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Research Article

Clinical utility of self- and informant-reported memory, attention, and spatial navigation in detecting biomarkers associated with Alzheimer disease in clinically normal adults

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Abstract

Objective: Preclinical Alzheimer disease (AD) has been associated with subtle changes in memory, attention, and spatial navigation abilities. The current study examined whether self- and informant-reported domain-specific cognitive changes are sensitive to AD-associated biomarkers. **Method:** Clinically normal adults aged 56–93 and their informants completed the memory, divided attention, and visuospatial abilities (which assesses spatial navigation) subsections of the Everyday Cognition Scale (ECog). Reliability and validity of these subsections were examined using Cronbach's alpha and confirmatory factor analysis. Logistic regression was used to examine the ability of ECog subsections to predict AD-related biomarkers (cerebrospinal fluid (CSF) $ptau_{181}/A\beta_{42}$ ratio ($N = 371$) or hippocampal volume ($N = 313$)). Hierarchical logistic regression was used to examine whether the self-reported subsections continued to predict biomarkers when controlling for depressive symptomatology if available ($N = 197$). Additionally, logistic regression was used to examine the ability of neuropsychological composites assessing the same or similar cognitive domains as the subsections (memory, executive function, and visuospatial abilities) to predict biomarkers to allow for comparison of the predictive ability of subjective and objective measures. **Results:** All subsections demonstrated appropriate reliability and validity. Self-reported memory (with outliers removed) was the only significant predictor of AD biomarker positivity (i.e., CSF $ptau_{181}/A\beta_{42}$ ratio; $p = .018$) but was not significant when examined in the subsample with depressive symptomatology available ($p = .517$). Self-reported memory (with outliers removed) was a significant predictor of CSF $ptau_{181}/A\beta_{42}$ ratio biomarker positivity when the objective memory composite was included in the model. **Conclusions:** ECog subsections were not robust predictors of AD biomarker positivity.

Keywords: preclinical Alzheimer disease; memory; attention; spatial navigation; Everyday Cognition Scale; biomarkers

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Introduction

Alzheimer disease (AD) is characterized by the deposition of amyloid plaques and neurofibrillary tangles in the brain, as well as early neurodegeneration of specific regions, such as the hippocampus, and these neuropathologic changes may be detected decades before the onset of clinical symptoms (Dubois et al., 2016; Jack et al., 2018). The stage at which a person is clinically normal but exhibits AD-related neuropathological changes is referred to as preclinical AD and is associated with increased risk of developing symptomatic AD (Davatzikos et al., 2011; Dubois et al., 2016; Dumurgier et al., 2017; Jack et al., 2018; Sperling et al., 2011). Although people with preclinical AD perform within expected limits (e.g., within 1.5 standard deviations of the age-corrected mean) on standardized psychometric tasks, there are subtle observable cognitive changes associated with this stage (Sperling et al., 2011). Previous work suggests that subtle changes in memory, attention, and spatial navigation abilities are associated with concurrent preclinical status and with risk of clinical progression.

Subtle changes in hippocampal-based episodic memory have been identified in preclinical AD cross-sectionally and as a predictor of clinical progression (for a review, see Collie & Maruff, 2000). Meta-analyses have found that amyloid burden is associated with concurrent episodic memory and subsequent decline in episodic memory in clinically normal older adults (Baker et al.,

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2017; Hedden et al., 2013). Notably, Hedden and colleagues (2013) observed a greater association of amyloid burden with episodic memory than global cognition.

It has been postulated that a breakdown in the attention network is directly associated with a decline in memory ability in AD (Balota & Duchek, 2015). Cross-sectionally, attention has been associated with CSF $A\beta_{42}$ and can discriminate between clinically normal older adults and early-stage AD (Aschenbrenner et al., 2015; Hutchison et al., 2010; Millar et al., 2017). Longitudinally, CSF $A\beta_{42}$ and total tau have been associated with declines on attention tasks (Aschenbrenner et al., 2015; Millar et al., 2017). Additionally, Balota and colleagues (2010) observed that attention predicted progression to symptomatic AD from clinical normality. Collectively, these findings suggest that attention is affected during the earliest AD stages.

Although there is a body of literature examining spatial navigation in both symptomatic AD and mild cognitive impairment (MCI; Cushman et al., 2008; Hort et al., 2007; Weniger et al., 2011), there is less information available on changes in spatial navigation in preclinical AD. Work from our group demonstrated that performance on a computerized spatial navigation task was associated with CSF $A\beta_{42}$ and $ptau_{181}$ in clinically normal older adults (Allison et al., 2016, 2019). Longitudinally, performance on this task was a predictor of clinical progression to symptomatic AD from clinical normality (Levine et al., 2020).

Due to the increasing prevalence of AD (Alzheimer's Association, 2021), there is a need for a widely distributable screening measure for identifying those at increased risk of developing symptomatic AD. Current methods (i.e., lumbar puncture, PET, MRI, and blood markers) used to assess neuropathological changes associated with disease progression are oftentimes invasive and/or expensive (Jack et al., 2018). Thus, these methods may not be accessible to people with limited finances or those living in rural areas with inadequate resources. Although standard neuropsychological and experimental tasks assessing memory, attention, and/or spatial navigation abilities are not invasive, they may not represent the most time- and cost-effective measures as they frequently require individuals to travel to a clinic or research laboratory. There is an emerging body of literature demonstrating potential utility of computerized cognitive assessment in preclinical AD (for a review, see Öhman et al., 2021); however, this requires participants to have access to expensive devices such as personal computers, smart phones, or tablets. Questionnaires are potentially less time consuming (e.g., typically taking 5–10 minutes), can require fewer materials to administer, and can be adjusted to ask both about current deficits and changes over time. Importantly, questionnaires are particularly accessible for individuals without the technology required for digital assessment and can be sent via mail or conducted over the phone. An easily distributable, time- and cost-effective screening tool that can be completed remotely would be a more ideal metric for identifying individuals in the population at the highest risk of AD. Furthermore, this tool could help streamline use of more conclusive biomarker-based procedures. As such, questionnaires assessing difficulties and/or changes in the domains sensitive to preclinical AD represent a potential screening tool for AD pathology.

In terms of preclinical AD samples, previous literature has primarily focused on subjective memory changes, with a significantly smaller body of literature examining subjective spatial navigation change and, to our knowledge, there is no published work examining subjective attention change. Self-reported memory decline has been associated with CSF biomarker burden and hippocampal neurodegeneration (e.g., Cantero et al., 2016; van der Flier et al., 2004; but see, Buckley et al., 2013; Kawagoe et al., 2019). Self- and informant-reported memory declines predict clinical progression from preclinical to symptomatic AD (e.g., Buckley et al., 2016; Ferreira et al., 2017; Rönnlund et al., 2015). Past research suggests that informant-reported memory may provide novel information to self-reported memory (Bellaali et al., 2021; Yim et al., 2017).

In terms of spatial navigation, self-reported current spatial navigation ability differentiated healthy older adult controls from cognitively impaired groups (Cerman et al., 2018). In addition, self-reported sense of direction has been associated with objective spatial navigation performance (Mitolo et al., 2015). Our group's work has yielded equivocal results; two cross-sectional studies observed an association between self-reported spatial navigation and CSF $A\beta_{42}$ in clinically normal older adults, but a longitudinal study failed to find an association between AD-associated biomarkers and change in self-reported spatial navigation ability (Allison et al., 2018, 2019; Levine et al., 2022). Notably, our group previously developed reliable and valid self- and informant-report questionnaires assessing change in navigation ability, wherein the self-reported questionnaire was significantly associated with concurrent CSF $A\beta_{42}$, but the informant-report was not (Allison et al., 2019). Importantly, the questionnaires did not show practice effects, whereas the learning phase of an objective cognitive mapping task did.

The Everyday Cognition Scale (ECog) represents a well-established, validated, and accessible self- and informant-reported questionnaire that has demonstrated utility in measuring cognitive change in the preclinical population and assesses three cognitive domains affected during the preclinical stage (i.e., memory, attention, and spatial navigation; Farias et al., 2008). Additionally, an online version of the self-reported ECog has been validated (Howell et al., 2021, 2022). Self- and informant-reported total ECog has been associated with clinical progression from clinical normality to symptomatic AD and with objective cognitive performance (Banh et al., 2021; Nosheny et al., 2019). Decline on the ECog has been associated with smaller superior temporal volumes bilaterally and greater accumulation of white matter hyperintensities in the temporal and parietal lobes over time in clinically normal older adults (Morrison et al., 2022, 2023). The short form of the self-reported ECog has been associated with PET amyloid positivity in individuals with MCI or dementia (Tsoy et al., 2021). In addition, the memory, attention, and spatial navigation subsections of the ECog were correlated with hippocampal volume in a sample that included clinically normal, MCI, and dementia participants (Farias et al., 2013). Additionally, the self-reported memory subsection was correlated with PET amyloid in a sample of clinically normal older adults and individuals with early-stage probable AD (Hsu et al., 2017). Another study identified individual self- and informant-reported items that were sensitive to progression from clinical normality to MCI (Marshall et al., 2014). Longitudinally, the informant-reported memory and spatial navigation subsections were associated with functional disability in participants who were clinically normal or MCI at baseline (Lau et al., 2015).

When examining subjective cognitive change as a potential screening measure, it is critical to consider additional, non-AD-related factors that may influence subjective reporting. Depression is one such factor that has been associated with self-reported and objective measures of cognitive ability. Notably, one study found that self-reported prospective memory and objective prospective memory were highly correlated in

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participants with low levels of memory complaints, but not participants with high levels of complaints (Zeintl et al., 2006). Instead, in the high-complaint group, self-reported prospective memory was associated with depressive symptomatology (Zeintl et al., 2006). This suggests a potential moderating effect of depressive symptoms on the association of self-reported memory and objective ability. Additionally, preclinical AD has been associated with increased risk of developing depression (Harrington et al., 2017). Given the association between depressive symptoms and self-reported cognition and the association between depression and the preclinical stage of AD, it is relevant to consider whether associations between self-reported cognitive change and preclinical AD-related biomarkers are independent of depressive symptoms. Because depression is associated with both preclinical AD and subjective cognition, it is central to examine whether endorsing both greater depressive symptoms and subjective cognitive complaints would lead to an additive ability to predict AD biomarker burden.

The existing literature examining self- and informant-reported cognitive change in preclinical AD has largely focused on global cognition rather than domain-specific cognition; as such, it is currently unclear whether questionnaire-based assessment of domain-specific cognitive change may represent an effective screening tool for preclinical AD. The first aim of the current study was to assess the reliability and validity of the ECog memory, attention, and spatial navigation subsections. The second aim was to examine the ability of ECog subsections to predict CSF $ptau_{181}/A\beta_{42}$ ratio or hippocampal volume biomarker positivity. Thirdly, we examined whether self-reported change continued to predict biomarker positivity when controlling for depressive symptomatology. We also assessed the interaction between self-reported cognitive change and depressive symptoms in predicting AD biomarkers in order to determine whether individuals with more depressive symptoms exhibited a stronger association between self-reported change and AD biomarker burden. Lastly, we examined neuropsychological composites of the same or similar domain to the ECog (e.g., memory, executive function, and visuospatial abilities) to assess whether subjective and objective measures differed in their ability to identify biomarker positivity.

Methods

Participants

Data used in this manuscript were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database on January 10, 2021 (adni.loni.use.edu). The ADNI was established in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner. The primary goal of ADNI is to test whether serial MRI, PET, and other biological markers, as well as clinical and neuropsychological assessment, can be combined to measure the progression of AD. All procedures were approved by local IRBs and participants provided informed consent to all procedures in accordance with the Helsinki Declaration. For further information, see: www.adni-info.org. The current study included all clinically normal participants (Clinical Dementia Rating Scale® = 0; Morris, 1993) within (±) 1 year of ECog (absolute value $m = 40.07$ days, $SD = 36.25$ days, absolute value range = 0–271 days, full range = −271 to 0 days) who completed the ECog and had CSF data available within 2 years of completing the ECog. Their informant data were included as well, when available. There were no further exclusionary criteria.

Everyday cognition scale

The ECog is a 39-item questionnaire, with self- and informant-reported versions, that assesses changes in functional activities across six cognitive domains (memory, language, visuospatial abilities, planning, organization, and divided attention) compared to 10 years earlier (Farias et al., 2008). The participant and informant ECog memory (eight items), divided attention (four items), and visuospatial abilities (seven items which assess spatial navigation ability) subsections were considered for the purposes of this study given evidence that these cognitive domains are impacted by preclinical AD. Ratings were made on a four-point Likert scale: 1 = better or no change compared to 10 years earlier, 2 = questionable/occasionally worse, 3 = consistently a little worse, 4 = consistently much worse. Items were averaged within each domain to include participants and informants who skipped items and, therefore, maximize sample size. When a participant had completed multiple ECogs, the first available was used.

Geriatric Depression Scale: short form (GDS)

The GDS is a 15-item self-reported questionnaire of depressive symptomatology. The GDS has strong reliability and validity (Sheikh & Yesavage, 1986; Herrmann et al., 1996; Lesher & Berryhill, 1994). The GDS was included if collected within thirty days of the ECog ($N = 197$; absolute value $m = 18.95$ days, $SD = 10.13$ days, full/absolute value range = 0–29 days).

Cerebrospinal fluid (CSF)

CSF collected by ADNI were analyzed using Elecsys immunoassays, following the Roche Study Protocol at the UPenn/ADNI Biomarker Laboratory as previously described (Bittner et al., 2016). CSF data were included if collected within (±) 2 years of completing the ECog (absolute value $m = 27.76$ days, $SD = 76.98$ days, absolute value range = 0–688 days, full range = −404 to 688 days). The sample used in CSF analyses included 371 participants and 366 informants.

Structural MRI

ADNI 3T MRI acquisition and pre-processing methods have been described (http://adni-info.org; Jack et al., 2008). MRI data were used if collected within (±) 2 years of completing the ECog (absolute value $m = 35.99$ days, $SD = 78.83$ days, absolute value range = 0–728 days, full range = −728 to 397 days). The hippocampus was the region-of-interest given its association with preclinical AD (Csernansky et al., 2005). The FreeSurfer image analysis was used for image processing and hippocampal delineation (Fischl et al., 2002). Volumetric data obtained through FreeSurfer procedure are highly correlated with manually generated volumes (Desikan et al., 2006; Fischl et al., 2002). Volumes were summed across hemispheres and estimated intracranial volume was used to adjust volumes for body size differences using an analysis of covariance approach (Buckner et al., 2004). The sample in hippocampal volume analyses included 313 participants and 309 informants.

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Table 1. Participant sample based on CSF $ptau_{181}/A\beta_{42}$ ratio

	Total sample	Biomarker normal	Biomarker positive
N	371	211	160
Gender (m/f)	154/217	94/117	60/100
Race (White/Black/American Indian/Asian/More than one race)	336/19/2/5/9	186/14/2/4/5	150/5/0/1/4
Ethnicity (% Non-Hispanic)	94.88%	93.84%	96.25%
Age (years) (mean (*SD*))*	73.03 (6.76)	71.34 (6.28)	75.25 (6.75)
Age range (years)	56–93	56–93	56–92
Education (years) (mean (*SD*))	16.67 (2.39)	16.86 (2.37)	16.43 (2.40)
Education range (years)	10–20	10–20	6–20
Self-reported memory (*N*; mean (*SD*))*	371; 1.65 (.51)	211; 1.60 (.52)	160; 1.71 (.49)
Self-reported attention (*N*; mean (*SD*))*	371; 1.51 (.56)	211; 1.46 (.54)	160; 1.58 (.58)
Self-reported navigation (*N*; mean (*SD*))	370; 1.15 (.25)	210; 1.14 (.24)	160; 1.17 (.25)
Informant-reported memory (*N*; mean (*SD*))	366; 1.33 (.40)	207; 1.35 (.42)	159; 1.31 (.38)
Informant-reported attention (*N*; mean (*SD*))	364; 1.29 (.48)	206; 1.28 (.49)	158; 1.30 (.47)
Informant-reported navigation (*N*; mean (*SD*))	366; 1.07 (.16)	207; 1.06 (.13)	159; 1.08 (.19)
Objective memory (*N*; mean (*SD*))*	371; 1.07 (.60)	211; 1.13 (.59)	160; .98 (.60)
Objective executive function (*N*; mean (*SD*))*	371; .94 (.84)	211; 1.11 (.84)	160; .72 (.78)
Objective visuospatial (*N*; mean (*SD*))	371; .20 (.64)	211; .22 (.63)	160; .16 (.65)
Geriatric Depression Scale (*N*; mean (*SD*))	197; .67 (1.01)	90; .67 (.83)	107; .66 (1.13)
CSF $ptau_{181}/A\beta_{42}$ ratio (*N*; mean (*SD*))*	371; .025 (.019)	211; .013 (.003)	160; .041 (.019)

Note. Biomarker normal status indicated by CSF $ptau_{181}/A\beta_{42}$ ratio ≤ 0.0198; Biomarker positive status indicated by CSF $ptau_{181}/A\beta_{42}$ ratio>0.0198; * indicates a significant difference between groups ($p < .05$).

Table 2. Participant sample based on hippocampal volume

	Total sample	Biomarker normal	Biomarker positive
N	313	208	105
Gender (m/f)*	126/187	74/134	52/53
Race (White/Black/American Indian/Asian/More than one race)	282/18/2/5/6	186/12/2/4/4	96/6/0/1/2
Ethnicity (% Non-Hispanic)	94.89%	93.33%	98.10%
Age (years) (mean (*SD*))*	72.84 (6.65)	70.95 (5.94)	76.60 (6.40)
Age range (years)	56–93	56–85	60–93
Education (years) (mean (*SD*))	16.59 (2.43)	16.59 (2.36)	16.60 (2.57)
Education range (years)	6–20	10–20	6–20
Self-reported memory (*N*; mean (*SD*))	313, 1.65 (.50)	208, 1.61 (.49)	105, 1.71 (.52)
Self-reported attention (*N*; mean (*SD*))	313, 1.51 (.58)	208, 1.50 (.57)	105, 1.53 (.59)
Self-reported navigation (*N*; mean (*SD*))	312, 1.15 (.25)	207, 1.13 (.23)	105, 1.19 (.28)
Informant-reported memory (*N*; mean (*SD*))	309, 1.35 (.40)	205, 1.34 (.42)	104, 1.35 (.37)
Informant-reported attention (*N*; mean (*SD*))	307, 1.31 (.51)	204, 1.29 (.51)	103, 1.34 (.51)
Informant-reported navigation (*N*; mean (*SD*))	309, 1.07 (.15)	205, 1.07 (.14)	104, 1.08 (.17)
Objective memory (*N*; mean (*SD*))*	313, 1.09 (.60)	208, 1.19 (.57)	105, .90 (.62)
Objective executive function (*N*; mean (*SD*))*	313, .933 (.85)	208, 1.10 (.82)	105, .60 (.85)
Objective visuospatial (*N*; mean (*SD*))*	313, .20 (.64)	208, .25 (.59)	105, .10 (.73)
Geriatric Depression Scale (*N*; mean (*SD*))	168, .70 (1.03)	110, .61 (.86)	58, .86 (1.29)
Hippocampal volume (cm^3) (*N*; mean (*SD*))*	313, 7475.68 (774.38)	208, 7902.57 (524.74)	105, 6630.02 (405.51)

Note. Biomarker normal status indicated by top two tertiles of sample based on hippocampal volume; Biomarker positive status indicated by bottom tertile of sample based on hippocampal volume; * indicates a significant difference between groups ($p < .05$).

Defining biomarker positivity

CSF $ptau_{181}/A\beta_{42}$ ratio with $a > 0.0198$ cutoff was used to identify biomarker positivity as this is highly associated with PET amyloid (Schindler et al., 2018). Using this methodology, 160 participants were categorized as biomarker positive and 211 participants were categorized as biomarker normal (Table 1). Of note, there is not an established cutoff to indicate preclinical status using hippocampal volume. Thus, when considering the hippocampus as a dichotomous marker of preclinical status, participants with volumes in the lowest tertile of the total sample were considered to be biomarker positive and participants with hippocampal volumes in the highest two tertiles were considered biomarker normal. Using this methodology, 105 participants were categorized as biomarker positive and 208 participants were categorized as biomarker normal (Table 2). Fifty-three participants were considered biomarker positive based on both biomarker measures.

Neuropsychological assessment

Memory, executive function, and visuospatial standardized composite scores were previously derived and validated using the ADNI neuropsychological battery (Choi et al., 2020; Crane et al., 2012; Gibbons et al., 2012). The memory composite was derived using confirmatory factor analyses (for details on psychometric development, see Crane et al., 2012) and included the Rey Auditory Verbal Learning Test (Rey, 1964), AD Assessment Schedule-Cognition list learning task (Mohs et al., 1997), Mini-Mental State Examination word recall (Folstein et al., 1975), and immediate and delayed recall on the Logical Memory subtest (Wechsler, 1987). The executive function composite was derived using item response theory (for details on psychometric development, see Gibbons et al., 2012) and included WAIS-R Digit Symbol Substitution (Wechsler, 1981), WAIS-R Digit Span Backwards (Wechsler, 1981), Trails A and B (Reitan & Wolfson, 1985),

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Category Fluency (Morris et al., 1989), and Clock Drawing (Goodglass & Kaplan, 1983). The visuospatial composite was derived using item response theory (for details on psychometric development, see Choi et al., 2020) and included a five-point clock copy (Goodglass & Kaplan, 1983), MMSE interlocking pentagon copy (Folstein et al., 1975), and ADAS-Cog constructional praxis (Mohs et al., 1997). Neuropsychological composite data were included if collected within (±) 1 year of completing the ECog (absolute value $m = 14.85$ days, $SD = 68.70$ days, absolute value range = 0–365 days, full range = −365 to 0 days).

Statistical analyses

Reliability and validity

Internal consistency of each ECog subsection was assessed using Cronbach's alpha. Confirmatory factor analyses assuming three-factor and one-factor models separately for the self- and informant-reported questionnaires were used to examine validity. We hypothesized that both self and informant models would support a three-factor structure in that each questionnaire will represent a separate factor. This would suggest that the questionnaires are measuring three separable cognitive functions. Model fit was evaluated using the comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Using previously published criteria, good fit was defined by CFI > .95, RMSEA < .06, and SRMR < .06 (Hu & Bentler, 1999). Acceptable fit was defined by CFI > .90, RMSEA < .08, and SRMR < .08 (Brown & Cudeck, 1993; Brown, 2006).

Predictive ability of questionnaires and neuropsychological composites

Logistic regression analyses were conducted using IBM SPSS Statistics 28. These analyses were conducted to determine whether ECog subsections and neuropsychological composites predicted biomarker positivity defined by either CSF $ptau_{181}/A\beta_{42}$ or hippocampal volume. Self- and informant-reports of the same domain were summed to create a combined subsection score, and this combined score was entered as a predictor in the logistic regression models. To compare self-reported and objective measures of the same or similar cognitive domain (i.e., memory, attention/executive functioning, and spatial navigation/visuospatial ability), both were included in the same model. Age, sex, and education were covariates in all models.

Consideration of depressive symptoms

If the self-reported ECog subsection was significant in the initial logistic regression model, a four-step hierarchical logistic regression was used to examine the unique predictive information provided by self-reported subsection when controlling for depressive symptoms. The dependent variable was CSF $ptau_{181}/A\beta_{42}$ or hippocampal volume biomarker positivity. In step one, demographic variables of age, sex, and education were entered as covariates. In step two, the subsection of interest was added to the model (i.e., memory, attention, or spatial navigation). In step three, depressive symptomatology was added to the model. Finally, the interaction between the ECog subsection and depressive symptoms was added to the model in step 4.

Predictor variables

For all logistic regression analyses, predictors were z-scored within our sample in order to obtain standardized beta coefficients, as well as to aid in interpretation and comparison of slopes across regression models.

Table 3. Internal consistency of ECog subsections

	α (95% CI)
Self-reported memory ($N = 371$)	.85 (.83–.88)
Self-reported attention ($N = 371$)	.85 (.83–.88)
Self-reported spatial navigation ($N = 370$)	.74 (.71–.78)
Informant-reported memory ($N = 366$)	.87 (.84–.89)
Informant-reported attention ($N = 364$)	.89 (.87–.91)
Informant-reported spatial navigation ($N = 366$)	.71 (.67–.75)

Note. α = Cronbach's Alpha; CI = Confidence Interval.

Outliers

Variables greater than three standard deviations from the group mean were identified as outliers. Results were the same with and without outliers, unless otherwise specified.

Results

Reliability

The self- and informant-reported memory and attention subsections demonstrated good internal consistency using Cronbach's alpha, whereas self- and informant-reported spatial navigation subsections demonstrated fair internal consistency (Table 3).

Validity

A CFA was conducted to assess whether self-reported ECog memory, attention, and spatial navigation were loaded onto three independent factors. Model fit indices were good (CFI = .956, RMSEA = .059) or acceptable (SRMR = .083) for the hypothesized latent structure, but the χ^2 test indicated potential model misspecification ($\chi^2(149) = 340.246$, $p < .001$). Additionally, a one-factor model was considered, assuming all self-reported questionnaires converged onto a single factor; however, model fit was poor (CFI = .876, RMSEA = .098, SRMR = .108, $\chi^2(152) = 695.991$, $p < .001$). Chi-square difference testing indicated that self-reported one- and three-factor models were significantly different ($\chi^2(3) = 129.511$, $p < .001$).

The same pattern was observed in informant-reported models, with the three-factor model providing better fit than the one-factor model, but with indications of model misspecification. The informant three-factor model provided some indication of good or acceptable fit (CFI = .951 and RMSEA = .072) but also showed indications of poor fit (SRMR = .120 and $\chi^2(149) = 433.994$, $p < .001$). The one-factor model demonstrated poor fit overall (CFI = .901, RMSEA = .102, SRMR = .160, $\chi^2(152) = 730.337$, $p < .001$). Chi-square difference testing indicated informant-reported one- and three-factor models were significantly different ($\chi^2(3) = 145.347$, $p < .001$).

Self- and informant-reported memory ($r(364) = .372$, $p < .001$) and attention ($r(362) = .369$, $p < .001$) were moderately correlated. Self- and informant-reported spatial navigation were significantly but weakly correlated ($r(363) = .104$, $p = .047$).

Predictive ability of questionnaires

CSF ratio

Self-reported memory demonstrated a trend toward predicting biomarker positivity, which became significant with outliers removed ($p = .052$ and $p = .018$, respectively). Self-reported

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Table 4. Logistic regression predicting biomarker positivity defined by CSF $ptau_{181}/A\beta_{42}$ ratio

	Standardized β	SE	OR	OR 95% CI	*p*-value
Self-reported memory (full sample; $N = 371$)	.217	.112	1.242	.998–1.545	.052
Self-reported memory (no outliers; $N = 364$)	.543	.229	1.721	1.099–2.695	.018*
Self-reported attention ($N = 371$)	.206	.109	1.229	.992–1.523	.060
Self-reported navigation ($N = 370$)	.059	.109	1.061	.857–1.314	.586
Informant-reported memory ($N = 366$)	−.094	.114	.911	.728–1.140	.413
Informant-reported attention ($N = 364$)	.089	.111	1.093	.879–1.359	.423
Informant-reported navigation ($N = 366$)	.104	.114	1.110	.888–1.387	.361
Combined-reported memory ($N = 366$)	.106	.112	1.112	.893–1.386	.343
Combined-reported attention ($N = 364$)	.194	.111	1.214	.978–1.508	.079
Combined-reported navigation ($N = 365$)	.123	.112	1.131	.908–1.408	.271
Objective memory ($N = 371$)	.160	.123	1.173	.921–1.484	.196
Objective executive function ($N = 371$)	.292	.125	1.340	1.050–1.710	.019*
Objective visuospatial ($N = 371$)	−.012	.113	.988	.791–1.235	.918

Note. SE = Standard Error; CI = Confidence Interval; OR = Odds Ratio; * indicates $p < .05$. Each predictor was examined in a separate model that included only the predictor of interest noted in the table and covariates (age, gender, education).

Table 5. Logistic regression predicting biomarker positivity defined by hippocampal volume

	Standardized β	SE	OR	OR 95% CI	*p*-value
Self-reported memory ($N = 313$)	.229	.132	1.257	.970–1.629	.083
Self-reported attention ($N = 313$)	.076	.128	1.079	.840–1.386	.552
Self-reported navigation ($N = 312$)	.207	.122	1.230	.968–1.563	.091
Informant-reported memory ($N = 309$)	−.005	.130	.995	.771–1.283	.967
Informant-reported attention ($N = 307$)	.113	.123	1.120	.881–1.424	.357
Informant-reported navigation ($N = 309$)	.053	.137	1.054	.807–1.378	.698
Combined-reported memory ($N = 309$)	.156	.150	1.168	.871–1.567	.299
Combined-reported attention ($N = 307$)	.117	.123	1.124	.883–1.432	.341
Combined-reported navigation ($N = 308$)	.217	.128	1.242	.966–1.596	.091
Objective memory ($N = 313$)	.311	.149	1.364	1.018–1.829	.038*
Objective executive function ($N = 313$)	.384	.150	1.468	1.093–1.971	.011*
Objective visuospatial ($N = 313$)	.148	.134	1.160	.893–1.507	.267

Note. SE = Standard Error; CI = Confidence Interval; OR = Odds Ratio; * indicates $p < .05$. Each predictor was examined in a separate model that included only the predictor of interest noted in the table and covariates (age, gender, education).

attention and spatial navigation were not predictors of biomarker positivity ($p = .060$ and $p = .586$, respectively). Informant-reported and combined self- and informant-reported subsections were not predictors of biomarker positivity ($ps > .079$). See Table 4 and Figure 1 for full results.

Hippocampal volume

Self-reported, informant-reported, and combined self- and informant-reported subsections were not predictors of biomarker positivity ($ps > .083$). See Table 5 and Figure 2 for full results.

Consideration of depressive symptoms

As self-reported memory was the only predictor of CSF $ptau_{181}/A\beta_{42}$ ratio biomarker positivity, this was the only subsection considered individually for these analyses (Table 6). In this more limited sample of participants with available GDS ($N = 197$), self-reported memory was no longer a predictor of CSF $ptau_{181}/A\beta_{42}$ ratio biomarker positivity ($p = .517$). This remained true when GDS, and the interaction between self-reported-memory and GDS, were added to the models ($p = .482$ and $p = .355$, respectively).

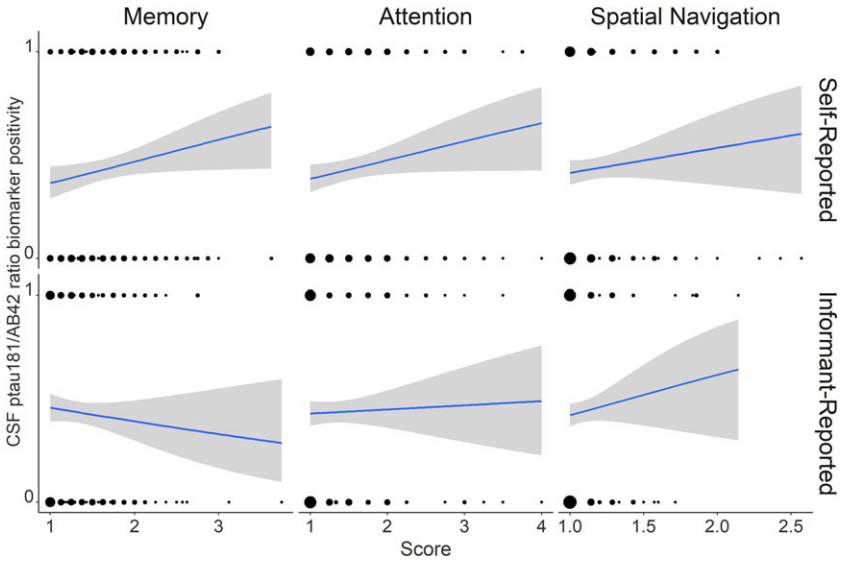

Figure 1. Logistic regression for self- and informant-reported memory, attention, and spatial navigation ECog subsections predicting CSF $ptau_{181}/A\beta_{42}$ ratio biomarker positivity.

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Table 6. Self-reported memory predicting biomarker positivity defined by CSF $ptau_{181}/A\beta_{42}$ ratio controlling for depressive symptoms ($N = 197$)

	Model AIC	Standardized β	SE	OR	OR 95% CI	*p*-value
Step 1 model	266					
Age		.555	.161	1.742	1.271–2.387	<.001*
Sex		.207	.156	1.230	.907–1.668	.184
Education		.163	.155	1.177	.869–1.595	.292
Memory						
Step 2 model	267.57					
Self-reported memory		.095	.147	1.100	.825–1.467	.517
Step 3 model	269.47					
Self-reported memory		.106	.151	1.112	.827–1.495	.482
Depressive symptoms		−.050	.153	.951	.705–1.283	.744
Step 4 model	268.94					
Self-reported memory		.145	.157	1.156	.850–1.573	.355
Depressive symptoms		.060	.172	1.062	.757–1.489	.728
Self-reported memory × depressive symptoms		−.245	.169	.783	.562–1.091	.148

Note. SE = Standard Error; CI = Confidence Interval; OR = Odds Ratio; * indicates $p < .05$. The association between self-reported memory and CSF $ptau_{181}/A\beta_{42}$ ratio was examined in the context of depressive symptoms because this was the only significant relationship observed in the full sample logistic regressions (Tables 4 and 5).

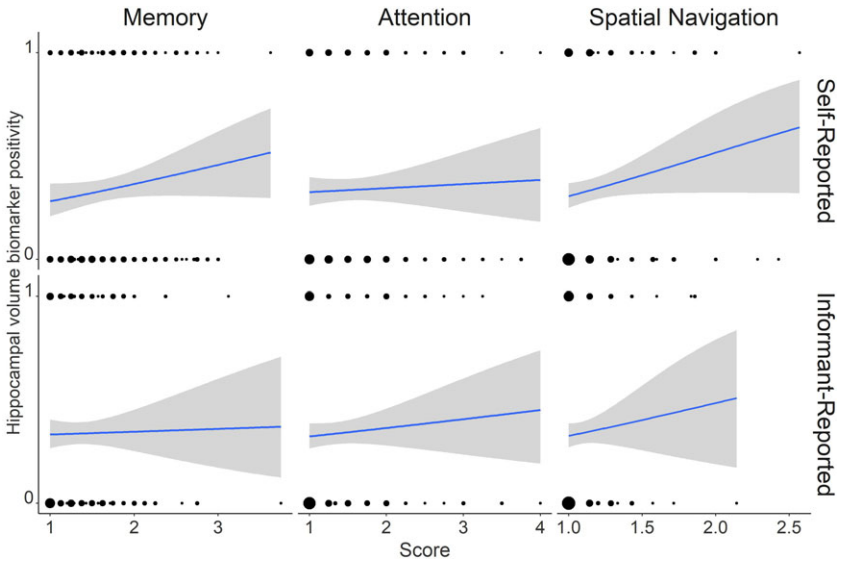

Figure 2. Logistic regression for self- and informant-reported memory, attention, and spatial navigation ECog subsections predicting hippocampal volume biomarker positivity.

Comparison to neuropsychological composites

CSF ratio

The objective executive function composite was a predictor of biomarker positivity ($p = .019$; Table 4). The objective executive function composite remained significant, whereas self-reported attention was not, when both were in the same model ($p = .029$ and $p = .095$, respectively). Self-reported memory (with outliers removed) was a predictor of biomarker positivity, whereas the objective memory composite was not, when both were in the same model ($p = .014$ and $p = .186$, respectively). Self-reported navigation and the objective visuospatial composite were not significant when both were in the same model ($p = .586$ and $p = .902$, respectively). See Table 7 for full results.

Hippocampal volume

The objective memory and executive function composites were predictors of biomarker burden ($ps < .038$; Table 5). The objective executive function composite remained significant, whereas self-reported attention was not, when both were in the same model ($p = .012$ and $p = .795$, respectively). When outliers were removed, the objective memory composite remained significant, whereas self-reported memory was not, when both were in the same model ($p = .027$ and $p = .177$, respectively). Self-reported navigation and the objective visuospatial composite were not significant when both were in the same model ($p = .094$ and $p = .285$, respectively). See Table 7 for full results.

Discussion

The current study suggests that the self- and informant-reported memory, attention, and spatial navigation ECog subsections are not robust predictors of CSF $ptau_{181}/A\beta_{42}$ ratio or hippocampal volume biomarker positivity. Only self-reported memory was a significant predictor of CSF $ptau_{181}/A\beta_{42}$ ratio biomarker positivity, which remained significant when the objective memory composite was added to the model (with outliers removed); however, self-reported memory was not a significant predictor of CSF $ptau_{181}/A\beta_{42}$ biomarker positivity in a more limited sample when controlling for depressive symptoms. None of the subsections were predictors of hippocampal volume biomarker positivity. These results demonstrate the limited ability of the ECog subsections to detect AD-associated biomarkers in clinically normal older adults and highlight the need to adjust current subjective measures or develop new measures to enhance clinical utility in the preclinical stage.

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Table 7. Comparison of self-reported subsections and objective neuropsychological composites

	Standardized β	SE	OR	OR 95% CI	*p*-value
CSF $ptau_{181}/A\beta_{42}$ ratio					
Memory ($N = 371$)					
Self-reported memory	.205	.112	1.227	.985–1.529	.068
Objective memory	.138	.124	1.148	.900–1.465	.266
Memory without outliers ($N = 362$)					
Self-reported memory	.577	.234	1.780	1.126–2.814	.014*
Objective memory	.173	.131	1.189	.920–1.536	.186
Attention/executive function ($N = 371$)					
Self-reported attention	.185	.111	1.203	.968–1.494	.095
Objective executive function	.274	.125	1.315	1.028–1.682	.029*
Navigation/visuospatial ($N = 370$)					
Self-reported navigation	.059	.109	1.061	.857–1.314	.586
Objective visuospatial	-.014	.113	.986	.789–1.232	.902
Hippocampal volume					
Memory ($N = 313$)					
Self-reported memory	.200	.133	1.221	.941–1.585	.134
Objective memory	.286	.151	1.332	.991–1.789	.057
Memory without outliers ($N = 310$)					
Self-reported memory	.370	.274	1.448	.846–2.478	.177
Objective memory	.350	.159	1.419	1.040–1.937	.027*
Attention/executive function ($N = 313$)					
Self-reported attention	.034	.131	1.035	.801–1.337	.795
Objective executive function	.379	.151	1.461	1.086–1.966	.012*
Navigation/visuospatial ($N = 312$)					
Self-reported navigation	.205	.123	1.228	.966–1.561	.094
Objective visuospatial	.143	.134	1.154	.887–1.501	.285

Note. SE = Standard Error; CI = Confidence Interval; OR = Odds Ratio; * indicates $p < .05$. All subsections were compared to same or similar objective composite, regardless of either predictor's significance in prior models (Tables 4 and 5).

Reliability and validity

Consistent with the existing literature, all subsections were within the fair to good range for internal consistency (DeVellis, 2012; Farias et al., 2011; Russo et al., 2018). When comparing the subsections, it is unclear why the spatial navigation subsection had relatively lower internal consistency compared to the memory and attention subsections. One possibility is that participants may be less adept at reflecting on their own navigation abilities, as the behaviors queried may not be engaged in on a regular basis (e.g., "reading a map and helping with directions when someone else is driving"). Similarly, informants may not be observing participants engaging in these navigation behaviors on a frequent enough basis (e.g., "finding his/her car in a parking lot;" Allison et al., 2019).

Confirmatory factor analyses supported that each domain-specific subsection represented a unique aspect of cognition. Importantly, this suggests that both participants and informants were able to differentially report changes across cognitive domains and were not simply reporting general cognitive change. Broadly, these results support the proposed concept of the development of a domain-specific questionnaire for preclinical AD.

Predictive ability of questionnaires

Given the overall reliability and validity of the subsections, we further examined the ability of ECog subsections to predict biomarker positivity. Significant results were only observed for self-reported memory and CSF $ptau_{181}/A\beta_{42}$ ratio biomarker positivity (with outliers removed). This is consistent with the substantial body of literature associating objective performance on neuropsychological and experimental memory tasks with AD biomarkers and progression along the AD continuum (Baker et al., 2017; Hedden et al., 2013); however, when these analyses were conducted in a smaller sample due to limited availability of GDS, self-reported memory was no longer a significant predictor of CSF $ptau_{181}/A\beta_{42}$ ratio biomarker positivity. The observed slope for self-reported memory was reduced by more than 50% in the smaller sample (full sample $\beta = .217$ and GDS sample $\beta = .095$), and the effect size also diminished (full sample OR = 1.242 and GDS sample OR = 1.100). Thus, self-reported memory, as measured by ECog, is not a robust predictor of preclinical AD-related pathology. Of note, repeating analyses increased the possibility of Type 1 error.

We may have observed limited associations between ECog subsections and biomarker positivity due to a skew in all ECog subsections wherein participants and informants reported little cognitive change (average score in sample ranging 1.07–1.65 out of 4). This skew was particularly noticeable in the spatial navigation subsections with 55% of participants and 74% of informants denying change across ECog items, followed by attention with 32% of participants and 60% of informants denying change across ECog items. Self-reported memory demonstrated the greatest distribution with only 9% of participants denying change across all items, but 34% of informants denied changes across all items. The greater distribution of self-reported memory data may have contributed to this being the only subsection with some evidence of a significant association with biomarker positivity. Notably, informants tended to report less cognitive change than participants across all domains, suggesting limited ability of informant reports to capture subtle cognitive changes associated with preclinical AD. This may be due to informants not readily observing the abilities queried on the ECog (e.g., "remembering the current date or day of the week" and "ability to do two things at once").

The spatial navigation subsection demonstrated the greatest skew toward participants and informants denying change. Notably, this

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subsection primarily focused on reading maps (two items) and navigating familiar environments (three items), and only had two items querying wayfinding in potentially novel locations. Navigating familiar environments is relatively easier than navigating novel environments for individuals with AD, and therefore changes in the latter may be more noticeable earlier in the disease process (Jheng & Pai, 2009). Furthermore, navigating familiar environments may be related to neural substrates that are not as impacted early in the AD process (e.g., caudate) vs. navigating a new environment, which tends to rely on brain regions that are impacted early (e.g., hippocampus; Kaplan et al., 2014; Park et al., 2014). A self-reported questionnaire developed by Allison and colleagues (2019) to detect subtle spatial navigation change in clinically normal older adults was sensitive to preclinical AD.

The lack of significant results in terms of hippocampal volume may relate to the methodology used to define biomarker positivity, as there is no established cutoff for hippocampal volume indicative of preclinical AD. Thus, a sample-specific cutoff was calculated using the bottom tertile based on the sample's distribution of hippocampal volume. In addition, cerebral amyloidosis is thought to be the first neuropathological change that occurs on the AD continuum with hippocampal volume change occurring later (Jack et al., 2018). The current samples consisted entirely of clinically normal participants, and it is possible that the participants in the sample did not exhibit hippocampal volume change that would be reliably associated with cognitive change.

A current conceptualization of subjective cognitive decline does not require the presence of informant-reported cognitive change (Jessen et al., 2014). Previous work suggests that informant-reported cognitive change may have particular utility in the later stages of the AD continuum (i.e., MCI and symptomatic AD), whereas self-reported cognitive change may be most useful in the preclinical stage (for a review, see Rabin et al., 2017). Null findings in informant-reported models may be a result of limiting our sample to clinically normal participants.

Comparison to neuropsychological composites

Self-reported memory remained a significant predictor of CSF $ptau_{181}/A\beta_{42}$ ratio biomarker positivity when the objective memory composite was added to the model with outliers removed; however, this result must be interpreted with caution in light of null findings in the more limited GDS sample. In terms of hippocampal volume biomarker positivity, the observation that the objective executive function and memory composites remained significant when controlling for self-reported change in attention and memory, respectively, is consistent with the substantial body of literature associating objective performance on memory and attention neuropsychological and experimental tasks with AD biomarkers and progression along the AD continuum (Baker et al., 2017; Balota et al., 2010; Hedden et al., 2013; Millar et al., 2017).

The visuospatial composite may have demonstrated limited discriminative ability because the skills assessed were limited to construction ability (e.g., copying a clock and interlocking pentagons) and did not include other skills highly associated with AD, such as topographical tasks (Salimi et al., 2018). Broadly, this is consistent with findings that neuropsychological assessments of memory and executive functioning have significant, but often small, associations with preclinical AD, whereas neuropsychological assessments of non-navigational visuospatial abilities are variably related to preclinical AD (for meta-analyses, see Bäckman et al., 2005 and Hedden et al., 2013; for a review, see Salimi et al., 2018).

Limitations

The ECog has several potential limitations that may have impacted its ability to produce robust discriminative accuracy for AD biomarkers in clinically normal older adults. First, the ECog assesses basic functioning, and such functions may not yet be impacted in preclinical AD; thus, the more subtle cognitive changes observed in preclinical AD may not be captured by the measure. As previously discussed, the ECog subsections were skewed toward participants and informants reporting no observed cognitive change across all items. Thus, the ECog is not capturing cognitive change noticed at the earliest stages of AD. The Subjective Cognitive Decline Initiative (SCD-I) working group has identified features that may increase the likelihood of observing subjective cognitive decline in preclinical AD, including onset of subjective cognitive decline within the last 5 years (Jessen et al., 2014). The ECog asks about changes observed over the past 10 years; thus, the ECog may be capturing more general age-related cognitive decline rather than preclinical-specific changes, limiting its predictive ability for biomarker positivity.

There are several limitations with using data from ADNI. First, our sample was approximately 95% Non-Hispanic White, limiting generalizability of our findings as there may be racial and ethnic differences in AD biomarker burden (for a review, see Gleason et al., 2022). While using the ADNI database allowed for the creation of a relatively large sample to examine current questions, neuropsychological composite scores were not available for attention and spatial navigation. Instead, we relied on related measures of executive functioning (of which attention is considered to be one facet) and visuospatial abilities (which are thought to be utilized during spatial navigation). This significantly limited our ability to directly compare the respective ECog subsections to these domains. In addition, data regarding informant cognitive status was not available. It is possible that informant's cognitive abilities may have impacted their ability to accurately assess the participant's cognitive change.

Additionally, analyses required coordination of multiple clinical and biomarker measures that were collected at varying times while the participant was enrolled in the ADNI study. This introduces the possibility of clinical or biomarker changes during the delay between measures. While we attempted to balance maximizing sample size and minimizing biomarker change over the time interval, we must acknowledge there may be an impact of time delay. Additionally, this approach resulted in varying sample sizes across analyses, thus limiting our ability to directly compare results across study aims.

Lastly, we examined multiple questions in this study: AD biomarker positivity was operationalized using both CSF $ptau_{181}/A\beta_{42}$ and hippocampal volume, significant models were rerun in a subsample with depressive symptomatology available, self-reported subsections were compared to objective neuropsychological composites, and sensitivity analyses were run to consider the influence of outliers. This resulted in 36 models (18 with and 18 without outliers) for examining the ability of individual and combined subsections to predict AD biomarker positivity, 6 models (3 with and 3 without outliers) to examine the impact of depressive symptomatology in previously significant models, and 12 models (6 with and 6 without outliers) to compare the predictive ability of self-reported subsections and

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objective neuropsychological composites (totaling 54 models). This increases our risk of Type 1 error.

Conclusion

Collectively, this study suggests that the ECog subsections have limited utility as screening tools for preclinical-related biomarkers. This highlights the need for questionnaires developed to specifically assess subtle cognitive changes associated with preclinical AD. The potential impact of depressive symptomatology on self-reported cognitive ability in the preclinical stage must be further examined in the context of more robust measures. Additionally, longitudinal analyses should be conducted to examine whether utility of participant and informant reports change as the participant progresses along the AD continuum. Through longitudinal analyses, we can further examine the dynamic nature of informant reports across the AD continuum and explore whether the predictive ability of informant reports improves when participants have progressed from the preclinical stage to symptomatic AD. Importantly, there needs to be a focus on potential ways to improve informants' ability to report cognitive changes in the preclinical stage of AD, such as querying behaviors that may be observed more often.

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Competing interests. None.

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