RESEARCH ARTICLE

Study partner-reported decline identifies cognitive decline and dementia risk

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Abstract

Objective: Identifying individuals at risk for cognitive decline, Mild Cognitive Impairment (MCI), and dementia due to Alzheimer's disease (AD) is a critical need. Functional decline is associated with risk and can be efficiently assessed by participants and study partners (SPs). We tested the hypothesis that SP-reported functional decline is an independent predictor of dementia risk and cognitive decline. **Methods:** In 1048 older adults in the Alzheimer's Disease Neuroimaging Initiative (ADNI), we measured associations between Everyday Cognition Scale scores (ECog, self- and SP-reported versions) and (1) baseline and longitudinal change in neuropsychological test (NPT scores) across multiple cognitive domains; (2) diagnostic conversion to MCI or dementia. Models included Mini Mental Status Exam (MMSE) score and ApoE ε4 genotype (APOE) as predictors. Model fits were compared with and without predictors of interest included. **Results:** SP-reported ECog was the strongest predictor of cognitive decline across multiple domains, as well as diagnostic conversion. Self-reported ECog was associated with baseline NPT scores in some cognitive domains, and diagnostic conversion to MCI in participants with biomarker evidence for AD (elevated brain β-amyloid, Aβ). Models including SP-reported ECog were significantly stronger at predicting outcomes. **Conclusions:** SP-reported functional decline is an independent indicator of cognitive decline and dementia risk, even when accounting for cognitive screening, genetic risk, demographics, and self-report decline. The results provide a rationale for greater utilization of SP-reported functional decline to identify those at risk for dementia due to AD and other causes.

Introduction

Identification of individuals at risk for cognitive decline, Mild Cognitive Impairment (MCI) and dementia, including dementia due to Alzheimer's disease (AD), is a critical need. In older adults, functional decline is associated with AD pathology,[1–3],and predicts future decline and disease progression.[4] Furthermore, preservation of everyday functioning is important to patients and their families.[5] Subjective functional decline can be measured by asking the individual him/herself or a study partner (SP) about recent changes in activities of daily living.

A number of validated instruments that measure subjective decline are used in AD clinical trials and research studies.[6–11] SP report of decline is associated with magnitude of cognitive impairment determined from neuropsychological test (NPT) assessment,[12,13] and with diagnosis of MCI and dementia due to AD.[10,13–16] SP report of impairment is associated moderately with abnormal levels of AD biomarkers, such as Positron Emission Tomography (PET) β-amyloid (Aβ) burden, and regional brain volume[1,17–19]; although some studies fail to find such a relationship.[20] Thus, there is accumulating evidence that the SP report of functional and cognitive abilities can provide important information for early identification of preclinical AD and for predicting objective cognitive status. The same relationship is not observed as consistently for self-reported subjective cognitive and functional decline, where factors such as depressed mood[21–23] and lack of awareness associated with dementia[13,24,25] limit its usefulness.

Although previous studies have examined the association between SP-reported cognitive and functional information and various outcomes related to cognitive decline and progression along the dementia disease continuum, the additional predictive power of SP-report compared to other predictors has not been established. Understanding this is important because it will indicate whether the SP report, in the absence of additional clinical measures, can help identify those at risk for or with disease. Such findings would support the approach of several initiatives to identify people at risk remotely, such as through registries,[26] including remotely collected, SP-reported Everyday Cognition scale (SP-ECog).[27] Determining the predictive value of SP-reported functional decline is likely to facilitate screening and recruitment for AD clinical trials, screening of older adults at risk for AD dementia and other dementias in various healthcare settings, and identification of individuals who are good candidates to receive future novel treatments. We investigated this issue using SP report of functional decline in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Novel aspects of our approach include (1) use of the ECog, which measures SP- and self-reported subjective decline in instrumental activities of daily living that map to multiple cognitive domains; (2) inclusion of cognitive screening tool (Mini Mental Status Exam, MMSE) and genetic risk (APOE) in our multivariable models; and (3) analysis of the association between baseline SP report of subjective decline and future decline in NPT scores across multiple domains. We tested the *a priori* hypotheses that: SP-ECog is significantly associated with baseline and longitudinal change in NPT scores, and diagnostic conversion from cognitively unimpaired (CU) to MCI or MCI to dementia. (2) SP-ECog is significantly associated with outcomes, even when accounting for self-reported ECog (Self-ECog), MMSE, APOE, and participant demographics; (3) Models without SP-ECog are significantly less powerful than those with SP-ECog at predicting outcomes; (4) SP-ECog is associated with cognitive decline and diagnostic conversion in Aβ+ participants. Analyses of associations in Aβ+ participants allow us to address the extent to which SP-report subjective decline, measured by ECog, can specifically identify cognitive decline, MCI, and dementia that is likely due to AD.

Methods

Participants

Data used in the preparation of this manuscript were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and NPT assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org. All ADNI data were downloaded from www.loni.usc.edu/ ADNI between September–November 2018. We included

all participants with Aβ PET imaging results, and completion of ECog (Table 1). Further details regarding ADNI inclusion and exclusion criteria can be found at http://adni.loni.usc.edu/methods/documents/.

Everyday cognition scale

The ECog includes 39 questions, asked of both the participant and the SP, that measure changes in functional activities compared to 10 years ago using a five point severity scale. Functional activities map to four cognitive domains.[7] Participants and SPs completed the ECog as part of their ADNI protocol: at baseline, month 6, and ongoing annual visits (new ADNI2 participants), or initial ADNI2 visit and ongoing annual visits (ADNI1 and ADNIGO follow-up participants). For analyses using longitudinal ECog, 844 participants with at least two self- and SP-ECog scores were included.

β-Amyloid (Aβ)

Full details of acquisition and analysis of ADNI florbetapir PET image data were previously described[28] and can be found at http://adni.loni.usc.edu/methods/. Briefly, 18F-AV45 (florbetapir) images were collected at multiple sites. Mean cortical standardized uptake value ratio (SuVR) was derived by normalizing average retention values of cortical regions to retention value of whole cerebellum. Aβ was dichotomized as positive or negative (SuVR> 1.11 or less than < 1.11, respectively) using previously established thresholds to identify the presence of Aβ pathology.[28,29]

Clinical diagnosis

Cognitively Unimpaired (CU) participants met ADNI inclusion criteria: MMSE scores of 24–30,[31] Clinical Dementia Rating (CDR) of 0 and memory box score of 0[6]; absence of major depressive disorder, memory dysfunction,[32] impairment in activities of daily living, MCI, or dementia; no memory complaints aside from those common to other normal subjects of that age range. MCI was defined using Petersen criteria.[33] Patients were required to demonstrate objective impairment on NPTs without evidence of impaired activities of daily living or dementia; scores of 24–30 on the MMSE; and 0.5 on the global CDR and CDR memory box score ≥ 0.5. Impairment on NPTs was defined as scores of 0.5-1.5 standard deviations below education-adjusted norms for early MCI and >1.5 standard deviations below education-adjusted norms for late MCI on the Logical Memory II subscale (Delayed Paragraph Recall) of the Wechsler Memory Scale–Revised,[32] Early MCI and late MCI participants were considered to be part of the MCI group for our

Table 1. Participants included in this study

	CU	MCI	Dementia	Total	*P*-value
Total N	420	482	146	1048	
Age, mean ± SD (range)	73.8 ± 5.79 (56.2–90.0)	72.4 ± 7.35 (55–91.4)	74.6 ± 8.21 (55.7–90.3)	73.3 ± 6.95 (55–91.4)	CU> MCI: **0.016** MCI < DEM: **0.002**
Female, *n* (%)	220 (52.4%)	197 (40.9%)	60 (41.1%)	477 (45.5%)	CU> MCI: **<0.001** MCI-DEM: 0.96
Education, mean ± SD (range)	16.5 ± 2.61 (6–20)	16.1 ± 2.83 (6–20)	15.7 ± 2.68 (9–20)	16.2 ± 2.74 (6–20)	CU> MCI: **0.04** MCI-DEM: 0.12
MMSE	29 ± 1.18 (24–30)	27.8 ± 1.76 (24–30)	23.1 ± 2.13 (19–28)	27.6 ± 2.5 (19–30)	CU> MCI: **<0.001** MCI> DEM: **<0.001**
ApoE ε4+	117 (27.9%)	238 (49.4%)	97 (66.4%)	452 (43.1%)	CU < MCI: *<0.001* MCI < DEM: **<0.001**
Aβ+, N (%)	135 (36.1%)	264 (61.7%)	125 (85.6%)	524 (50.0%)	CU < MCI: **<0.001** MCI < DEM: **<0.001**
SP-ECog, mean ± SD (range)	1.23 ± 0.335 (1–3.35)	1.95 ± 0.759 (1–3.97)	2.73 ± 0.662 (1.13–3.95)	1.77 ± 0.794 (1–3.97)	CU < MCI: **<0.001** MCI < DEM: **<0.001**
Self-ECog, mean ± SD (range)	1.41 ± 0.336 (1–2.74)	1.81 ± 0.56 (1–3.82)	1.89 ± 0.6 (1–3.66)	1.66 ± 0.531 (1–3.82)	CU < MCI: **<0.001** MCI-DEM: 0.14

CU, Cognitively Unimpaired; MCI, Mild Cognitive Impairment; DEM, Dementia; MMSE, Mini Mental Status Exam. *P*-values represent differences between indicated diagnostic groups, based on Mann–Whitney text for continuous variables or Chi-square test for categorical variables. *P* values less than 0.05 are indicated by bold italics.

analyses. Dementia was defined as memory complaint by the participant or SP that was confirmed by the SP, abnormal memory function documented by scoring below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale–Revised, MMSE between 20 and 26 (inclusive), CDR of 0.5 or 1, and NINCDS/ADRDA criteria[34] for probable AD.

Diagnostic conversion

Conversion from CU to MCI, and from MCI to dementia, were defined by the ADNI protocol. Briefly, ADNI site physicians reviewed current visit measures. When a conversion event was triggered, the site's clinical monitor reviewed the CDR for that visit. The monitor resolved any issues with the site Principal Investigator and instructed the site to reverse the conversion if incorrectly reported. Ron Petersen, clinical core Principal Investigator for ADNI, then reviewed scores or asked for the clinical monitor to resolve scoring issues. The Conversion Committee then reviewed the participant's diagnosis summary, progress report, and consensus diagnosis form. Differences in diagnosis were resolved.

Neuropsychological tests

Cognitive measures assessed included the MMSE,[30] Alzheimer's Disease Assessment Scale-cognitive subscale, 13-item version (ADAS13), delayed memory score from the ADAS13 (ADAS dMem),[33] immediate and delayed memory recall from the Wechsler Memory Scale (iLogMem, dLogMem), immediate and delayed Rey Auditory Verbal Learning Test (iAVLT, dAVLT),[34] Trail Making Test parts A and B (Trails A and Trails B),[35] Category Fluency,[36] and, Boston Naming Test.[37] Participants took NPTs according to the ADNI protocol (http://adni.loni.usc.edu/study-design/). Briefly, in ADNI1, all participants took NPTs at baseline; at months 3, 6, and 18; and at annual follow-up visits thereafter. Additionally, ADNI1 CU participants took NPTs at months 24 and 36; MCI participants took NPTs at months 12 and 24. In ADNIGO, eMCI participants took NPTs at screening, baseline, months 3 and 6, and annual follow-up thereafter. In ADNI2, CU and MCI participants took NPTs at baseline and 3 months, and annual follow-up thereafter. Dementia participants in ADNI 2 took NPTs at baseline and months 3, 6, and 18 months. In ADNI3, all participants took NPTs at baseline and months 24 and 48. Additionally, MCI and dementia participants took NPTs at months 12 and 36; and MCI participants took NPTs at annual follow-up thereafter.

APOE

*APOE ε*4 genotype was determined by blood test at ADNI screening visit. APOE was dichotomized as positive (at least one *APOE ε*4 allele) or negative (absence of any *APOE ε*4 alleles).

Statistical analysis

The objectives of the statistical analysis were to assess and compare magnitudes of the associations of age, education, MMSE, SP-ECog, Self-ECog, gender, and APOE with change in repeated NPTs, and, diagnostic conversion. Variables were compared between diagnostic groups using Mann–Whitney test for continuous variables and chi-square tests for categorical variables.

Associations with NPTs

We fit separate linear mixed effects models to each NPT score, stratified by diagnostic group. Each model included random intercepts and time effects, main effect terms for Self-ECog, SP-ECog, age, education, MMSE, gender and APOE status, and interactions of each predictor with time. The time by predictor interaction terms were used to assess the magnitude of the association of each predictor with change in NPT score. Trails A and B scores were log transformed and estimates back transformed to percentage effect. We also performed similar analyses in a cohort limited to Aβ+ participants. We accounted for multiple comparisons (multiple NPTs) using false discovery rate analysis.

Associations with diagnostic conversion

Weibull survival regression models were used to accommodate interval censored observations.[38] We did not observe the exact dates of conversion, only that the conversion happened between two study visits. To assess the associations of longitudinal changes in ECog with conversion, we obtained participant-specific changes in each ECog variable by fitting linear mixed effects models with random intercepts and slopes and time as the single predictor with each ECog variable as an outcome.

Likelihood ratio tests

For the Weibull survival models described above, three variations of each model were run (1) including all variables: Age, education, MMSE, SP-ECog, Self-ECog, gender, APOE; (2) excluding SP-ECog; (3) excluding Self-ECog, APOE, and MMSE. The relative predictive strength of the various models was assessed using Likelihood Ratio (LR) tests. All analyses were completed using SAS Version 9.4.

Results

Associations between subjective decline and neuropsychological test scores

Overall results

We measured associations between ECog and NPT scores (baseline and longitudinal change in scores) in CU and MCI participants. In both CU and MCI, higher (worse) SP-ECog scores were associated with greater decline in ADAS13, LogMem, and AVLT. In MCI, higher SP-ECog scores were also associated with greater decline in Boston Naming and Trails B. (Fig. 1A). We also found associations between ECog (self- and SP-reported) and baseline NPT test scores, summarized in Figure 1B. Besides ECog, additional variables were significantly associated with decline in some NPTs (Table 2).

Associations between subjective decline and NPT scores in Aβ+ participants

In order to determine whether ECog predicts cognitive decline in those at high risk for developing dementia due to AD, we examined associations between ECog and NPT scores in Aβ+ participants. In CU Aβ+ participants, higher SP-ECog scores were associated with greater decline in dLogMem, iAVLT, dAVLT, and Trails B. Conversely, higher Self-ECog scores were associated with lower levels of decline in Trails B (Fig. 1A). In MCI Aβ+ participants, higher SP-ECog scores were associated with greater decline in ADAS13, ADAS dMem, iLogMem, and dLogMem. Higher Self-ECog scores were associated with lower levels of decline in iAVLT. We also found associations between ECog (self- and SP-reported) and baseline NPT test scores in Aβ+ participants, summarized in Figure 1B.

Associations between subjective decline and diagnostic conversion

Overall results

SP-ECog was significantly associated with conversion from CU to MCI, and MCI to dementia (Table 3). In both cases, SP-ECog was the strongest predictor of conversion based on magnitude of Hazard Ratios. In contrast, Self-ECog was significantly associated with CU to MCI conversion, but not MCI to dementia conversion. Removing SP-ECog from the model resulted in a significant decrease in the predictive value of the model predicting CU to MCI conversion (LR = 27, $P < 0.001$) and of the model predicting MCI to dementia conversion (LR = 108, $P < 0.001$). Removing Self-ECog, MMSE, and APOE from the model, but retaining SP-ECog in the

model, resulted in a significant decrease in the model predictive power for predicting CU to MCI conversion (LR = LR = 14.8, $P = 0.002$), and MCI to dementia conversion (LR = 239, $P < 0.001$).

Associations between subjective decline and conversion in Aβ+ participants

In Aβ+ participants, Self-ECog but not SP-ECog was significantly associated with CU to MCI conversion (Table 3). Removing SP-ECog from the model did not result in a significant decrease in the predictive value of the model (LR = 3.0, $P = 0.082$). Removing Self-ECog, MMSE, and APOE from the model, but retaining SP-ECog in the model, resulted in a significant decrease in the model predictive power (LR = 11.9, $P = 0.008$). In Aβ+ participants, SP-ECog was significantly associated with MCI to dementia conversion (Table 3). A model excluding SP-ECog was significantly less powerful at predicting conversion to dementia than the full model (LR = 27, $P < 0.001$). A model excluding Self-ECog, MMSE, and APOE; but including SP-ECog, was not significantly different than the full model (LR = 3.9, $P = 0.27$).

Longitudinal ECog

Models including longitudinal change in Self-ECog and SP-ECog instead of baseline measures yielded similar results for all outcomes measured. The one exception was for the analysis of CU to MCI conversion. In this case, removing longitudinal Self-ECog, MMSE, and APOE from the model, but retaining longitudinal SP-ECog in the model, resulted in no significant decrease in the model predictive power (LR = 4.2, $P = 0.24$).

Discussion

The major findings of this study are: (1) SP-reported functional decline, measured using ECog, is associated with baseline cognition and cognitive decline across multiple domains; as well as diagnostic conversion to MCI or to dementia. The associations remain significant in multivariable models accounting for self-reported functional decline (Self-ECog), cognitive screening test (MMSE), genetic risk (APOE), and participant demographics. These results demonstrate that SP-reported functional decline adds predictive power over and above more objective measures. (2) Conversely, self-reported ECog is not significantly associated with cognitive decline across most domains, or with conversion from MCI to Dementia. Therefore, SP-reported decline is superior to self-report for identifying cognitive decline and dementia risk. (3) Associations between ECog and dementia risk-related

A. Associations with longitudinal change in NPT scores

	CU					MCI			
	all CU		Aβ+			all MCI		Aβ+	
	Self ECog	*SP ECog*	*Self ECog*	*SP ECog*		*Self ECog*	*SP ECog*	*Self ECog*	*SP ECog*
ADAS13	NS	**	*	NS		NS	**	NS	**
ADAS dMem	NS	NS	NS	NS		NS	NS	NS	**
iLogMem	NS	**	*	NS		NS	**	NS	**
dLogMem	NS	**	*	**		NS	NS	*	**
iAVLT	NS	**	NS	**		NS	**	**	NS
dAVLT	NS	**	NS	**		NS	**	NS	NS
Cat. Fluency	NS	NS	NS	NS		NS	NS	NS	NS
Boston Naming	NS	NS	*	NS		NS	**	NS	NS
Trails A	NS	NS	*	NS		NS	*	NS	NS
Trails B	NS	NS	**	**		NS	**	NS	NS

B. Associations with baseline NPT scores

	CU					MCI			
	all CU		Aβ +			all MCI		Aβ +	
	Self ECog	*SP ECog*	*Self ECog*	*SP ECog*		*Self ECog*	*SP ECog*	*Self ECog*	*SP ECog*
ADAS13	**	**	NS	NS		NS	**	NS	**
ADAS dMem	**	NS	**	NS		NS	**	NS	**
iLogMem	**	NS	NS	NS		NS	**	NS	*
dLogMem	NS	NS	NS	NS		NS	**	NS	**
iAVLT	**	NS	NS	NS		NS	**	NS	**
dAVLT	NS	NS	NS	NS		NS	**	NS	**
Cat. Fluency	**	NS	*	NS		NS	**	NS	**
Boston Naming	NS	NS	NS	NS		NS	NS	NS	NS
Trails A	NS	**	NS	NS		**	**	**	NS
Trails B	NS	**	NS	*		**	**	**	NS

Figure 1. Associations between Neuropsychological test scores and ECog. Associations with longitudinal change in NPT scores (A) or baseline NPT scores (B) are color-coded according to statistical significance in linear mixed effects models. Dark green (**): Higher (worse) ECog score associated with worse NPT score, $P < 0.001$, significant after multiple comparison correction. Light green (*): Higher (worse) ECog score associated with worse NPT score, $P < 0.05$, not significant after multiple comparison correction. Yellow (NS): No significant association between NPT score and ECog, $P > 0.05$. Pink (*): Higher (worse) ECog score associated with better NPT score, not significant after multiple comparison correction. Red (**): Higher (worse) ECog score associated with better NPT score, $P < 0.001$, significant after multiple comparison correction

Table 2. Associations between predictors and longitudinal change in NPT scores

	CU	MCI
ADAS13		Age, Female
ADAS dMem		Age, Female
iLogMem		Age
dLogMem		Age
iAVLT	Edu	Age, Female
dAVLT		Age
Category fluency		
Trails A	Male	Age
Trails B		

Results of linear mixed effects models measuring the associations between the variables of age, gender, education, APOE, and MMSE; and change in NPT scores (columns) broken down by diagnostic group (CU, MCI). Variables indicated in each cell are those that had a significant variable by time from baseline score interaction term for a given NPT, $P < 0.015$ (remained significant after multiple comparison adjustment). Edu, Education; Age, advanced age was associated with greater decline in NPT scores; APOE, APOE+ was associated with greater decline in NPT scores; MMSE, lower MMSE scores were associated with greater decline in NPT scores; Male, greater decline in NPTs in males; Female, greater decline in NPTs in females.

Table 3. Associations with Diagnostic conversion

Variable	Hazard ratio	95% CI
CU to MCI: All participants		
SP-ECog	**3.21***	1.83–6.83
Self-ECog	**3.10†**	1.57–7.80
APOE+	1.27	0.80–2.44
Age	1.03	0.98–1.10
MMSE	1.00	0.85–1.25
Edu	0.90‡	0.85–0.97
Female	0.72	0.51–1.20
CU to MCI: Aβ+ participants		
Self-ECog	**4.30†**	1.54–20.49
SP-ECog	1.79	0.96–4.68
APOE+	1.56	0.73–2.44
Gender	1.12	0.56–3.42
Age	1.07	0.99–1.21
Edu	0.96	0.88–1.11
MMSE	0.77	0.64–1.05
MCI to dementia: All participants		
SP-ECog	**3.11***	2.23–4.69
APOE+	**2.32†**	1.54–3.87
Female	**1.67†**	1.16–2.65
Edu	1.06‡	1.00–1.14
Age	1.02	1.00–1.05
Self- ECog	0.97	0.76–1.34
MMSE	**0.84†**	0.79–0.91
MCI to dementia: Aβ+ participants		
SP-ECog	**2.49***	1.72–4.02
Female	**2.07***	1.31–3.79
APOE+	**1.67***	1.04–2.33
Self- ECog	1.16	0.84–1.79
Edu	**1.10†**	1.02–1.21
Age	1.03	1.00–1.08
MMSE	**0.80***	0.75–0.89

Variables are listed in order of magnitude of Hazards Ratio. Edu, Education; CI, Confidence interval. Bolded values indicate significant associations, $*P < 0.001$, $†P < 0.01$, $‡P < 0.05$.

outcomes vary by Aβ status. This includes domain-specific associations between ECog and cognitive decline in Aβ+ participants, as well as greater predictive value of Self-ECog to identifying diagnostic conversion from CU to MCI in the Aβ+ subgroup. Taken together, these novel results provide a rationale for greater utilization of functional decline to identify those at risk for or with AD, and for development of improved methods to efficiently capture SP- and self-reported data.

Associations with NPTs

Previous studies found associations between subjective decline and baseline cognition,[13] or between cognitive complaints and NPT decline in CU and MCI.[20,39] Novel aspects of our study were identification of associations between subjective decline and decline in NPT scores across multiple cognitive domains; inclusion of many years of longitudinal NPT scores; use of the ECog, which measures changes in activities of daily living that map to multiple cognitive domains; and the use of multivariable models accounting for APOE, MMSE, and participant demographics.

Several interesting findings emerged from this approach. In CU, participants themselves more accurately identified their current memory and verbal fluency abilities compared to their SPs (Fig. 1B), but SPs were better than participants in identifying low baseline attention and executive function (Trails A and B), as well as predicting *decline* in overall cognition and memory (Fig. 1A). These results are novel and surprising, and do not support our *a priori* hypothesis that in CU participants, who are not likely to lack insight about their own functioning level,

participant self-report and SP-report would be equally predictive of cognitive status and decline. Our findings contrast those of,[40] which found that self-reported subjective cognitive concerns predict future cognitive decline in the Preclinical Alzheimer's Cognitive Composite (PACC). The differences may stem from differences in instruments used (ECog vs. Subjective Cognitive Complaints; individual NPTs vs. PACC) and in the study population.

In MCI, SP-ECog scores were significantly associated with most baseline and longitudinal scores. Thus, in MCI SP-report outperforms self-report in identifying cognitive status across multiple cognitive domains, including memory. Surprisingly, there were no significant associations between participants' self report of decline and actual decline in any NPTs for CU or MCI. (Fig. 1A). Our findings argue for greater reliance on SPs to recognize early changes in everyday functioning that map to future cognitive decline. Such information can be used to identify CU individuals at risk for cognitive decline for clinical trials and in various healthcare settings.

To determine the extent to which subjective decline, measured by ECog, specifically identifies cognitive decline associated with increased risk for AD, we measured the associations between ECog and NPT scores in Aβ+ participants. There were three major findings from these analyses. First, associations between SP-ECog and cognitive decline in Aβ+ CU closely matched the associations found in the entire MCI group. This can be explained by the fact that Aβ+ CU have worse prognoses in terms of cognitive decline, and therefore more closely resemble MCI participants.

Second, in Aβ+ participants, for some NPTs, participants who self-reported greater decline had significantly *less* objective decline in NPT scores over time. In MCI, this inverse relationship between self-reported decline and actual decline in MCI is likely due to loss of insight about one's own level of functioning. However, the inverse relationship between self-report decline and actual decline in Aβ+ CU is surprising, and its cause requires further exploration. Aβ+ CU older adults are unlikely to have impairments affecting their insight about recent changes in their functional abilities. Their failure to report changes that reflect actual changes in cognition may therefore be due to other factors, such as anxiety or denial about recent changes in function.

Third, in Aβ+ MCI, significant associations between SP-reported ECog and decline in NPT scores were restricted to ADAS13 and a few memory tests. This contrasts with findings in the overall MCI cohort, in which SP-ECog is also significantly associated with decline in executive function (Trails) and lexical retrieval (Boston Naming). This finding may reflect the fact that the Aβ+ MCI groups are more amnestic than the overall MCI cohort. This idea is described in more detail below.

A major goal of this work was to assess the predictive power of SP-ECog in relation to other variables. We found that in MCI, advanced age was significantly associated with greater decline in multiple NPTs, and females had significantly greater decline in some NPTs (Table 2). Conversely, MMSE, APOE, and education had limited predictive power, as shown by the lack of significant associations between these variables and longitudinal change in NPTs in our multivariable models. Therefore, in predicting future cognitive decline, subjective decline eclipses the contribution of genetic risk and cognitive screening instrument in identifying older adults at risk. These findings, argue compellingly for the use of SP-reported decline to identify older adults at risk for cognitive decline, including CU individuals.

Associations with diagnostic conversion

Previous reports demonstrate that SP report of memory problems could distinguish CU from dementia due to AD and predict future diagnosis of AD dementia.[41,42] Few studies have explored the relationship between ECog and diagnostic conversion.[14] In addition to the use of the ECog, the novelty of our multivariable approach was to identify the relative predictive power of subjective decline compared to other variables. We found that SP-ECog was the strongest predictor of diagnostic conversion from CU to MCI or from MCI to dementia, compared to other variables. Furthermore, removing SP-ECog from the models resulted in a significant decrease in the predictive power of both models.

In order to determine the ability of SP-ECog and other predictors to specifically identify risk of conversion to MCI or dementia likely due to AD, we performed the same analyses in only Aβ+ participants. In the Aβ+ subgroup, only Self-ECog significantly predicted conversion to MCI, whereas, SP-ECog was significantly associated with conversion from MCI to dementia. Therefore, self report of subjective decline has a unique ability to predict conversion in Aβ+ CU. No variables other than ECog were significantly associated with CU to MCI conversion. The results argue for greater utilization of both self-reported and SP-reported subjective decline to identify older adults at risk for MCI likely due to AD.

What is the underlying cause of different results when we consider only Aβ+ individuals? A simple interpretation is that, since Aβ+ participants decline more than Aβ- participants, the association between predictors and outcomes is stronger in Aβ+ participants. As described above, this could explain why SP-ECog is more strongly associated with cognitive decline in Aβ+ CU. But why, then, is SP-ECog more strongly associated with diagnostic conversion to MCI in the overall cohort versus the Aβ+

subgroup? SP-ECog may be detecting changes that lead to decline in cognition and conversion to MCI that is not due to AD, but is instead due to other causes. A related idea is that the ability of study partners to detect functional decline is somewhat cognitive domain specific. Although all ADNI MCI participants meet criteria for amnestic MCI, Aβ- participants are likely to be less amnestic than those who are Aβ+. SPs may be better able to predict conversion from CU to MCI in Aβ- participants because SPs can detect decline in domains other than memory, such as language, and attention. Some recent evidence supports the idea of domain specificity in subjective decline.[43,44] Further studies exploring the relationship between SP-reported subjective decline across different domains and AD related outcomes, including biomarkers other than Aβ, are necessary to address these issues.

Possibility for remote collection

These results are especially important in the light of recent evidence for feasibility and validity of remotely collected ECog.[26,27] Since remote assessments can be administered efficiently to a large number of individuals using few resources, they could be used for longitudinal monitoring in clinical trials. Furthermore, use of SP-reported decline provides the opportunity to identify decline in older adults reluctant to seek care themselves, has low influence from cultural or educational backgrounds, and can be applied widely in the community without requiring any formal clinical setting.[41,45] A crucial next step is to validate remote assessments against traditional in-clinic assessments; such studies are ongoing using an online platform for remote assessments of participants and SPs.[27]

Limitations

We limited our subjective measure to ECog. In future studies, it will be important to include additional subjective measures, such as cognitive complaints, memory concerns, and behavioral and neuropsychiatric symptoms. These may confer additional predictive power compared to subjective decline.[46,47] Clinical diagnosis of CU and MCI in ADNI relies on Clinical Dementia Rating (CDR) scores, which are derived in part from SP- and self report of functional impairment. This could confound the association between ECog and diagnostic conversion. We did not explore the ability of ECog to predict other important biomarkers and risk factors, such as Tau and functional connectivity, which have been found to be significantly associated with self-reported subjective cognitive decline, concerns, and complaints.[48,49] Finally, lack of diversity

and the specific inclusion/exclusion criteria in ADNI somewhat limit generalizability of our results.

Conclusions

SP-ECog significantly predicts cognitive decline across multiple domains, and diagnostic conversion to MCI or to dementia. SP-ECog confers additional, independent predictive power over and above Self-ECog, cognitive screening (MMSE), APOE, and demographics. Analyses limited to Aβ+ older adults confirm the predictive power of subjective decline in those at risk for AD, and suggest some cognitive-domain specificity associated with subjective decline. These findings have important implications for using self- and SP-reported measures to identify those at risk for cognitive decline, MCI, dementia, and dementia due to AD in clinical research and healthcare settings.

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Author Contributions

RLN, JN, PSI, RSM, and MWW contributed to the conception and design of the study. RLN, CJ, and JN contributed to the analysis of data. RLN drafted a significant portion of the manuscript and figures. Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni. usc.edu/wp-content/uploads/how_to_apply/ADNI_Ac knowledgement_List.pdf.

Conflicts of Interest

RLN, JN, PSI, JN, and RSM have no potential conflicts of interest to disclose related to the work in this manuscript. MWW reports personal fees from Bioclinica, personal fees from Cerecin/Accera, personal fees from Genentech, grants and personal fees from NIH, personal fees from Indiana University, personal fees from CHU Toulouse, personal fees from St. George University, personal fees from Eli Lilly, personal fees from Roche, personal fees from Lynch Group GLC, personal fees from Dolby Family Ventures, personal fees from Nestec/Nestle, personal fees from Health & Wellness Partners for American Academy of Neurology Conference, personal fees from AC Immune, personal fees from Alzheimer's Association, personal fees from Merck, personal fees from Bionest Partners, personal fees from Alzheon, Inc., personal fees from University of Tokyo, personal fees from Australian Catholic University, personal fees from University of Melbourne, personal fees from National Cntr for Geriatrics & Gerontology (Japan), grants from Department of Defense (DOD), grants from Johnson & Johnson (J&J), grants from Connie & Kevin Shanahan, grants from General Electric Research Labs (GE), grants from PCORI, grants from California Dept. of Public Health, grants from VUmc Vanderbilt University Medical Center, grants from University of Michigan, grants from Ray & Dagmar Dolby Fund, grants from Biogen, grants from Hillblom Foundation, grants from Stroke Foundation, grants from Siemens, grants from Veterans Administration. All relationships stated above are outside the submitted work.

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