitive impairment was present in the sample at baseline; the average MMSE [21] score was 29.16 ± 0.94. The average GDS-15 [23] score at baseline was 0.98 ± 1.36, indicating a very minimal level of depressive symptomology in the sample.

Participants in the sample underwent between two and nine annual visits. The average number of follow-up visits was significantly greater in the SCD- group (4.7 ± 1.9) compared to the SCD+ group (4.3 ± 1.9, $p < 0.001$). Of note, we accounted for the influence of follow-up duration on longitudinal cognitive performance by calculating rate of change slopes from all available longitudinal data on every participant.

3.2. Baseline Functional Abilities

On average, ratings of everyday functional abilities were very minimal in both the SCD- and SCD+ groups, indicating that neither group had any objective impairment at baseline. Nonetheless, as predicted, the average baseline FAQ rating, which ranged from 0 (normal) to 3 (dependent), was significantly higher in the SCD+ group (0.40 ± 1.45) relative to the SCD- group (0.16 ± 0.98, $p < 0.001$).

3.3. Cognitive Test Scores

Table 2 shows summary statistics from group comparisons of baseline scores and longitudinal rate of change estimates (slopes) for the nine neuropsychological test scores examined in this study. On measures of auditory attention span (WMS-R Digit Span Forward and Backward), neither baseline scores nor longitudinal rate of change estimates differed significantly between the two groups.

On episodic memory tests (WMS-R Logical Memory Immediate Recall and Delayed Recall), the groups did not differ significantly from each other at baseline. Over the period of follow-up, both groups showed improvements in both Immediate Recall and Delayed Recall scores. However, the SCD- group showed significantly greater annual improvements on both tests relative to the SCD+ group.

Object naming scores (Boston Naming Test) in the SCD+ group were significantly worse at baseline and declined significantly more over the period of follow-up compared to the SCD- group. The SCD+ group also had worse baseline semantic fluency than the SCD- group, even though the longitudinal rate of change estimates did not differ between the two groups.

Psychomotor speed at baseline was worse in the SCD+ group on WAIS-R Digit Symbol Coding and Part B (but not Part A) of the Trail Making Test compared to the SCD- group. Both groups showed decline in psychomotor speed over the period of follow-up. However, the SCD+ group showed significantly greater decline on all three tests compared to the SCD- group.

APOE ε4 status had no significant effect on any baseline test score (all $p > 0.005$). Over the period of follow-up, ε4 carriers had significantly greater decline than non-carriers on the WMS-R Logical Memory Immediate and Delayed Recall tests ($p = 0.0002$ and < 0.0001, respectively). Longitudinal rate of change estimates did not differ between ε4 carriers and non-carriers on any other test (all $p > 0.01$). No interactions between APOE ε4 status and SCD were observed (all $p > 0.01$).

3.4. Clinical Progression over the Follow-up Period

As predicted, final visit diagnoses of both MCI and dementia were more common in the SCD+ group compared to the SCD- group (both $p < 0.001$). In the SCD- group, 79% of participants remained “Cognitively Normal” throughout the period of follow-up, while the others had the final visit status of either MCI (11%), dementia (5%), or “impaired, not MCI” (5%). In contrast, 66% of participants in the SCD+ group were “Cognitively Normal” at their final visit, whereas 18% were diagnosed with MCI, 10% were diagnosed with dementia, and 6% were designated “impaired, not MCI.”

4. Discussion

The goal of the present study was to identify objective functional and cognitive markers associated with SCD in a large cohort of older adults from the NACC database. At baseline, all participants were classified as “Cognitively Normal” for their age based on standardized clinical and neuropsychological assessments [20]. As predicted, SCD was associated with small but statistically significant reductions in baseline functional abilities and in baseline and longitudinal cognitive performance measured with standardized tests from the UDS 2.0 neuropsychological battery [29].

Specifically, we found that baseline SCD was associated with reduced longitudinal practice effects on tests of episodic memory. Over the period of follow-up, both groups showed annual improvements in immediate and delayed recall of a short story (WMS-R Logical

Memory). However, the older adults without SCD benefitted significantly more from repeated exposure to the story than did those with SCD. Prior studies have found that episodic memory practice effects are attenuated in patients with MCI and early Alzheimer-type dementia compared to cognitively normal older adults [35,36]. Other reports have suggested that short-term practice effects may predict pathologic Alzheimer disease and clinical prognosis in amnestic MCI [37,38]. Our findings add to this promising literature by suggesting that practice effects may also be reduced in the presence of SCD and may therefore represent a sensitive neuropsychological metric for detecting cognitive changes that precede MCI.

As hypothesized, we also found that SCD was associated with significant reductions in psychomotor speed. Consistent with prior findings [39], psychomotor speed measures were not vulnerable to practice effects. Rather, in this domain, the older adults showed annual decline over the period of follow-up, which was significantly greater in those with SCD compared to those without SCD. These findings suggest that timed measures of psychomotor slowing may represent sensitive neuropsychological metrics for identifying subtle pre-MCI cognitive changes.

At baseline, both groups performed within normal limits on all neuropsychological tests. However, we identified significant group differences on two tests of psychomotor speed and on language tests of object naming and semantic fluency. The differences in baseline psychomotor speed and category fluency may reflect the precision of timed tests at capturing very slight distinctions. The group difference in object naming was unexpected because this domain is not known to be vulnerable to MCI and dementia. Importantly, all of the observed baseline differences were very subtle and would be undetectable at the individual level.

We took several steps to account for demographic and clinical variables that have been shown to influence SCD and objective cognitive performance. For example, prior studies have found that SCD differentially affects women and individuals with high educational attainment and that neuropsychological test scores vary across different racial and ethnic groups [40-42]. These factors did not influence our results given that both groups had similar demographic composition. We excluded participants with clinically significant depression from the present study because depression has been shown to be a strong predictor of SCD [24,25]. Further, the SCD groups in our sample did not significantly differ based on family history of dementia or APOE ε4 status, which are two well-established risk factors for Alzheimer disease [27]. The proportion of APOE ε4 allele carriers in our sample was similar to the prevalence estimates found in other cognitively normal adult samples [34].

We included APOE ε4 status in our analyses of neuropsychological test scores in order to more closely examine relationship between SCD and genetic Alzheimer risk. Consistent with prior findings [43], the ε4 carriers in our sample had significantly greater decline in episodic memory than non-carriers, which was independent of the longitudinal memory differences that we found between the SCD groups. This result is consistent with prior work suggesting that APOE ε4 positivity and SCD may have an additive effect on episodic memory decline [34].

The present study had several limitations that must be addressed. First, the sample, similar to the NACC database from which it was drawn, contained a disproportionate representation of female gender, non-Hispanic, White race, and high educational attainment relative to the general population. Second, the presence of SCD in our sample was determined based on a single yes-no question, rather than a more detailed method of inquiry. Many self-report measures have been used to assess SCD. One recent report indicated that 34 self-report measures are being used across 19 international studies of SCD [26]. At present, there is no "gold standard" method of SCD assessment [44]. However, the single item used in our study did not allow us to assess SCD severity and it may have restricted our ability to capture complaints in domains other than memory, which can be affected early in non-amnestic types of dementia. However, in our experience, individuals with impairments in attention, language, and visuospatial abilities often perceive themselves as experiencing "forgetfulness" and memory difficulties. In fact, what individuals tend to subjectively experience as memory difficulties may actually represent slight changes in cognitive speed or efficiency. As mentioned in the methods section, the proportion of participants with SCD in our sample (19.5%) was generally consistent with prevalence estimates reported in other studies of community-dwelling older adults [1,17].

The current findings help to characterize the objective clinical changes that occur in cognitively normal older adults with SCD. By examining a large cohort, we had adequate statistical power to detect very subtle differences between groups with and without SCD. However, these slight distinctions do not have clinical relevance for distinguishing SCD at the individual level. At baseline, both groups performed well within normal limits on standardized paper-and-pencil assessments, which appear to lack sensitivity to reliability detect very slight differences in smaller groups or individuals. Rather, the findings suggest that episodic memory practice effects and psychomotor speed may be particularly vulnerable to *objective* decline in SCD. More sensitive neuropsychological metrics may be needed to reliably identify the same cognitive markers of SCD that we detected in a large database. Future studies should investigate episodic memory practice effects and more refined measures of psychomotor speed in an effort to distinguish individuals on the basis of SCD in smaller samples.

The current study contributes to important research aimed at identifying individuals at preclinical stages of Alzheimer disease who will progress to dementia. Prior studies suggest that the combination of SCD and *in vivo* Alzheimer biomarkers predict rapid cognitive decline and progression to MCI and Alzheimer-type dementia, although neither of these factors alone is sufficient to identify clinically asymptomatic individuals [45]. In recent longitudinal studies, the cognitive trajectories of biomarker-negative older adults (stage 0) were not easily distinguishable from those with biomarker evidence of either amyloid (stage 1) or neurodegeneration (stage 3/SNAP) [46-47]. Our findings suggest that SCD may be a helpful additive factor for differentiating these preclinical biomarker stages and thus identifying who is at greatest risk.

Our findings suggest that objective cognitive and functional changes are present, albeit very subtle, in groups with SCD. The results add to the existing literature by showing that the domains vulnerable to change in SCD are the same domains that are affected early in MCI

and Alzheimer-type dementia. The study provides support for the larger hypothesis that SCD represents a very early stage in the development of Alzheimer-type dementia.

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Research in Context

SYSTEMATIC REVIEW

We searched the PubMed database in order to identify published research on the topic of subjective cognitive decline (SCD). The manuscript includes citations to relevant empirical studies and recent systematic reviews.

INTERPRETATION

We found that objective baseline and longitudinal clinical variables differed as a function of SCD. The results add to the existing literature by showing that the domains vulnerable to change in SCD are the same as those affected early in mild cognitive impairment and Alzheimer-type dementia. The findings provide support for the larger hypothesis that SCD represents a very early stage in the development of Alzheimer-type dementia.

FUTURE DIRECTIONS

We propose that more sensitive neuropsychological metrics, such as tests that capture millisecond-level reaction time, should be used in future studies to reliably identify the types of cognitive markers of SCD that we detected in a large database.

Table 1

Descriptive features of the sample by group

Variable	SCD-	SCD+	P value
N	3152	763	
Age at baseline, mean (SD)	75.5 (7.1)	75.9 (7.6)	0.11
Gender, % female	67.5	66.6	0.63
Education, mean (SD) years	15.7 (2.8)	15.8 (2.9)	0.17
Race, % White	86.8	85.4	0.90
Ethnicity, % Hispanic or Latino	3.4	3.0	0.64
Primary language, % English	97.4	96.5	0.90
APOE ε4 status, % ε4 allele carriers	26.7	27.8	0.20
Family history of dementia, % positive	51.0	54.2	0.12

Abbreviations: SCD = subjective cognitive decline

Table 2

Average baseline score and annual rate of change for each neuropsychological test[a]

Neuropsychological Test (range of scores)	Baseline Raw Scores			Annual Rate of Change		
	SCD-	SCD+	P value	SCD-	SCD+	P value
Auditory Attention Span						
WMS-R Digit Span Forward (0-12)	8.55	8.45	0.230	- 0.037	- 0.040	0.500
	0.13	0.15		0.008	0.009	
WMS-R Digit Span Backward (0-12)	6.84	6.81	0.720	- 0.031	- 0.037	0.120
	0.10	0.12		0.003	0.004	
Episodic Memory						
WMS-R Logical Memory Immediate (0-25)	13.79	13.36	0.012	0.153	0.093	**< 0.001** *
	0.16	0.20		0.015	0.019	
WMS-R Logical Memory Delayed (0-25)	12.54	12.05	0.008	0.210	0.130	**< 0.001** *
	0.16	0.20		0.020	0.020	
Psychomotor Speed						
WAIS-R Digit Symbol Coding (0-100)	46.63	44.79	**< 0.001** *	- 0.44	- 0.58	**< 0.001** *
	0.97	1.03		0.04	0.05	
Trail Making Test Part A (0-150 seconds)[b]	34.66	35.88	0.056	0.58	0.88	**< 0.001** *
	0.99	1.09		0.09	0.10	
Trail Making Test Part B (0-300 seconds)[b]	89.52	96.89	**< 0.001** *	3.30	4.03	**< 0.001** *
	3.14	3.44		0.22	0.27	
Language						
Semantic Fluency (0-70)	35.06	33.81	**0.001** *	- 0.260	- 0.310	0.053
	0.40	0.48		0.040	0.040	
Boston Naming Test (0-30)	27.33	26.90	**< 0.001** *	- 0.018	- 0.078	**< 0.001** *
	0.16	0.18		0.011	0.014	

[a]Values are mean (SE). Annual Rate of Change (slope) represents the average change in score per annual visit over the follow-up period.

[b]Higher scores indicate worse performance

*Significant between-group difference (Bonferroni-adjusted $p < 0.0055$)

Abbreviations: SCD = subjective cognitive decline; WMS-R = Wechsler Memory Scale - Revised; WAIS-R = Wechsler Adult Intelligence Scale – Revised