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Memory impairment and Alzheimer's disease pathology in individuals with MCI who underestimate or overestimate their decline

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Abstract

Objectives: The aim of this study was to examine whether the discrepancy between participant and informant estimation of memory decline can predict MCI prognosis.

Methods: Analyses involved data from individuals with MCI enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) who filled the Everyday Cognition questionnaire. Participants who underestimated (N = 112) and overestimated (N = 157) their memory decline were compared on memory tasks, brain volume, and cerebrospinal markers, at study entry and after 24 months.

Results: Individuals who underestimated their memory decline performed more poorly on memory tests, had smaller hippocampus volume, and greater Alzheimer's disease pathology than did individuals who overestimated their cognitive decline. Longitudinal comparisons demonstrated that individuals who underestimated their decline deteriorated more significantly in memory and in brain measures.

Conclusions: Underestimation of memory decline should raise clinicians' suspicion of the existence of AD pathology in individuals with MCI.

KEYWORDS
awareness, biomarkers, memory assessment, subjective cognitive complaint, Anosognosia, unawareness

1 | INTRODUCTION

Large community-based studies have shown that up to 60% of older adults complain of memory decline,[1] yet the significance of such complaints is highly controversial. There is ample evidence that subjective complaints are a risk factor for conversion from normal cognition to mild cognitive impairment (MCI) and subsequently to dementia.[2-4] However, not all studies find a relationship between subjective and objective deficits,[5,6] possibly due to anosognosia or inaccurate self-estimation of deficit in individuals with MCI.[7] In the current study, we examine whether a simple calculation of the tendency to underestimate or overestimate memory decline holds diagnostic and prognostic values in the assessment of MCI.

Research suggests that there is individual variability in awareness of memory decline in MCI.[8] Edmonds et al.[7] found that individuals with MCI who have greater objective cognitive deficits tend to underestimate their decline relative to their informants. In addition, some studies demonstrate that lack of awareness of deficit is an independent predictor of conversion from MCI to dementia,[9,10] and that individuals with MCI who are less aware of their deficits show a more

[†]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/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

rapid decline in cognitive functions than do individuals who are more aware of their decline.[11] Cacciamani et al.[12] argue that individuals with cognitive concerns who exhibit low awareness, as measured by a discrepancy between their own reports and those provided by informants, are likely to have preclinical Alzheimer's disease (AD) pathology. Thus, it might be useful to compare participant and informant estimates of memory decline in order to determine the etiology and prognosis of MCI. However, previous studies of the discrepancy between participant and informant estimates of decline have employed various different measures to calculate this discrepancy, including sample-specific cutoffs that are difficult to apply in the clinic.[7,9,10,13] For clinicians to use a discrepancy score routinely, they should be able to calculate it as simply and as intuitively as possible.

In the current study, we subtracted informant estimate of memory decline from participant estimate, and classified participants into two groups of underestimation and overestimation. We examine whether these two groups differ in objective memory performance at baseline as well as after 24 months, and whether they differ in brain volume and in AD pathology burden as reflected in cerebrospinal (CSF) measures. Individuals with subjective memory complaints show decreased grey matter volume relative to individuals with no such complaints, especially in the mesial-temporal lobe.[14] Moreover, individuals with memory complaints show hippocampal subfield changes that are similar to the pattern seen in AD.[15] Thus, the presence of cognitive complaints might indicate underlying neurodegenerative changes that correspond to the preclinical stage of AD. We also look at CSF levels of amyloid beta 1-42 ($A\beta_{1\text{-}42}$) and hyper-phosphorylated tau protein ($p\text{-}tau_{181\text{-}p}$) as indications of disease burden, since low CSF $A\beta_{1\text{-}42}$ together with high $p\text{-}tau_{181\text{-}p}$ are indicative of prodromal AD.[16]

We hypothesize that individuals with MCI who underestimate their memory decline relative to their informants will demonstrate greater memory impairment than individuals who overestimate their decline. We also assume that there will be greater AD pathology in individuals who underestimate their memory decline than in individuals who overestimate their decline. Our aim is to show that a simple calculation of evaluation discrepancy can help predict which individuals with MCI will be at a higher risk of developing AD.

2 | METHODS

Data used for this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was initiated in the US in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and non-profit organizations. Michael W. Weiner, MD, was the Principal Investigator for this initiative. A full list of all research partners can be found on the ADNI website. ADNI was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, US 21CFR Part 50-Protection of Human Subjects, and Part 56-Institutional Review Boards, following all relevant state and federal HIPAA regulations.

Key points

- Individuals who underestimate their decline perform more poorly on memory tests
- Individuals who underestimate their decline have smaller hippocampus volume and lower $A\beta_{1\text{-}42}$ levels
- Individuals who underestimate their decline deteriorate more significantly in memory and in brain measures over 24 months
- Underestimation of decline may increase the likelihood of AD pathology in individuals with MCI

2.1 | Participants

The sample for the current study included all individuals enrolled in ADNI2 who completed the Everyday Cognition (ECog) questionnaire at study entry and at 24 months, and received a diagnosis of MCI at their initial screening. We used only ADNI2 data because in other phases some of the variables were not collected. To be defined as MCI, individuals had to have a subjective memory concern as reported by the participant, a study partner, or a clinician; score 24 or above on the Mini-Mental State Exam (MMSE)[17]; receive a rating of 0.5 on the Clinical Dementia Rating (CDR)[18]; and report no depression, as verified by a score of 5 or below on the Geriatric Depression Scales (GDS).[19] Another inclusion criteria was having a study partner who had frequent contact with the participant (eg, an average of 10 hours per week or more), and could attend all clinic visits for the duration of the protocol. Participants and study partners provided written informed consent before any protocol-specific procedures began.

3 | MATERIALS AND PROCEDURES

3.1 | Everyday Cognition Questionnaire (ECog)

The ECog questionnaire[20] examines changes in functioning in the domains of memory, language, visuospatial abilities, planning, organization, and divided attention. Participants were asked to rate the ability to perform everyday tasks now as compared to the ability to do these same tasks 10 years earlier. Ratings were provided on a four-point scale: 1 = there has been no change in ability, or performance is better compared to 10 years earlier; 2 = occasionally performs the task worse than 10 years earlier but not all the time; 3 = consistently performs the task a little worse than 10 years earlier; 4 = consistently performs the task much worse than 10 years earlier. There was also an option to mark “I don't know”, which was later removed from the data file (the dataset included only 11 [0.2%] such responses). Both participants and study-partners completed the questionnaire and instructions were adjusted as necessary. This made it possible to compare self-report and informant-report. We used the eight memory items, including

statements such as: "Remembering a few shopping items without a list", "Remembering things that happened recently (such as recent outings, events in the news)". We calculated the average ratings on these items as provided by the participant and by the informant.

3.2 | Neuropsychological assessment

Memory was examined by the Rey Auditory Verbal Learning Test (RAVLT),[21] as well as by the Logical Memory sub-test of the Wechsler memory Scale (WMS).[22] The RAVLT assesses the ability to learn a list of 15 items over five trials. The variables used for the current study were immediate memory and delayed recall. Immediate memory was examined after presentation and recall of a distracter list, and delayed recall was examined 30 minutes later. Each score could range between 0 and 15. The Logical Memory test examines the ability to acquire a short paragraph that is read aloud to the participant. Immediate memory is the number of items recalled correctly following story presentation, and delayed memory is the number of items recalled correctly at least 30 and no more than 40 minutes later. Every piece of information received 1 point, leading to a score between 0 and 25 on the immediate and the delayed tasks.

3.3 | Structural neuroimaging

Participants underwent brain magnetic resonance imaging (MRI) scans, using a 3 T scanner. Specific protocols are described elsewhere.[23] Volumetric data were derived from the UCSF Cross-sectional free-surfer analysis of the ADNI2 MRI scans. Cortical reconstruction and volumetric segmentation were performed with the Free-surfer image analysis suite (freely available at http://surfer.nmr.mgh.harvard.edu/). FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths.[24] Neuroimaging data were obtained within 180 days of the ECog ratings. For the current analyses, we looked at whole brain volume, intra-cranial volume, and the ratio between them as documented at study entry, as well as at hippocampus volume at study entry and at 24 months.

3.4 | Cerebrospinal fluid (CSF) measures

Lumbar puncture was performed as described in the ADNI manual (http://www.adni-info.org/). CSF samples were collected at study entry and at 24 months, and CSF amyloid beta 1-42 ($A\beta_{1\text{-}42}$) and hyperphosphorylated tau ($p\text{-}tau_{181\text{-}p}$) levels were measured based on standardized protocols outlined by the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center.[25] High levels of $p\text{-}tau_{181\text{-}p}$ indicate neurofibrillary tangle pathology, and low levels of $A\beta_{1\text{-}42}$ indicate amyloid plaque pathology. We treated $A\beta_{1\text{-}42}$ values greater than 1700 as 1700. We also looked at the ratio between these two variables, since it predicts decline in individuals with MCI.[26,27]

3.5 | Statistical analysis

First, we divided all participants into two groups according to the discrepancy score between participant and informant ratings on the ECog memory scale at study entry. Next, we conducted an initial Multivariate Analyses of Variance (MANOVA) that compared groups on all dependent variables together. This analysis was performed to protect against a Type I error. We then ran a series of ANOVAs with groups as a between-subject variable, and memory performance, brain volume, and CSF markers, as well as testing time (study entry, 24 months) as within-subject variables.

4 | RESULTS

The analyses involved data from 284 participants with MCI, including 128 women and 156 men, with an age range of 55-91 (mean = 71.36, SD = 7.39), and an education level of 9-20 years (mean number of years of education = 16.35, SD = 2.62). At study entry, MMSE scores ranged from 24 to 30 (mean = 27.99, SD = 1.72).

We calculated the discrepancy score by subtracting the average ECog ratings of each informant at study entry from the average ratings of the corresponding participant. One informant provided no ratings, and 14 participant-informant dyads provided identical ratings of decline, resulting in 269 remaining dyads. There were 112 participants who provided lower ratings of their memory decline than did their study partners, and 157 participants who provided higher ratings of their memory decline than did their study partners. Groups had similar proportions of women, similar education levels, similar MMSE scores, and similar depression levels, but they differed significantly in age and ECog measures (see Table 1).

TABLE 1 Demographic information by group at study entry

	Underestimating	Overestimating	Sig. (2-tailed)
N	112	157	
Women	43 (38.39%)	76 (48.41%)	.103
Age	72.76 (SD = 7.10)	70.44 (SD = 7.40)	.010*
Years of education	16.31 (SD = 2.65)	16.37 (SD = 2.63)	.862
MMSE scores	27.78 (SD = 1.79)	28.07 (SD = 1.66)	.169
GDS scores	1.61 (SD = 1.48)	1.80 (SD = 1.41)	.287
ECog-Participant	2.07 (SD = .61)	2.53 (SD = .65)	.000*
ECog-Informant	2.85 (SD = .72)	1.81 (SD = .57)	.000*

Note: ECog numbers refer to the assessment of memory alone.
Abbreviations: MMSE, Mini-Mental State Exam; GDS, Geriatric Depression Scale; ECog, Everyday Cognition questionnaire.

Next, we conducted a MANOVA that examined group differences for all dependent variables together, with age as a covariate. The analysis was significant for group at both study entry, Pillai's Trace = .166, F(11, 206) = 3.727, $P < .001$, and at 24 months, Pillai's Trace = .220, F (11, 108) = 2.766, $P < .001$.

Figure 1 presents mean scores on the memory measures at study entry as well as after 24 months, according to group. Individuals who underestimated their decline performed more poorly than individuals who overestimated their decline, and this was true for all measures. To examine memory performance, we conducted two three-way ANOVAs that controlled for age at study entry, and compared a between-subject variable of group (underestimating, overestimating), a within-subject variable of memory measure (immediate, delayed), and a within-subject variable of testing time (study entry, 24 months). The first analysis examined RAVLT scores, showing a significant difference between the two groups, $F(1, 254) = 39.461$, $P < .001$, $\eta^2 = .134$, so that individuals who underestimated their decline performed more poorly than individuals who overestimated their decline. Although performance immediately after presentation was better than performance after a 30-minute delay, once age and group were entered into the analysis, the difference did not reach significance, $F(1, 254) = 3.663$, $P = .057$, $\eta^2 = .014$. Across groups and RAVLT measures, there was no significant difference between study entry and 24 months, $F(1, 254) = 1.310$, *ns*, $\eta^2 = .005$. The interaction between group, memory measure, and testing time was significant, $F(1, 254) = 4.645$, $P = .032$, $\eta^2 = .018$. Thus, individuals who underestimated their decline showed a slight decrease in performance over time, whereas individuals who overestimated their decline showed a slight increase in immediate recall performance over time. No other interaction was significant.

The second analysis of memory performance examined WMS scores, showing a significant group difference, $F(1, 254) = 34.856$, $P < .001$, $\eta^2 = .121$. Individuals who underestimated their decline performed more poorly across WMS measures than did individuals who overestimated their decline. Across groups and testing time, there was a significant difference between immediate and delayed memory performance, with better performance immediately after presentation than after a delay, $F(1, 254) = 7.660$, $P = .006$, $\eta^2 = .029$. Across groups and memory measure, performance at study entry was worse than performance at 24 months, demonstrating a test-retest improvement in scores, $F(1, 254) = 4.639$, $P = .032$, $\eta^2 = .018$. The interaction between group and memory measure was significant, $F(1, 254) = 10.555$, $P = .001$, $\eta^2 = .040$, revealing a larger difference between immediate and delayed story recall in individuals who underestimated their decline relative to individuals who overestimated their decline. The interaction between group and testing time was not significant, $F(1, 254) = 3.130$, $P = .078$, $\eta^2 = .012$. The interaction between memory measure and testing time was significant, $F(1, 254) = 6.440$, $P = .012$, $\eta^2 = .025$, demonstrating a smaller difference between immediate and delayed recall at study entry relative to 24 months. The three-way interaction of group, memory measure, and testing time, was not significant, $F(1, 254) = .751$, $P = .387$, $\eta^2 = .003$.

Next, we looked at brain volume. No significant group difference emerged in whole brain volume, in intra-cranial volume, or in the ratio between these two measures, as documented at study entry. To examine hippocampus volume, we conducted a two-way ANOVA that controlled for age at study entry, gender, whole brain volume at study entry, and days between the MRI scan and the ECog administration at study entry, with a between-subject variable of group (underestimating, overestimating), and a within-subject variable of testing time (study entry, 24 months). Hippocampus volume data on the two testing times were available for 203 participants, 87 (77.68%) in the underestimating group, and 116 (73.89%) in the overestimating group. The analysis revealed a significant group difference, $F(1, 198) = 8.549$, $P = .004$, $\eta^2 = .042$. Individuals who underestimated their decline had smaller hippocampus volume than did individuals who overestimated their decline. There was no difference between study entry and

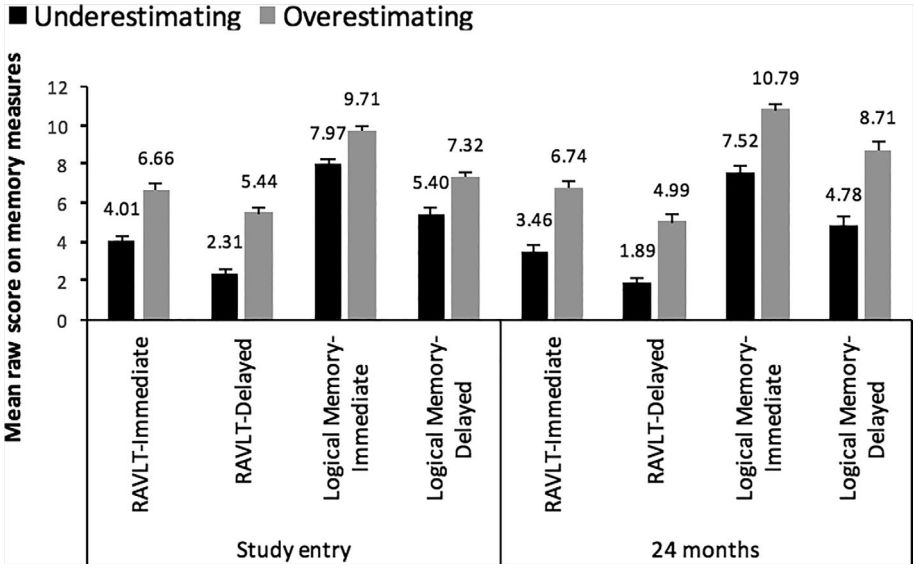

FIGURE 1 Mean raw scores on the memory measures at study entry and after 24 months, by group. *All measures differed significantly ($P < 0.01$) between the two groups (underestimating and overestimating)

24 months, $F(1, 198) = .568$, $P = .452$, $\eta^2 = .003$. However, the interaction between group and testing time was significant, $F(1, 198) = 8.796$, $P = .003$, $\eta^2 = .043$, as individuals who underestimated their decline showed a larger decrease in hippocampus volume over time than did individuals who overestimated their decline (see Figure 2).

To examine $A\beta_{1\text{-}42}$ and p-$tau_{181\text{-}p}$ levels, we conducted three separate ANOVAs that controlled for age at study entry, with a between-subject variable of group (underestimating, overestimating), and a within-subject variable of testing time (study entry, 24 months). These analyses used $A\beta_{1\text{-}42}$ levels from 58 (51.79%) individuals who underestimated their decline and from 79 (50.32%) individuals who overestimated their decline, and who had data on both testing times. Levels of p-$tau_{181\text{-}p}$ for both testing times were available for 57 (50.89%) individuals who underestimated their decline and for 79 (50.32%) individuals who overestimated their decline. The first analysis demonstrated a significant group difference in $A\beta_{1\text{-}42}$, $F(1, 134) = 11.615$, $P = .001$, $\eta^2 = .080$, with lower $A\beta_{1\text{-}42}$ levels in individuals who underestimated their decline than in individuals who overestimated their decline (see Table 2). Although there were greater levels of $A\beta_{1\text{-}42}$ at study entry relative to 24 months, the main effect of testing time did not reach significance, $F(1, 134) = 3.245$, $P = .074$, $\eta^2 = .024$. The interaction between group and testing time was not significant as well, $F(1, 134) = .312$, $P = .577$, $\eta^2 = .002$. The second analysis demonstrated a significant group difference in p-$tau_{181\text{-}p}$, $F(1, 133) = 12.627$, $P = .001$, $\eta^2 = .087$, with greater p-$tau_{181\text{-}p}$ levels in individuals who underestimated their decline than in individuals who overestimated their decline (see Table 2). The main effect of testing time was not significant, $F(1, 133) = 1.796$, $P = .183$, $\eta^2 = .013$, and there was no interaction between group and testing time, $F(1, 133) = .693$, $P = .407$, $\eta^2 = .005$. The third analysis demonstrated a significant group difference in the ratio of p-$tau_{181\text{-}p}$ to $A\beta_{1\text{-}42}$, $F(1, 133) = 14.892$, $P = .001$, $\eta^2 = .101$, with a higher ratio in individuals who underestimated their decline than in individuals who overestimated their decline (see Table 2). The main effect of testing time was not significant, $F(1, 133) = 1.122$, $P = .291$, $\eta^2 = .008$, and there was no interaction between group and testing time, $F(1, 133) = .164$, $P = .686$, $\eta^2 = .001$.

TABLE 2 CSF markers by testing time and group

Measure	Time	Underestimating	Overestimating
$A\beta_{1\text{-}42}$	Study entry	842.33 (352.92)	1088.02 (426.38)
	24 months	792.82 (344.27)	1045.30 (446.76)
p-$tau_{181\text{-}p}$	Study entry	35.64 (18.11)	25.28 (12.90)
	24 months	36.63 (18.33)	27.06 (15.15)
p-$tau_{181\text{-}p}$/ $A\beta_{1\text{-}42}$	Study entry	.051 (.037)	.029 (.024)
	24 months	.057 (.041)	.034 (.036)

5 | DISCUSSION

This study compared memory performance, brain volume, and CSF markers of AD pathology in individuals with MCI who either underestimated or overestimated their memory decline relative to their informants. In line with our hypothesis, individuals who underestimated their decline performed more poorly on two tests of memory, had smaller hippocampus volume, and demonstrated greater burden of AD pathology, as measured by $A\beta_{1\text{-}42}$ and p-$tau_{181\text{-}p}$ CSF levels. These effects emerged at baseline and after 24 months, showing that underestimation of memory decline might help in determining the diagnosis and prognosis of individuals with MCI.

As for the memory measures, we found that individuals who underestimated their memory decline relative to their informants performed more poorly on all tests than did individuals who overestimated their decline. On a test of word recall, individuals who underestimated their decline showed a slight decrease in performance over time, while individuals who overestimated their decline showed

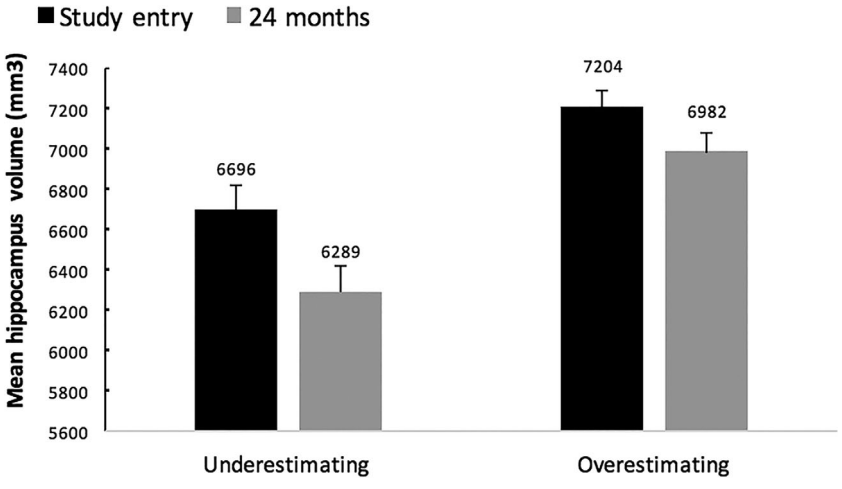

FIGURE 2 Mean hippocampus volume by testing time and group. *All measures differed significantly between the two groups (underestimating and overestimating)

a slight increase in performance over time. The increase in performance demonstrates a practice effect, which is unlikely to occur in individuals with impaired memory. There was no interaction between group and testing time for story recall, but the difference between immediate and delayed story recall was larger for individuals who underestimated their decline than for individuals who overestimated their decline. This finding may indicate that individuals who underestimate their decline show more rapid forgetting than individuals who overestimate their decline. These results are in line with Edmonds et al.'s report[7] that individuals with amnestic MCI underestimated their cognitive decline, as well as with the finding that greater anosognosia was associated with worse cognitive functioning in MCI.[9,10]

There was no indication of an overall brain volume difference between groups. This pattern of results contrasts with some previous studies that compared individuals with MCI who converted to dementia and individuals who did not convert to dementia (eg, [28]). Nevertheless, as expected, hippocampus volume was smaller in individuals who underestimated their decline relative to individuals who overestimated their decline. Furthermore, although across the two groups together there was no difference between study entry and 24 months, the interaction between group and testing time was significant, showing that hippocampus volume decreased more steeply in individuals who underestimated their decline than in individuals who overestimated their decline. Similarly, there were lower $A\beta_{1\text{-}42}$ levels, greater p-$tau_{181\text{-}p}$ levels, and therefore higher ratio of p-$tau_{181\text{-}p}$ to $A\beta_{1\text{-}42}$ in individuals who underestimated their decline than in individuals who overestimated their decline. These results fit well with Cacciamani et al.'s[12] findings of increased amyloid burden and cortical hypometabolism in individuals with subjective cognitive complaints who underestimated their performance relative to their informants. Thus, the current analyses are consistent with the proposed model of progression of AD, according to which the accumulation of amyloid-beta and tau, together with hypometabolism, lead to cognitive decline.[29] Note, though, that there are conflicting observations regarding the correlation between $A\beta_{1\text{-}42}$ levels and deterioration in cognitive functions,[30] and similar inconclusive evidence for longitudinal changes in p-tau both in individuals with MCI and in individuals with AD.[31] These observations might explain why testing time had no significant effect on CSF measures in the current analysis.

Paradoxically, overestimation of cognitive decline might seem to indicate a faulty cognitive process, and yet it serves as an indication of better cognitive performance. It is possible that individuals who overestimate their decline suffer from depression or anxiety and that their inaccurate estimation reflects their emotional state. Indeed, depression or anxiety lead to excessive worrying in general[32,33] and to anxiety over AD and dementia in particular.[34-37] However, as ADNI recruitment criteria excluded individuals with depression, and groups did not differ in GDS scores, overt depression is unlikely to explain the current findings. Further research with other populations should look into the association between overestimation of memory decline and depression symptoms. We note that excessive worrying might actually lead to better prevention, involving medical interventions, psychotherapy, physical exercise or other such lifestyle choices.

We acknowledge that our study has some weaknesses. First, we investigated individuals with MCI from the ADNI database, and previous studies have argued that there is a high rate of false-positive diagnosis of MCI in ADNI.[7,38] Nonetheless, we believe that the crucial measure is the discrepancy in estimation between participants and informants rather than the diagnosis of MCI. Second, we relied on the participant-informant discrepancy method, assuming that informants' estimates are more accurate than participants' estimates. However, informants' reports can be biased as well.[39-42] While ADNI provides no information on informants, Cacciamani et al.[12] found no difference in informant characteristics of individuals with low or high awareness. It is thus unlikely that the current findings represent only informants' biased estimation.

6 | CONCLUSION

To conclude, a combination of cross-sectional and longitudinal comparisons shows that underestimation of memory decline can help clinicians predict AD pathology in individuals with MCI.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in [adni.loni.usc.edu].

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REFERENCES

1. Singh-Manoux A, Dugravot A, Ankri J, et al. Subjective cognitive complaints and mortality: does the type of complaint matter? *J Psychiatr Res*. 2014;48(1):73-78.
2. Mendonca MD, Alves L, Bugalho P. From subjective cognitive complaints to dementia: who is at risk?: a systematic review. *Am J Alzheimers Dis Other Demen*. 2016;31(2):105-114.
3. Mitchell AJ, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr Scand*. 2014;130(6):439-451.
4. Reisberg B, Shulman MB, Torossian C, Leng L, Zhu W. Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimers Dement*. 2010;6(1):11-24.
5. Lenehan ME, Klekociuk SZ, Summers MJ. Absence of a relationship between subjective memory complaint and objective memory impairment in mild cognitive impairment (MCI): is it time to abandon subjective memory complaint as an MCI diagnostic criterion? *Int Psychogeriatr*. 2012;24(9):1505-1514.
6. Buckley R, Saling MM, Ames D, et al. Factors affecting subjective memory complaints in the AIBL aging study: biomarkers, memory, affect, and age. *Int Psychogeriatr*. 2013;25(8):1307-1315.
7. Edmonds EC, Delano-Wood L, Galasko DR, Salmon DP, Bondi MW. Alzheimer's disease neuroimaging I. subjective cognitive complaints contribute to misdiagnosis of mild cognitive impairment. *J Int Neuropsychol Soc*. 2014;20(8):836-847.
8. Roberts JL, Clare L, Woods RT. Subjective memory complaints and awareness of memory functioning in mild cognitive impairment: a systematic review. *Dement Geriatr Cogn Disord*. 2009;28(2):95-109.
9. Gerretsen P, Chung JK, Shah P, et al. Anosognosia is an independent predictor of conversion from mild cognitive impairment to Alzheimer's disease and is associated with reduced brain metabolism. *J Clin Psychiatry*. 2017;78(9):e1187-e1196.
10. Therriault J, Ng KP, Pascoal TA, et al. Anosognosia predicts default mode network hypometabolism and clinical progression to dementia. *Neurology*. 2018;90(11):e932-e939.
11. Munro CE, Donovan NJ, Amariglio RE, et al. The impact of awareness of and concern about memory performance on the prediction of progression from mild cognitive impairment to Alzheimer disease dementia. *Am J Geriatr Psychiatry*. 2018;26(8):896-904.
12. Cacciamani F, Tandetnik C, Gagliardi G, et al. Low cognitive awareness, but not complaint, is a good marker of preclinical Alzheimer's disease. *J Alzheimers Dis*. 2017;59(2):753-762.
13. Kalbe E, Salmon E, Perani D, et al. Anosognosia in very mild Alzheimer's disease but not in mild cognitive impairment. *Dement Geriatr Cogn Disord*. 2005;19(5–6):349-356.
14. Hu X, Teunissen CE, Spottke A, et al. Smaller medial temporal lobe volumes in individuals with subjective cognitive decline and biomarker evidence of Alzheimer's disease-data from three memory clinic studies. *Alzheimers Dement*. 2019;15(2):185-193.
15. Perrotin A, de Flores R, Lamberton F, et al. Hippocampal subfield Volumetry and 3D surface mapping in subjective cognitive decline. *J Alzheimers Dis*. 2015;48(Suppl 1):S141-S150.
16. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13(6):614-629.
17. Folstein MF, Folstein SE, McHugh PR. "mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
18. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140:566-572.
19. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982;17(1):37-49.
20. Farias ST, Mungas D, Reed BR, et al. The measurement of everyday cognition (ECog): scale development and psychometric properties. *Neuropsychology*. 2008;22(4):531-544.
21. Rey AL. examen psychologique dans les cas d'encéphalopathie traumatique. *Arch Psychol*. 1941;28:21.
22. Wechsler D. *Wechsler Memory Scale - Revised*. New-York: *The Psychological Corporation*; 1987.
23. Jack CR Jr, Bernstein MA, Fox NC, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging*. 2008;27(4):685-691.
24. Iscan Z, Jin TB, Kendrick A, et al. Test-retest reliability of freesurfer measurements within and between sites: effects of visual approval process. *Hum Brain Mapp*. 2015;36(9):3472-3485.
25. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of beta-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dement*. 2016;12(5):517-526.
26. Landau SM, Harvey D, Madison CM, et al. Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology*. 2010;75(3):230-238.
27. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol*. 2009;65(4):403-413.
28. Niemantsverdriet E, Ribbens A, Bastin C, et al. A retrospective Belgian multi-center MRI biomarker study in Alzheimer's disease (REMEMBER). *J Alzheimers Dis*. 2018;63(4):1509-1522.
29. Jack CR Jr, Holtzman DM. Biomarker modeling of Alzheimer's disease. *Neuron*. 2013;80(6):1347-1358.
30. Lee JC, Kim SJ, Hong S, Kim Y. Diagnosis of Alzheimer's disease utilizing amyloid and tau as fluid biomarkers. *Exp Mol Med*. 2019;51(5):53.
31. Lleo A, Alcolea D, Martinez-Lage P, et al. Longitudinal cerebrospinal fluid biomarker trajectories along the Alzheimer's disease continuum in the BIOMARKAPD study. *Alzheimers Dement*. 2019;15(6):742-753.
32. Perrotin A, La Joie R, de La Sayette V, et al. Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: differential affective and imaging correlates. *Alzheimers Dement*. 2017;13(5):550-560.
33. Reid LM, Maclullich AM. Subjective memory complaints and cognitive impairment in older people. *Dement Geriatr Cogn Disord*. 2006;22(5–6):471-485.
34. Corner L, Bond J. Being at risk of dementia: fears and anxieties of older adults. *Nurs Older People*. 2004;16(5):8.
35. Cutler SJ, Hodgson LG. Anticipatory dementia: a link between memory appraisals and concerns about developing Alzheimer's disease. *Gerontologist*. 1996;36(5):657-664.
36. Cutler SJ, Hodgson LG. Correlates of personal concerns about developing Alzheimer's disease among middle-aged persons. *Am J Alzheimers Dis Other Demen*. 2001;16(6):335-343.
37. Kessler EM, Bowen CE, Baer M, Froelich L, Wahl HW. Dementia worry: a psychological examination of an unexplored phenomenon. *Eur J Ageing*. 2012;9(4):275-284.
38. Edmonds EC, Weigand AJ, Thomas KR, et al. Increasing inaccuracy of self-reported subjective cognitive complaints over 24 months in empirically derived subtypes of mild cognitive impairment. *J Int Neuropsychol Soc*. 2018;24(8):842-853.
39. Bregman N, Kave G, Shiner T, Biran I. Alzheimer's disease neuroimaging I. dissociation in awareness of memory and language decline in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2019;34(4):548-554.

40. Dassel KB, Schmitt FA. The impact of caregiver executive skills on reports of patient functioning. *Gerontologist*. 2008;48(6):781-792.
41. Wadley VG, Harrell LE, Marson DC. Self- and informant report of financial abilities in patients with Alzheimer's disease: reliable and valid? *J Am Geriatr Soc*. 2003;51(11):1621-1626.
42. Conde-Sala JL, Rene-Ramirez R, Turro-Garriga O, et al. Factors associated with the variability in caregiver assessments of the capacities of patients with Alzheimer disease. *J Geriatr Psychiatry Neurol*. 2013;26(2):86-94.

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