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Longitudinal Assessment of Self- and Informant-Subjective Cognitive Complaints in a Sample of Healthy Late-Middle Aged Adults Enriched with a Family History of Alzheimer's Disease

Christopher R. Nicholas,[1,2,3] N. Maritza Dowling,[4] Annie M. Racine,[3] Lindsay R. Clark,[1,2,3] Sara E. Berman,[3] Rebecca L. Koscik,[2] Sanjay Asthana,[1,3] Bruce Hermann,[2,5] Mark A. Sager,[2] AND Sterling C. Johnson[1,2,3]

[1]Geriatric Research Education and Clinical Center, Wm. S. Middleton Veterans Hospital, Madison, Wisconsin
[2]Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
[3]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin
[4]Department of Biostatistics & Research, School of Nursing, George Washington University, Washington, DC
[5]Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

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Abstract

Objectives: The purpose of this study was to investigate the longitudinal trajectory of self- and informant-subjective cognitive complaints (SCC), and to determine if SCC predict longitudinal changes in objective measures (OM) of cognitive function. **Methods:** The study included healthy and cognitively normal late middle-aged adults enriched with a family history of AD who were evaluated at up to three visits over a 4-year period. At each visit (Visit 1–3), self- and informant-SCC and OM were evaluated. Linear mixed models were used to determine if the longitudinal rate of change of self- and informant-SCC were associated with demographic variables, depressive symptoms, family history (FH), and apolipoprotein epsilon 4 (APOE4) status. The same modeling approach was used to examine the effect of Visit 1 SCC on longitudinal cognitive change after controlling for the same variables. **Results:** At Visit 1, more self-SCC were associated with fewer years of education and more depressive symptoms. SCC were also associated with poorer performance on cognitive measures, such that more self-SCC at Visit 1 were associated with poorer performance on memory and executive functioning measures at Visit 1, while more informant-SCC were associated with faster rate of longitudinal decline on a measure of episodic learning and memory. FH and APOE4 status were not associated with SCC. **Discussion:** Self- and informant-SCC showed an association with OM, albeit over different time frames in our late middle-aged sample. Additional longitudinal follow-up will likely assist in further clarifying these relationships as our sample ages and more pronounced cognitive changes eventually emerge. (*JINS*, 2017, *23*, 617–626)

Keywords: Self-report, Dementia, Aging, Neuropsychology, Memory, Executive function

INTRODUCTION

Subjective cognitive complaints (SCC) based on self- and informant reports may be sensitive to early cognitive changes that arise years before onset of Mild Cognitive Impairment (MCI) or dementia due to Alzheimer's disease (AD) (Howieson et al., 2008; Rajan, Wilson, Weuve, Barnes, & Evans, 2015). Studies have shown that SCC are associated with an increased risk of clinical conversion to MCI and AD (Caselli et al., 2014; Gifford et al., 2014; Hsu, Huang, Tu, & Hua, 2014; Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014), supporting the possible clinical utility of SCC as a diagnostic marker. If this is the case, SCC should correlate with objective measures of cognitive performance (OM) before diagnostic conversion.

Longitudinal studies using multiple time points and controlling for known confounding factors (e.g., depressive symptoms), have generally found a modest relationship between SCC and OM (Crumley, Stetler, & Horhota, 2014; Hulur, Hertzog, Pearman, & Gerstorf, 2015; Mascherek & Zimprich, 2011; Parisi et al., 2011) although some have not (Pearman, Hertzog, & Gerstorf, 2014). Differences in methodology and sample characteristics may in part account for these discrepancies.

Correspondence and reprint requests to: Sterling C. Johnson, J5/1M, Clinical Science Center, 600 Highland Avenue, Madison, WI 53792. E-mail: scj@medicine.wisc.edu

Within the preclinical timeframe, when neuropathological and cognitive changes are only beginning to emerge (Jessen et al., 2014; Morris, 2005); measuring the association between SCC and OM may assist in characterizing the initial clinical course of at-risk individuals. The current study uses data from the Wisconsin Registry for Alzheimer's disease Prevention (WRAP), a longitudinal cohort enriched for AD risk factors of family history (FH) and apolipoprotein epsilon 4 (APOE4) carrier status (Sager, Hermann, & La Rue, 2005), to determine if SCC (self- and informant-based) change over time, and if baseline SCC predict OM that are sensitive to possible early preclinical changes.

Based on previous research, and because our sample consists of cognitively healthy, late middle-aged adults whom would at most be exhibiting subtle cognitive changes, we expected to observe a modest association between SCC and OM. In addition, given that FH and APOE4 status have each been associated with SCC and change in OM (Dik et al., 2001; La Rue et al., 1996; McPherson, La Rue, Fitz, Matsuyama, & Jarvik, 1995); and that knowledge of one's status may be a source of bias when evaluating one's cognitive status (Lineweaver, Bondi, Galasko, & Salmon, 2014), we also explored the association between these risk factors and SCC.

METHODS

Sample

Data for this study came from the WRAP, a longitudinal registry of 1545 cognitively normal, adult participants (mean age at study entry = 53.6 years; *SD* = 6.6; range = 40.6–73.8 years), of which 72.4% have a parental family history of AD (Sager et al., 2005) (see Table 1). All WRAP participants completed questionnaires about their familial, socio-demographic, and health status and underwent a comprehensive clinical and neuropsychological assessment at WRAP study entry (i.e., WRAP baseline), a second visit 4 years later (Visit1) and subsequent visits approximately every 2 years thereafter (Visits 2 & 3).

The current study included three assessments, each 2 years apart, over a 4-year time period (Visits 1–3). Visit 1 was used as the initial assessment for these analyses because collection of informant-SCC did not begin at WRAP study entry, but rather at Visit 1. Participants who were neurologically healthy and cognitively normal at WRAP study entry and who had completed at least Visit 1 and one follow-up (Visit 2 and/or Visit 3) were included in the analysis. Based on this criteria, samples sizes varied for each analysis depending on the combination of predictor and outcome variables (n-size range = 1148–1261). The University of Wisconsin Institutional Review Board approved all study procedures and each participant signed informed consent before participation.

Assessment

SCC were assessed using the Memory Functioning Questionnaire (Gilewski, Zelinski, & Schaie, 1990; Zelinski, Gilewski, & Anthony-Bergstone, 1990) for self-SCC and the short version of the Informant Questionnaire on Cognitive Decline in Elderly (IQCODE) (Jorm & Jacomb, 1989) for informant-SCC. The MFQ is a well-validated, 64-item self-report measure with four subscales identified by factor analysis (Gilewski et al., 1990). For this study, we used the 18-item Frequency of Forgetting (FF) scale of the MFQ as our self-SCC measure since it has been shown to correspond to memory performance (Zelinski et al., 1990). For this subscale, participants are asked to rate "How often do the following aspects of memory present a problem for you…" on a 7-point Likert scale (scored 1–7; 1 = "Always", 7 = "Never") for 18 different aspects of memory (e.g., memory for names, faces, appointments, etc.).

For the current study, two items from the FF scale were removed from the analysis due to missing data ("Losing the thread of thought in public speaking" and "Taking a test"). Therefore, ratings were summed across the 16 items to get a total FF score (range, 16–112), with lower FF scores corresponding to a greater frequency of complaints. While the FF/MFQ was initiated at WRAP study entry, only FF data obtained at the same time as IQCODE data (Visits 1–3) are used in these analyses. Test–retest reliability correlations between Visit 1 and Visit2 indicated high stability for FF in this sample ($r = 0.728$; $p < .001$).

The IQCODE is a well-validated (Jorm, 2004), 16-tem self-report measure asking the informant to rate the study participant on a 5-point Likert-scale (scored 1–5) ranging from "Much Improved" to "Much Worse" about the participant's memory and other domains of cognitive function across everyday situations. A score greater than 48 indicates more informant reported cognitive difficulties. The informant was a spouse, family member, or close acquaintance. The IQCODE was initiated at Visit 1 and asked the informant to compare the participant's cognitive functioning to approximately *10 years ago*. At Visits 2 and 3, informants were asked to make comparisons to the last visit approximately *2–3 years ago.* Test–retest reliability correlations between Visit 2 and Visit 3 (Visit 1 includes a different reference point) indicated low stability for the IQCODE in this sample ($r = 0.310$; $p < .001$).

Depressive symptomatology was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The scale consists of 20 Likert-scale questions (scored 0–3) ranging from "Rarely/None of the Time" to "Most/All of the Time" about the frequency of depressive symptoms over the past week. A score of 16 or higher indicates clinically significant mild depression.

OM were collected from the larger WRAP neuropsychological battery (Sager et al., 2005) conducted at each visit. Based on the literature indicating that measures of episodic memory and executive functioning are sensitive to early preclinical changes (Albert, Moss, Tanzi, & Jones, 2001), the following cognitive measures were selected from the neuropsychological battery: Rey-Auditory Verbal Learning-Total (RAVLT; Rey, 1964) (sum of trials 1–5; possible range of 0 to 75) and Delayed Recall (possible range of 0 to 15); and Trail Making Test B (Reitan, 1958).

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Family History and APOE4 Status

To verify the diagnosis of AD in the parent, parental medical records, autopsy reports, or results of the dementia questionnaire (Kawas, Segal, Stewart, Corrada, & Thal, 1994) were obtained and reviewed by a multidisciplinary diagnostic consensus conference (Jonaitis et al., 2013; Koscik et al., 2014; Sager et al., 2005). Absence of FH of AD was verified through detailed medical history surveys and phone interview with the participants. Genotyping for APOE4 status was done previously in WRAP and described elsewhere (Johnson et al., 2011). Participants were unaware of their APOE4 status.

Statistical Analyses

Linear mixed models (Laird & Ware, 1982) were used to determine if the rates of change of self- and informant-SCC were associated with demographic (age, sex, and education) variables, depressive symptoms, FH, and APOE4 status. The same modeling approach was used to examine the effect of Visit 1 SCC on cognitive change after controlling for the same variables. A key advantage of linear mixed models is that if missing data are missing at random, the estimation process makes full use of all available data from each subject. Age centered at the Visit 1 mean was the metric of time in each model, and occurred in 2-year intervals between each visit (biennial units). The distribution of the outcome measures was approximately normal.

Model building proceeded in several steps. First, we estimated the unconditional means model using time and estimated intra-cluster correlations using family as the clustering variable. We tested models using a random intercept and slope. A model with uncorrelated intercept and slope was examined first and a model that allowed the correlation between intercept and slope was examined second. A fully parameterized (unstructured) covariance matrix seemed appropriate for the tested models. Since intra-class correlations ranged from 0.06 to 0.17, all models included family-cluster as a random effect, which varied in family size (1–9 participants) and number of families (780–926).

The second modeling step incorporated all predictors and interactions of interest. All interactions were retained in the model regardless of significance. To facilitate model interpretation, continuous predictors were mean centered. All models were estimated using restricted maximum likelihood. Random effects were assessed by likelihood-ratio (χ^2) tests. A t-value of >1.96 was used as the measure of statistical significance for fixed effects. Model diagnostics included examining collinearity using variance inflation factor and plotting model residuals against normal quantiles to examine departure from normality. Simple slopes were plotted to represent significant SCC by time interactions. Analyses were conducted using the lme4 package in R (R Core Team).

RESULTS

Demographics

Demographic characteristics and correlations are based on the total WRAP sample at Visit 1 ($n = 1261$) and were similar to the analytical samples which varied in n-size depending on the combination of predictor and outcome variables (n-size range = 1148–1261) (see Table 1). SCC and OM means were also based on the total WRAP sample at Visit 1 and were similar to analytic samples (see Table 1). Results pertaining to associations with SCC from our linear mixed effects analyses are reported below.

Table 1. Demographic data and correlations

Variable	Visit 1 Mean (*SD*)	1	2	3	4	5	6	7	8	9	10	11	12
1 Age	58.68 (6.49)	1											
2 WRAT-III	105.66 (9.40)	.048	1										
3 Education (years)	16.16 (2.77)	.027	.449**	1									
4 FH (positive %)	73.40%	−.194**	−.095**	−.119**	1								
5 APOE4 (positive %)	38.40%	−.069*	−.030	−.026	.227**	1							
6 Sex (female %)	70.20%	.024	−.044	.103**	−.048	−.033	1						
7 CES-D	7.10 (7.13)	−.080**	−.016	−.072*	.041	.019	−.056*	1					
8 Frequency of Forget	76.5 (12.52)	−.012	.103**	.111**	−.049	.013	−.019	−.405**	1				
9 IQCODE	47.89 (4.66)	.039	−.001	−.011	.014	.005	.047	.055	−.106**	1			
10 RAVLT-Total	50.80 (8.51)	−.218**	.233**	.148**	.014	−.014	−.290**	−.058*	.110**	−.002	1		
11 RAVLT-Delayed	10.43 (2.96)	−.156**	.228**	.149**	.004	−.022	−.262**	−.034	.101**	−.018	.771**	1	
12 Trails B (sec)	61.66 (25.53)	.321**	−.215**	−.115**	−.060*	−.023	.073**	.138**	−.135**	.006	−.274**	−.209**	1

Notes. Data is based on the total WRAP sample at Visit 1 (n = 1261). Values in parentheses are standard deviations. Note correlations are two-tailed, * $p < 0.05$ and ** $p < 0.001$. Lower scores on Frequency of Forgetting and scores greater than 3 on the IQCODE equate to more subjective complaints. Higher scores on the CES-D indicate more depressive symptoms. FH = Family History; APOE4 = apolipoprotein E4; CES-D = Center for Epidemiologic Studies Depression Scale; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; RAVLT = Rey Auditory Verbal Learning Test, WRAT-III = Wide Range Achievement Test-III standard score (Wilkinson, 1993).

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Table 2. Predictors of Longitudinal SCC

	Frequency of forgetting			IQCODE		
Covariate	Estimate	*SE*	t-Value	Estimate	*SE*	t-Value
Intercept	77.762	2.101	37.01*	46.31	0.787	58.72*
Sex $_{(1 = male; 0 = female)}$	−1.208	0.688	−1.76	0.432	0.256	1.69
Education	0.270	0.116	2.33*	0.061	0.043	1.42
CES-D $_{(0\text{-}44)}$	−0.682	0.043	−15.70*	0.031	0.016	1.84
APOE4 $_{(1 = positive; 0 = negative)}$	0.674	0.667	1.01	−0.146	0.243	−0.60
FH $_{(1 = positive; 0 = negative)}$	−1.126	0.792	−1.42	0.168	0.294	0.57
Age	−0.491	0.265	−1.86	−0.034	0.115	−0.30
Sex*Age	0.070	0.088	0.79	−0.053	0.038	−1.39
Education*Age	0.014	0.015	0.98	0.005	0.006	0.77
CES-D*Age	0.001	0.006	0.24	0.000	0.003	0.11
APOE4*Age	−0.021	0.086	−0.24	0.007	0.037	0.18
FH*Age	0.096	0.102	0.94	−0.033	0.044	−0.74
Random effects	Variance	*SD*		Variance	*SD*	
Within-level	69.667	8.347		4.794	2.189	
Between-level	23.337	4.831		1.097	1.047	
Residual Variance	43.012	6.56		15.150	3.893	

Notes. Time = Age centered at Visit 1 mean. Visits 1-3 occur at two-year intervals. Lower scores on Frequency of Forgetting and scores greater than 48 on the IQCODE equate to more subjective complaints. Higher scores on the CES-D indicate more depressive symptoms. SCC = Subjective cognitive complaints as measured by Frequency of Forgetting and the IQCODE; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; FH = Family History; APOE4 = apolipoprotein E4; CES-D = Center for Epidemiologic Studies Depression Scale.
*t-value > 1.96 = $p < 0.05$.

Relationship Between Demographic Variables and Visit 1 and Longitudinal SCC

For Visit 1 self-SCC, more complaints (lower scores on FF) were moderately associated with less education (β = 0.270; *SE* = 0.116; t = 2.33) and highly associated with more depressive symptoms (higher scores on the CES-D) (β = –0.682; *SE* = 0.043; t = –15.70) at Visit 1. Visit 1 informant-SCC as well as longitudinal self- and informant-SCC were not associated with any other variables. FH and APOE4 status were not associated with Visit 1 or longitudinal SCC (see Table 2).

Relationship of Visit 1 SCC and Longitudinal Cognitive Performance

RAVLT-Total

For Visit 1 self-SCC, more complaints (lower scores on FF) were modestly associated with lower Visit 1 RAVLT-Total scores (β = 0.041; *SE* = 0.018; t = 2.26), but not longitudinal rate of change. Visit 1 informant-SCC were not associated with Visit 1 RAVLT-Total scores. In contrast, Visit 1 informant-SCC were associated with a faster rate of longitudinal decline of RAVLT-Total scores (β = –0.015; *SE* = 0.006; t = –2.49) such that more complaints (higher scores on the IQCODE) predicted, on average, a –0.015 point biennial decrease in RAVLT-Total scores (see Table 3; data were collected every 2 years). Decomposing this interaction into simple slopes revealed that informant-SCC scores +1 *SD* above the mean (indicating more complaints) showed a steeper rate of decline while scores –1 *SD* below the mean showed a slower rate of decline (Figure 1).

RAVLT-Delayed

For Visit 1 self-SCC, more complaints (lower scores on FF) were modestly associated with lower Visit 1 RAVLT-Delayed scores (β = 0.016; *SE* = 0.006; t = 2.45), but not longitudinal scores. No other association was observed between self- or informant-SCC and RAVLT-Delayed scores (see Table 4).

Trails B

For Visit 1 self-SCC, more complaints (lower scores on FF) were modestly associated with a slower time on Trails B at Visit 1(β = –0.100; *SE* = 0.006; t = –1.99). No other association was observed between self- or informant-SCC and Trails B time (see Table 5).

Exploratory

Post hoc analyses investigating TMT B:A ratio (Golden, Osmon, Moses, & Berg 1981) as a more specific measure of executive functioning and RAVLT learning over trials (LOT; Ivnik et al., 1992) as a measure of possible improvement in learning across the five learning trials were not associated with self- or informant-SCC.

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Table 3. Visit 1 SCC predicting RAVLT-Total scores

	Frequency of forgetting			IQCODE		
Covariate	Estimate	*SE*	t-Value	Estimate	*SE*	t-Value
Intercept	42.181	1.996	21.14*	43.934	2.629	16.71*
Sex (1 = male; 0 = female)	−5.945	0.460	−12.94*	−6.032	0.475	−12.69*
Education	0.501	0.078	6.44*	0.487	0.080	6.06*
CES-D (0-44)	−0.055	0.032	−1.74	−0.084	0.031	−2.72*
APOE4 (1 = positive; 0 = negative)	−0.449	0.445	−1.01	−0.335	0.456	−0.73
FH (1 = positive; 0 = negative)	0.052	0.529	0.10	−0.409	0.550	0.74
SCC	0.041	0.018	2.26*	0.048	0.046	1.05
Age	−0.224	0.255	−0.88	0.595	0.343	1.73
Sex*Age	−0.103	0.059	−1.72	−0.121	0.061	−1.99*
Education*Age	−0.007	0.010	−0.66	−0.003	0.010	−0.26
CES-D*Age	0.000	0.004	−0.06	−0.004	0.004	−0.89
APOE4*Age	−0.008	0.059	−0.14	0.001	0.060	0.03
FH*Age	−0.027	0.069	0.40	−0.015	0.071	0.21
SCC*Age	0.002	0.002	0.86	−0.015	0.006	−2.49*
Random effects	Variance	*SD*		Variance	*SD*	
Participant-level	31.989	5.656		33.480	5.786	
Cluster-level	8.117	2.849		0.000417	0.020	
Residual	21.120	4.596		21.010	4.584	

Notes. Time = Age centered at Visit 1 mean. Visits 1–3 occur at two-year intervals. Lower scores on Frequency of Forgetting and scores greater than 48 on the IQCODE equate to more subjective complaints. Higher scores on the CES-D indicate more depressive symptoms. SCC = Subjective cognitive complaints as measured by Frequency of Forgetting and the IQCODE; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; FH = Family History; APOE4 = apolipoprotein E4; CES-D = Center for Epidemiologic Studies Depression Scale.
*t-value > 1.96 = $p < 0.05$.

DISCUSSION

We investigated longitudinal models of self- and informant-SCC in a cohort of healthy late middle-aged adults with familial and genetic risks factors for AD. Separate linear-mixed effects modeling revealed that self- and informant-SCC did not exhibit biennial change over time, and only Visit 1 self-SCC was associated with years of education and Visit 1 symptoms of depression. When Visit 1 self- and informant-SCC were used as predictors of OM, more self-SCC were associated with poorer Visit 1 scores on all three OM cognitive functioning, while informant-SCC were associated with a faster rate of biennial longitudinal decline in RAVLT-Total scores. Below we focus our discussion on associations with SCC.

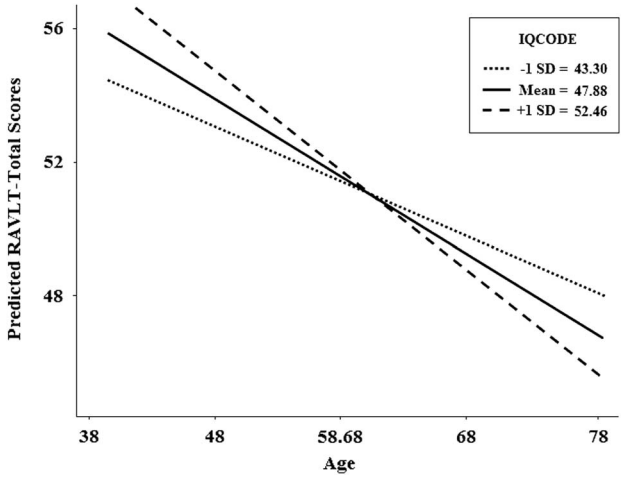

Fig. 1. Simple slopes representing the IQCODE predicting biennial rate of change on the RAVLT-Total for participants scoring +1 *SD* above (dashed line) and -1 *SD* below (dotted line) mean (solid line) IQCODE scores (higher scores equate to more informant complaints). X-axis = age as the time metric; y-axis = predicted RAVLT-Total scores. RAVLT = Rey Auditory Verbal Learning Test; *SD* = standard deviation.

Visit 1 and Longitudinal SCC

Self- and informant-SCC did not change over a relatively short longitudinal timeframe, and only education level and Visit 1 depressive symptoms were associated with Visit 1 self-SCC. The association of more Visit 1 self-SCC and fewer years of education, may align with the well-known protective effects (e.g., cognitive reserve; use of compensation strategies) of education on cognitive decline and rate of conversion to dementia (Karp et al., 2004; Letenneur et al., 2000; Qiu, Bäckman, Winblad, Agüero-Torres, & Fratiglioni, 2001; Stern et al., 1994; van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007). However, studies have observed steeper rates of decline in self-SCC (more complaints) in more highly educated individuals (Hulur, Hertzog, Pearman, Ram, & Gerstorf, 2014; Hulur et al., 2015; Zelinski, Burnight, & Lane, 2001); and when

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Table 4. Visit 1 SCC predicting RAVLT-Delayed Recall scores

	Frequency of forgetting			IQCODE		
Covariate	Estimate	*SE*	t-Value	Estimate	*SE*	t-Value
Intercept	7.113	0.699	10.17*	8.226	0.922	8.92*
Sex $_{(1 = male; 0 = female)}$	−1.829	0.161	−11.37*	−1.849	0.167	−11.09*
Education	0.172	0.027	6.31*	0.171	0.028	6.06*
CES-D $_{(0\text{-}44)}$	−0.001	0.011	−0.10	−0.011	0.011	−1.00
APOE4 $_{(1 = positive; 0 = negative)}$	−0.169	0.157	−1.08	−0.149	0.161	−0.93
FH $_{(1 = positive; 0 = negative)}$	0.051	0.186	0.27	−0.075	0.193	0.39
SCC	0.016	0.006	2.45*	0.006	0.016	0.40
Age	0.048	0.090	0.53	0.205	0.122	1.68
Sex*Age	−0.035	0.021	−1.63	−0.046	0.021	−2.14*
Education*Age	−0.012	0.004	−3.33*	−0.010	0.004	−2.74*
CES-D*Age	0.001	0.002	0.39	−0.001	0.001	−0.57
APOE4*Age	0.037	0.021	1.76	0.034	0.021	1.61
FH*Age	−0.021	0.025	−0.86	−0.020	0.025	−0.77
SCC*Age	0.001	0.001	1.51	−0.002	0.002	−0.77
Random effects	Variance	*SD*		Variance	*SD*	
Participant-level	3.755	1.938		4.120	2.029	
Cluster-level	1.143	1.069		0.846	0.920	
Residual	2.566	1.602		2.532	1.591	

Notes. Time = Age centered at Visit 1 mean. Lower scores on Frequency of Forgetting and scores greater than 48 on the IQCODE equate to more subjective complaints. Higher scores on the CES-D indicate more depressive symptoms. SCC = Subjective cognitive complaints as measured by Frequency of Forgetting and the IQCODE; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; FH = Family History; APOE4 = apolipoprotein E4; CES-D = Center for Epidemiologic Studies Depression Scale.
*t-value > 1.96 = $p < 0.05$.

self-SCC complaints are present, appear to be more predictive of cognitive decline and AD risk compared to that in less educated individuals (Chary et al., 2013; van Oijen et al., 2007. Thus, there may be a period of delay of self-reported cognitive changes in at-risk individuals who are highly educated, and then eventually convert at a faster rate later in time after accumulation of neurodegenerative processes (Stern, Albert, Tang, & Tsai, 1999). Given the relatively high education status (mean = 16 years) and younger age of our sample (Visit 1 mean = 58 years) within this preclinical timeframe, continued longitudinal evaluation will help determine if this purported pattern is consistent with their longitudinal trajectory.

A greater frequency of depressive symptoms were associated with more Visit 1 self-SCC, but did not predict longitudinal self-SCC, which some have reported (Hulur et al., 2015; Snitz et al., 2015). Depressive symptoms are often associated with SCC (Brigola et al., 2015; Chin, Oh, Seo, & Na, 2014; La Rue et al., 1996; Lehrner et al., 2014) and may represent an inaccurate and/or a negatively biased self-appraisal (Crane, Bogner, Brown, & Gallo, 2007) characteristically found in depressed patients (Beck, Rush, Shaw, & Emery, 1979), thus warranting their inclusion as a covariate when investigating the unique relationship between self-SCC on objective cognitive performance.

However, a recent longitudinal population-based study (Hulur et al., 2015) showed that correlated changes in self-SCC and memory performance were reliably stronger in individuals endorsing more depressive symptoms. Thus, this may actually reflect an accurate appraisal (i.e., depressive realism) of changes in cognitive function (Pearman et al., 2014) and in effect highlight the potential clinical value of the association between depressive symptoms and SCC.

SCC and OM

Visit 1 self- and informant-SCC diverged with regards to their association with OM, in that self-SCC were associated with all Visit 1 OM (RAVLT-Total & Delayed, Trails B), and informant-SCC only predicted, albeit modestly, a faster rate of biennial decline in episodic memory (RAVLT-Total). Our findings of an association between self-SCC and OM, such that more complaints corresponded to poorer performance on OM, is consistent with previous research (Snitz, Morrow, Rodriguez, Huber, & Saxton, 2008; Zelinski et al., 1990), and may highlight the possibility that questions about memory complaints on the FF scale may generalize and/or be interpreted to involve other cognitive domains such as executive functioning, given the significant association with Trails B in addition to the RAVLT tests (Jessen et al., 2014).

Informant-SCCs were associated with a decline in longitudinal episodic memory (RAVLT-Total) which is consistent with longitudinal studies showing the utility of informant reports as indicators of cognitive changes (Gifford et al., 2015; Jorm et al., 1996). Simple slopes revealed

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Table 5. Visit 1 SCC predicting Trails B time

	Frequency of forgetting			IQCODE		
Covariate	Estimate	*SE*	t-Value	Estimate	*SE*	t-Value
Intercept	80.068	5.352	14.96*	72.788	6.843	10.64*
Sex $_{(1 = \text{male; } 0 = \text{female})}$	5.220	1.244	4.20*	5.219	1.247	4.19*
Education	–1.022	0.209	–4.884*	–0.911	0.210	–4.35*
CES-D $_{(0\text{-}44)}$	0.514	0.089	5.80*	0.572	0.083	6.85*
APOE4 $_{(1 = \text{positive; } 0 = \text{negative})}$	1.078	1.202	0.90	1.185	1.198	0.99
FH $_{(1 = \text{positive; } 0 = \text{negative})}$	–0.880	1.396	–0.63	0.260	1.410	0.19
SCC	–0.100	0.050	–1.99*	–0.086	0.119	–0.72
Age	1.854	0.705	2.630*	1.562	0.967	1.62
Sex*Age	0.200	0.167	1.20	0.241	0.168	1.44
Education*Age	–0.047	0.028	–1.69	–0.046	0.028	–1.65
CES-D*Age	0.021	0.012	1.71	0.021	0.012	1.79
APOE4*Age	–0.084	0.167	–0.51	–0.114	0.168	–0.68
FH*Age	–0.014	0.197	–0.073	–0.024	0.198	–0.12
SCC*Age	–0.00	0.007	–0.02	0.005	0.017	0.32
Random effects	Variance	*SD*		Variance	*SD*	
Participant-level	218.621	14.786		205.816	14.346	
Cluster-level	38.887	6.236		32.594	5.709	
Residual	237.452	15.410		221.814	14.893	

Notes. Time = Age centered at Visit 1 mean. Lower scores on Frequency of Forgetting and scores greater than 48 on the IQCODE equate to more subjective complaints. Higher scores on the CES-D indicate more depressive symptoms. SCC = Subjective cognitive complaints as measured by Frequency of Forgetting and the IQCODE; IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; FH = Family History; APOE4 = apolipoprotein E4; CES-D = Center for Epidemiologic Studies Depression Scale.
*t-value > 1.96 = $p < 0.05$.

that informant-SCC scores + 1 *SD* (M = 52.48; more complaints) above the mean (M = 47.89; minor-to-no complaints) showed a relatively steeper rate of decline than scores around or below the mean. While a mean score of 52.48 (~3.28) is still below the recommended clinical cut-off of 3.44 (Jorm, 2004), it would be interesting to explore in future follow-up analyses to determine the clinical relevance in our sample.

A recent longitudinal study found that informant-only and mutual complaints (self- and informant) were predictors of decline in global cognition and processing-speed, but not episodic memory (e.g., RAVLT-Total) in healthy older individuals (approximate mean age = 72 years) (Gifford et al., 2015). Informant-SCC may be more sensitive to global changes (Jorm et al., 1996); therefore, while the RAVLT-Total measures initial auditory episodic learning of unstructured verbal information, it could also represent the participant's general ability to learn new information, which, over time, could manifest as subtle yet observable deficits in daily functioning (Cargin, Collie, Masters, & Maruff, 2008; Gross, Rebok, Unverzagt, Willis, & Brandt, 2011).

While speculative, this interpretation may be consistent with the fact that the IQCODE in our study requires informants to evaluate the participant across a variety of cognitive functions, in effect possibly allowing for broader measurement of observable cognitive and/or functional changes than memory performance as assessed by the FF scale. Nevertheless, we chose not to investigate the correlation between self- and informant SCC due to these important differences.

Family History and APOE4 Status

Given that our sample is enriched with AD FH and APOE4 positive adults; and the observed association between these familial/genetic factors and increased SCC (Dik et al., 2001; Kryscio et al., 2014; La Rue et al., 1996; Risacher et al., 2015; Samieri et al., 2014; Small et al., 2001; Tsai, Green, Benke, Silliman, & Farrer, 2006), we investigated the association between SCC and FH and APOE4 status. Our analyses revealed that neither FH nor APOE4 status was associated with Visit 1 or longitudinal self- and informant-SCC. Unlike our participants who were unaware of their APOE4 status, a recent study found that individuals aware of their APOE4 status had more cognitive complaints and performed worse on testing compared to their unknowledgeable counterparts (Lineweaver et al., 2014).

More complaints were also observed in younger individuals with an early-onset FH compared to individuals with a late-onset FH (La Rue et al., 1996; McPherson et al., 1995). These participants were comparable in age to our sample, thus the individuals with late-onset FH who had fewer complaints were likely over a decade younger than the onset of their relative's symptoms and, therefore, possibly less inclined to feel vulnerable to cognitive changes than participants with an early-onset FH. Future analyses in which we distinguish between early and late-onset in our sample may assist in clarifying if characteristics of FH are associated with self- or informant SCC.

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LIMITATIONS AND CONCLUSION

In summary, self- and informant-SCC did not significantly change longitudinally, and with exception of Visit 1 informant-SCC predicting longitudinal RAVLT-Total scores, no other model or *post hoc* analysis with Visit 1 self- or informant-SCC predicted longitudinal changes in cognitive performance. While this is consistent with some studies (Cargin et al., 2008; Pearman et al., 2014), several studies, after controlling for depressive symptoms, found correlated longitudinal changes between self-SCC and OM. (Hulur et al., 2015; Parisi et al., 2011; Snitz et al., 2015; Zimprich & Kurtz, 2015). Methodological differences may partially account for some of this inconsistency in that our study included a brief total longitudinal time-frame (mean interval across 3 visits = 4 years), with a relatively healthy and younger cohort (Visit 1 mean = 58 years) that may be exhibiting stable performance on OM compared to older individuals.

Previous longitudinal studies modeling FF as a random effect have demonstrated that age predicts individual declines in FF possibly due to the expectation that memory will decline with age (Lane & Zelinski, 2003); however, participants in the current study may still be too young to apply this heuristic to their own memory function. Moreover, a recent study with a similarly aged cohort and longitudinal timeframe (Hulur et al., 2015) did observe a correlation between memory complaints and OM, though this study had a considerably larger sample size (>15,000) and, therefore, possibly increased power to detect generally modest effects (Hertzog & Pearman, 2013).

Additional limitations include our separate linear mixed effects models approach, as several studies reporting covariation between SCC and OM used latent growth curve modeling (Hulur et al., 2015; Mascherek & Zimprich, 2011; Parisi et al., 2011; Snitz et al., 2015; Zimprich & Kurtz, 2015); which could be particularly useful as our sample ages and likelihood of variability in cognitive function increases. Also, the low test–retest reliability of the IQCODE is inconsistent with previous reliability measurements (Jorm & Jacomb, 1989; Jorm, Scott, Cullen, & MacKinnon, 1991; Jorm, 2004) and again may be partially due to the relatively healthy status and younger age of our sample.

Possible informant contamination effects related to informant anxiety, mood, and burden have also been associated with the IQCODE, but were not collected in this study. In addition, the FF of the MFQ and IQCODE measure different constructs (memory performance *vs.* cognitive/functional changes, respectively) and vary with regards to including a reference point when assessing cognitive function (no reference point for FF *vs.* "10 years ago" and "2–3 years ago" for IQCODE), thus restricting direct comparisons between the two measures. Lastly, the unique characteristics of our sample may limit our comparison to other studies as the majority of our participants were enrolled based on having a positive FH of AD and are highly educated compared to studies using community/population-based samples (Hertzog & Pearman, 2013).

The current study found that self- and informant-SCC in healthy late middle-aged adults did not show measurable longitudinal change, but were predictors of OM at baseline and longitudinal timeframes, respectively. Methodological and demographic characteristics of our study, particularly the relatively short longitudinal time-frame and younger mean age of our sample, may have contributed to our limited longitudinal findings as well as lack of an association between familial and genetic risk factors and SCC. Additional longitudinal follow-up will likely assist in further clarifying these relationships as our sample ages and more pronounced clinically relevant cognitive changes eventually emerge.

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