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Extension and refinement of the predictive value of different classes of markers in ADNI: Four-year follow-up data

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Abstract

Background: This study examined the predictive value of different classes of markers in the progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) over an extended 4-year follow-up in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.
Methods: MCI patients were assessed for clinical, cognitive, magnetic resonance imaging (MRI), positron emission tomography–fluorodeoxyglucose (PET-FDG), and cerebrospinal fluid (CSF) markers at baseline and were followed on a yearly basis for 4 years to ascertain progression to AD. Logistic regression models were fitted in clusters, including demographics, *APOE* genotype, cognitive markers, and biomarkers (morphometric, PET-FDG, CSF, amyloid-β, and tau).
Results: The predictive model at 4 years revealed that two cognitive measures, an episodic memory measure and a Clock Drawing screening test, were the best predictors of conversion (area under the curve = 0.78).
Conclusions: This model of prediction is consistent with the previous model at 2 years, thus highlighting the importance of cognitive measures in progression from MCI to AD. Cognitive markers were more robust predictors than biomarkers.

Keywords: Mild cognitive impairment; Alzheimer's disease; Cognition; MRI; PET-FDG; CSF

1. Introduction

The prevalence of dementia is approximately 24.3 million people worldwide, with predictions that this amount will be doubled every 20 years [1]. Among the causes of dementia, Alzheimer's disease (AD) is the most common. AD dementia is currently considered as an end state after consistent pathologic brain changes have accumulated, perhaps years before the earliest clinical symptoms manifest.

Relatively few studies have directly compared the differential contribution of different kinds of markers (biomarkers and cognitive markers) in their predictive utility for the conversion from mild cognitive impairment (MCI) to AD. This motivated us to undertake a systematic and comprehensive examination of several classes of markers. In a previous study, we found that a combination of delayed verbal episodic memory measures and a middle temporal lobe cortical thickness measure were the strongest predictive factors of the conversion to AD from MCI in a follow-up period of 2 years using a sample from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [2].

Since our initial report, several studies investigating a combination of different markers have obtained similar findings. Ewers and colleagues [3] found that memory measures (free recall) and executive function measures had comparable predictive accuracy to that of biomarkers within the ADNI database using an approach involving a cross-validation paradigm to differentiate AD from elderly control subjects that was later applied to the prediction of MCI conversion to AD. Heister and colleagues found that MCI patients with a combination

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of learning impairment and increased hippocampal atrophy had the highest risk of conversion to AD [4]. Jedynak and colleagues [5], using advanced statistical methods, found that inflection of a delayed memory measure preceded that of other biomarkers (cerebrospinal fluid [CSF] levels and hippocampal volumes) on the progression from MCI to AD in the ADNI database. This set of findings was recently the subject of an editorial that highlighted the otherwise often undervalued importance of cognitive measures as early markers of AD progression [6].

In this study, the first aim was to derive a model for prediction and contrast it with our prior model findings over a longer follow-up period of 4 years in the ADNI database. Given the often undervalued but widespread phenomenon of failure to replicate findings in published biomedical research [7,8], we believe that confirming the validity of a model of prediction for the transition from MCI to AD is of great value and it contributes to the clarification of the processes implicated in transition.

We appreciate that this is not a replication in a separate and independent sample. Nevertheless, as an extension and refinement of our results, we think that this approach will be a step toward validation of our overarching findings (that cognitive measures were robust predictors of conversion from MCI to AD).

We hypothesized that measures of episodic memory and brain morphometric measures will still be predictive of the development of AD in a longer follow-up. To further test this hypothesis, we also included new biomarkers that we did not evaluate in our previous work: (1) a recently proposed factor that has been implicated in the risk of AD development, namely CSF linear combination of amyloid-β $(A\beta)_{1\text{-}42}$ and phosphorylated tau $(\text{p-tau})_{181\text{p}}$ [9]; and (2) fluorodeoxyglucose positron emission tomography (FDG-PET) biomarkers, specifically the hypometabolic convergence index (HCI), a single measure intended to reflect the extent to which the pattern and magnitude of cerebral hypometabolism in an individual correspond to that in probable AD patients [10]. HCI has been shown to be predictive of AD progression in MCI alone or in combination with hippocampal volume.

2. Methods

2.1. Participants

Data used in the preparation of this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI). Data were downloaded on April 18, 2012.

In the study presented here, we restricted our analyses to the MCI subjects recruited by ADNI-1 followed for a period of 4 years. Furthermore, we also sought to extend our model, including a recently proposed model of the combination of Aβ and p-tau for the prediction of conversion, within the same analytic framework that we used in our previous study. Inclusion criteria for MCI and healthy subjects are described elsewhere [2] and on the ADNI website (http://www.adni-infor.org). In brief, MCI patients had Mini-Mental State Exam (MMSE) [11] scores between 24 and 30 (inclusive), a memory complaint, objective memory loss, a Clinical Dementia Rating (CDR) [12] score of 0.5, absence of significant impairment in other cognitive domains, and preserved activities of daily living. In an attempt to ascertain conversion to AD, we excluded MCI subjects whose conversion to AD was not verified at another additional follow-up (i.e. at least two consecutive visits being diagnosed as AD and no reversion to MCI. All participants signed written informed consent for participation in the ADNI as approved by the institutional review board at each participating center.

2.2. Procedures

2.2.1. CSF measures

Details of acquisition are available on the ADNI webpage and upon request from the authors. Concentrations of $A\beta_{1\text{-}42}$, total tau (t-tau), and $\text{p-tau}_{181\text{p}}$ in CSF have been reported as strongly associated with the development of AD [13] and accurate in identifying incipient AD [14]. We used log-transformed values for $A\beta_{1\text{-}42}$, t-tau, and $\text{p-tau}_{181\text{p}}$ as well as for $\text{t-tau}/A\beta_{1\text{-}42}$, $\text{p-tau}_{181\text{p}}/A\beta_{1\text{-}42}$, and $A\beta_{1\text{-}42}/\text{p-tau}_{181\text{p}}$ ratios. Because some reports have indicated that the influence of $A\beta_{1\text{-}42}$ on brain volumetric and cognitive decline measures only occurs in the presence of elevated $\text{p-tau}_{181\text{p}}$ [9,15], we also included a measure of the linear combination of $A\beta_{1\text{-}42}$ and $\text{p-tau}_{181\text{p}}$ that has not been previously tested on their predictive utility for conversion to AD. According to published ADNI proposed CSF cutoffs values [16], we classified the subjects on the basis of high or positive (>23 pg/mL) and low or negative (<23 pg/mL) $\text{p-tau}_{181\text{p}}$ levels and low or positive (<192 pg/mL) and high or negative (>192 pg/mL) $A\beta_{1\text{-}42}$ levels. We calculated a new ordinal variable with the combination of these cutoffs levels that yielded four levels: high Aβ and low p-tau codified as 1, high Aβ and high p-tau codified as 2, low Aβ and low p-tau codified as 3, and finally low Aβ and high p-tau codified as 4. Subjects classified as having low Aβ (positive Aβ) and high p-tau (positive p-tau) were greater in the MCI converters group (82.1%) compared with nonconverters (53.1%) ($\chi^2 = 16.27$, $P = .001$).

2.2.2. PET-FDG acquisition and processing

A PET-FDG measure involving a voxelwise approach, the HCI, was used. This is a single measure intended to reflect the extent to which the pattern and magnitude of cerebral hypometabolism in an individual correspond to that in probable AD patients [10]. It also has been shown to be predictive of AD progression in MCI alone or in combination with hippocampal volume and episodic memory [17].

A specified reconstruction algorithm for each scanner type was implemented according to a standardized protocol to acquire FDG-PET data (www.loni.ucla.edu/ADNI/Data/ADNI_Data.shtml). All images were preprocessed by the

ADNI positron emission tomography (PET) coordinating center. The processing involved a voxelwise approach to analyze the data using statistical parametric mapping (SPM) performed by the Banner Alzheimer's Institute. In brief, an HCI was calculated for each subject as detailed in Chen and colleagues [10]; this index is intended to characterize the extent of cerebral metabolic rate for glucose (CMRgl) reductions in each person compared with the reductions in people with probable AD.

2.2.3. Magnetic resonance imaging acquisition and processing

The scans used in this study were obtained from 1.5T scanners at different sites involved in ADNI with minor variations in the magnetic resonance imaging (MRI) protocol that were based on the specific configuration of each scanner. For the purpose of the study presented here, volumetric measures of the whole brain, ventricles, and left and right hippocampus, as well as cortical thickness measures of the left and right middle temporal, inferotemporal, and entorhinal cortex, were investigated as derived by Freesurfer. A detailed description of the MRI protocol and methods is available on the ADNI webpage and upon request from the authors.

2.2.4. Cognitive assessment

The ADNI neuropsychological protocol followed guidelines to maximize inter-rater reliability and standard administration. The measures included in this study were the following: Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) word recall, recognition, naming, number cancellation, and constructional and ideational praxis tests [18]; the Clock Drawing test [19]; the Wechsler Memory Scale logical memory and Digit Span test [20]; the Rey auditory verbal learning test (AVLT) [21]; the semantic category fluency test [22]; the Trail Making test parts A and B [23]; and the Wechsler Adult Intelligence Scale digit symbol substitution test [24].

2.3. Statistical analyses

Demographic, clinical, biomarker, and cognitive markers were compared between groups using *t* tests. χ^2 tests were used to compare dichotomous variables.

To estimate the potential effects to predict conversion from MCI to AD of different sets of baseline variables, we fitted logistic regression models following a stepwise procedure. The primary outcome of interest was a change in the diagnostic (from MCI to AD) anytime during the 4 years of follow-up. We followed the same approach as in our previous study [2], structured as follows. First, we tested the predictive validity, sensitivity, and specificity of the best model we obtained in 2 years of follow-up but now applied to the 4-year follow-up data. Next, we performed sets of logistic regression analyses grouped in different clusters of variables: demographic variables and genetic risk factor (*APOE*), CSF biomarkers, MRI biomarkers, the PET-FDG HCI biomarker, and cognitive markers. This approach was undertaken to overcome the difference on sample sizes for each of the markers. From this set of clustered regression models, we then selected only the significant predictors (selection of entry was set at $P < .05$) and combined them to obtain a final model of prediction of conversion to AD. A coefficient of determination in the form of pseudo-R^2 was used as a measure of the relative predictive power of the models. The predictive accuracy of the model was calculated using receiver operating characteristic curve (ROC) analysis. Note that age, sex, and education were forced in all models.

3. Results

At baseline, 371 patients with MCI were included in the study: 53% were men, and the age ranged from 55 to 90 years. All of the MCI patients had completed cognitive assessment at baseline, 330 (88%) of them underwent successful MRI, and 163 (44%) underwent successful lumbar puncture.

Of the 371 patients diagnosed as MCI at baseline, 150 (40%) developed AD during follow-up (mean time until conversion 20.44 months; range 5.75–52.63). One-hundred sixty-eight MCI patients were stable at last follow-up (mean follow-up time 33.28 months; range 7.26–61.44).

Demographic, clinical characterization, and *APOE* genotype status of the subjects are displayed in Table 1. Cognitive, brain morphometry, and CSF measures are displayed in Tables 2 and 3. The differences between MCI stable and conversion groups were similar to those found in our previous report comprising 2 years of follow-up [2]. Differences in almost all clinical staging variables, cognitive variables, brain morphometric variables, FDG-PET, and CSF measures were found between both groups. Regarding cognitive measures, MCI nonconverters showed similar performance to MCI converters only in Digit Span test (Table 2). CSF measures, brain morphometry measures, and FDG-PET HCI (Table 3), a measure that was not included in our previous study, also detected differences between both MCI groups at baseline (except for ventricular volume, which was similar between MCI nonconverters and MCI converters).

3.1. Application of prior "best model"

By applying the best predictive model of conversion obtained at 2 years of follow-up (AVLT delayed, logical memory delayed, and left middle temporal lobe thickness) to the current 4 years of data, we obtained a pseudo-R^2 of 0.29 for the model (as compared with 0.34 at 2 years). The area under the curve (AUC) was 0.77 (as compared with 0.80 at 2 years), with a percentage of cases classified correctly of 68%, a sensitivity of 66%, and a specificity of 70% at a probability level of 0.50. The positive predictive value was 0.65, and the negative predictive value was 0.70.

Table 1
Baseline demographic, clinical, functional, and *APOE* genotype data

Data	MCI nonconverters (n = 168)	MCI converters (n = 150)	Statistical test	P
Sex (M/F)	109/59	90/60	$\chi^2 = 0.81$	.37
Age, mean (SD)	75.02 (7.51)	74.92 (7.03)	t316 = 0.12	.90
Years of education, mean (SD)	15.77 (3.11)	15.63 (2.91)	t316 = 0.41	.68
CDR sum of boxes, mean (SD)	1.44 (0.78)	1.82 (0.93)	t316 = −3.95	<.0001
MMSE, mean (SD)	27.42 (1.72)	26.67 (1.71)	t316 = 3.86	<.0001
APOE status	ε2ε2 = 0	ε2ε2 = 0	$\chi^2 = 19.58$	<.0001
	ε2ε3 = 12	ε2ε3 = 3		
	ε2ε4 = 3	ε2ε4 = 5		
	ε3ε3 = 82	ε3ε3 = 46		
	ε3ε4 = 56	ε3ε4 = 70		
	ε4ε4 = 15	ε4ε4 = 26		
	ε4 carrier (42%)	ε4 carrier (64%)		
FAQ score, mean (SD)*	2.54 (3.43)	5.36 (4.77)	t316 = −6.08	<.0001

Abbreviations: MCI, mild cognitive impairment; M, male; F, female; SD, standard deviation; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; FAQ, Functional Assessment Questionnaire.
*Missing data for two MCI nonconverters.

3.2. Use of clustered regression models

In the clustered logistic regression models for the prediction of conversion from MCI to AD at 4 years, the findings suggested a very similar pattern to the 2-year follow-up findings (Table 4). *APOE* was a significant predictor of conversion in the demographic and genetic risk factor cluster. Among the cognitive markers, AVLT Trial 5 was a significant predictor of conversion (instead of AVLT delayed in the 2-year study); ADAS-Cog memory scale entered in the model as opposed to the 2-year study, in which it did not predict conversion. The same brain cortical thickness measures as those found in the 2 years of follow-up (left middle temporal cortex thickness and left hippocampal volume) were still the best predictors of conversion at 4 years. Among the CSF biomarkers, the t-tau/$A\beta_{1\text{-}42}$ ratio remained a predictor of conversion, as it was at 2 years, whereas the new classification variable of the linear combination of Aβ and p-tau did not reach predictive statistical significance. The HCI index of FDG-PET at baseline was also predictive of conversion to MCI in this univariate model.

When all of the significant predictors of the clustered models (see "winners" model in Table 4) were entered in a single predictive logistic regression model, only the cognitive measures, AVLT Trial 5 and Clock Drawing test score, were found to best predict the development of AD in the MCI group of patients (pseudo-R^2 = 0.32). The ROC for this model showed an AUC of 0.78, a percentage of cases classified correctly of 78%, a sensitivity of 58%, and a specificity of 74% at a cutoff point of 0.50 (Figure 1). The positive predictive value was 0.65, and the negative predictive value was 0.67.

3.3. Contrast between old and new model of prediction

Last, we performed a χ^2 test to compare the areas under the two different ROC curves. This statistical test takes

Table 2
Baseline cognitive status

	MCI nonconverters (n = 168)	MCI converters (n = 150)	Statistical test	P
ADAS memory, mean (SD)	14.00 (5.19)	17.69 (4.43)	t316 = −6.78	<.0001
ADAS nonmemory,* mean (SD)	2.71 (2.10)	3.72 (2.54)	t313 = −3.88	<.0001
Logical Memory Immediate, mean (SD)	7.73 (3.02)	6.42 (3.09)	t316 = 3.81	<.0001
Logical Memory Delayed, mean (SD)	4.47 (2.65)	2.84 (2.44)	t316 = 5.68	<.0001
Clock Drawing test, mean (SD)	4.41 (0.81)	3.95 (1.08)	t316 = 4.31	<.0001
AVLT Trial 5, mean (SD)	8.24 (2.78)	6.43 (1.97)	t316 = 6.66	<.0001
AVLT Delayed, mean (SD)	3.72 (3.69)	1.57 (2.11)	t316 = 6.27	<.0001
AVLT Recognition, mean (SD)	10.41 (3.49)	8.69 (3.73)	t316 = 4.26	<.0001
Category Fluency, mean (SD)	13.91 (3.71)	12.74 (3.37)	t316 = 2.92	.004
Trails A, mean (SD)	40.39 (16.00)	48.68 (25.58)	t316 = −3.50	.001
Trails B,‖ mean (SD)	115.04 (61.74)	151.30 (80.79)	t313 = −4.50	<.0001
Digit Span, mean (SD)	7.17 (1.80)	7.19 (1.67)	t316 = −0.09	.93
Digit Symbol, mean (SD)	39.52 (10.61)	34.41 (10.58)	t316 = 4.30	<.0001

Abbreviations: ADAS, Alzheimer's Disease Assessment Scale; AVLT, auditory verbal learning test; FDG-PET, fluorodeoxyglucose-positron emission tomography; HCI, hypometabolic convergence index; MCI, mild cognitive impairment; SD, standard deviation.
*Missing data for one MCI nonconverter and two MCI converters.
‖Missing data for three MCI nonconverters.

Table 3
Baseline brain morphometry and CSF biomarkers

Brain morphometry	MCI nonconverters (n = 152)	MCI converters (n = 132)	Statistical test	P
Whole brain, mean (SD)*	1,004,472 (103,950)	979,445 (115,133)	t282 = 1.92	.06
Ventricles, mean (SD)*	43,850 (22,151)	46,619 (18,878)	t282 = −1.12	.26
Left hippocampus, mean (SD)*	3236 (503)	2987 (493)	t282 = 4.21	<.0001
Right hippocampus, mean (SD)*	3424 (542)	3152 (568)	t282 = 4.13	<.0001
Left middle temporal cortical thickness, mean (SD)†	2.49 (0.19)	2.35 (0.21)	t282 = 5.79	<.0001
Right middle temporal cortical thickness, mean (SD)†	2.54 (0.18)	2.41 (0.23)	t282 = 5.20	<.0001
Left entorhinal cortical thickness, mean (SD)†	2.96 (0.51)	2.76 (0.45)	t282 = 3.54	<.0001
Right entorhinal cortical thickness, mean (SD)†	3.09 (0.53)	2.86 (0.51)	t282 = 3.72	<.0001

FDG-PET	MCI nonconverters (n = 88)	MCI converters (n = 74)	Statistical test	P
HCI, mean (SD)	7.14 (3.47)	9.75 (3.88)	t160 = −4.52	<.0001

CSF biomarkers	MCI nonconverters (n = 82)	MCI converters (n = 84)	Statistical test	P
Aβ, mean (SD)	5.09 (0.35)	4.94 (0.26)	t164 = 3.13	.002
t-tau, mean (SD)	4.38 (0.52)‡	4.61 (0.40)	t164 = −3.06	.003
p-tau, mean (SD)	3.33 (0.52)	3.58 (0.42)§	t164 = −3.46	.001
t-tau/Aβ, mean (SD)	−0.71 (0.74)‡	−0.34 (0.54)	t164 = −3.64	<.0001
p-tau/Aβ, mean (SD)	−1.76 (0.77)	−1.36 (0.57)	t164 = −3.81	<.0001

Abbreviations: MCI, mild cognitive impairment; SD, standard deviation; FDG-PET, fluorodeoxyglucose-positron emission tomography; HCI, hypometabolic convergence index; CSF, cerebrospinal fluid; Aβ, amyloid-β; t-tau; total tau; p-tau, phosphorylated tau.

*Measured in cubic millimeters.

†Measured in millimeters.

‡n = 79, three subjects had Aβ but not t-tau.

§n = 85, one subject had p-tau but not t-tau or Aβ.

into account both AUCs (prior and current model) and their respective standard errors ($\chi^2 = [AUC_1 - AUC_2]^2/[s_1^2 + s_2^2]$). The results showed that both models were not statistically different ($\chi^2 = 0.35$; $P = .56$).

3.4. Patterns of decline in the different classes of markers

Figure 2 shows the difference (in effect size [ES]) between baseline and the different follow-ups for both groups of MCI subjects (converters and nonconverters). The group of MCI subjects who converted to AD showed greater decline in function (ES ranging from medium to large), as measured with the Functional Assessment Questionnaire (FAQ) [25], and in cognitive measures such as ADAS-Cog, AVLT Trial 5, and semantic fluency (with ES in the small to large range). ES for CSF and brain morphometry measures were small, except for a medium effect of middle temporal thickness, ventricular volume, left entorhinal cortex thickness, and the HCI. The group of MCI nonconverters had ES in the low to low-medium range, except for FAQ and middle temporal thickness from both hemispheres, which were medium (0.59 and 0.5, respectively).

4. Discussion

In this prospective study investigating a combination of different classes of biomarkers and cognitive markers in predicting development of AD in MCI patients during a follow-up period of 4 years, two cognitive measures, a verbal episodic memory measure of learning (AVLT Trial 5), and a screening measure (Clock Drawing test) assessing a combination of semantic knowledge, visual motor ability, and executive function, were found to be the most significant predictors. Furthermore, these findings are strengthened by a complementary analysis in which patterns of decline on the different markers showed that cognitive measures (plus a measure of function) had larger ES in the MCI subgroup that progressed to AD.

In our previous study in the same sample, but with a shorter follow-up of 2 years, we found that two episodic delayed memory measures (plus left middle temporal thickness) were the variables that best predicted conversion to AD [2]. Application of this former predictive model to the current 4-year data yielded an AUC of 0.77 (sensitivity = 66% and specificity = 70%). In comparison to our initial 2011 model, this reflected a decrease in specificity but an increase in sensitivity in the measures' ability to predict conversion to AD in 4 years of follow-up. Nevertheless, and critically, AUC and the pseudo-R^2 of our initial model at 2 years of follow-up were fully comparable to the new "winners" model at 4 years of follow-up (AUC = 0.78).

Several studies from ADNI, including our original study, have demonstrated that cognitive tests are robust predictors of MCI to AD conversion and HC-MCI discrimination [2–5,17]. Studies conducted in other MCI populations (i.e., outside of ADNI) have found results similar to ours when combining different classes of markers [26,27]. Furthermore some findings place verbal episodic memory impairments (recall and learning) at least 5 years before dementia onset [28–30]. An interesting study has indicated that memory decline may be indicative of subclinical AD

Table 4
Clustered logistic regression models of conversion over 4 years

	OR (95% CI)	$\Delta R^2/P$
Demographics and *APOE* ($\chi^2 = 15.07/P = .005$; AUC = 0.62)		
APOE	2.41 (1.50-3.91)	$\Delta R^2 = 0.07/P = .0003$
Cognitive markers ($\chi^2 = 84.23/P < .0001$; AUC = 0.78)		
AVLT Trial 5	0.83 (0.73-0.95)	$\Delta R^2 = 0.19/P < .0001$
Logical Memory delayed	0.83 (0.74-0.93)	$\Delta R^2 = 0.05/P = .0003$
Clock Drawing test	0.65 (0.48-0.86)	$\Delta R^2 = 0.03/P = .001$
Trail Making test, part A	1.02 (1.00-1.03)	$\Delta R^2 = 0.03/P = .01$
ADAS-Cog memory	1.08 (1.01-1.15)	$\Delta R^2 = 0.02/P = .02$
Brain morphometric measures ($\chi^2 = 50.45/P < .0001$; AUC = 0.74)		
Left middle temporal lobe thickness	0.03 (0.007-0.12)	$\Delta R^2 = 0.16/P < .0001$
Left hippocampus volume	0.999 (0.998-0.999)	$\Delta R^2 = 0.06/P = .0002$
FDG-PET measure ($\chi^2 = 17.96/P < .0001$; AUC = 0.70)		
HCI	1.21 (1.10-1.34)	$\Delta R^2 = 0.15/P = .0007$
CSF biomarkers ($\chi^2 = 14.66/P = .005$; AUC = 0.66)		
p-tau/Aβ ratio	2.34 (1.45-3.91)	$\Delta R^2 = 0.12/P = .0005$
"Winners" model, i.e., including only previous significant measures ($\chi^2 = 19.64/P = .001$; AUC = 0.78)		
AVLT Trial 5	0.65 (0.47-0.85)	$\Delta R^2 = 0.20/P = .001$
Clock Drawing test	0.43 (0.21-0.85)	$\Delta R^2 = 0.12/P = .006$

Abbreviations: OR, odds ratio; CI, confidence interval; AUC, area under the curve; AVLT, auditory verbal learning test; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; CSF, cerebrospinal fluid; Aβ, amyloid-β; FDG-PET, fluorodeoxyglucose-positron emission tomography; HCI, hypometabolic convergence index.

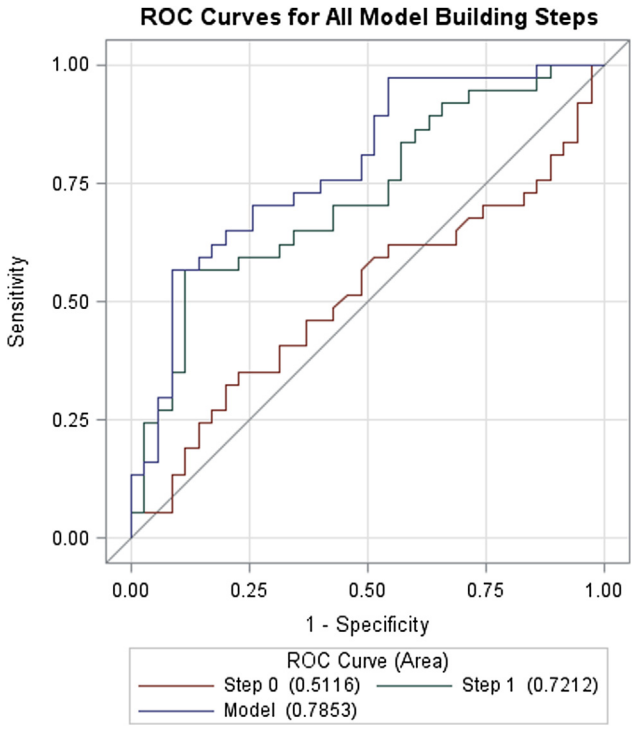

Fig. 1. ROC of the "winners" logistic regression model. The red line indicates the three demographic variables (age, gender, and education) forced into the model; the green line indicates the first variable to enter in the model, auditory verbal learning test trial 5 (AVLT Trial 5) with an AUC of 0.72; the blue line indicates the last variable to enter the model, the Clock Drawing test score with an AUC of 0.78. Abbreviations: ROC, receiver operating characteristic curve; AUC, area under the curve.

in otherwise healthy individuals as demonstrated by amyloid accumulation in PET-amyloid imaging [31]. Individual AUC for neuropsychological predictors (AVLT) was in some cases as high as for the combination models [27]. Nevertheless, studies outside of ADNI have reported higher AUC probabilities as compared with our AUCs. Differential characteristics of the MCI samples under examination and different sampling procedures may have played a role in this discrepancy because other studies derived from ADNI have reported similar AUCs to ours when comparing MCI patients that converted to AD to those who remained stable [3].

There are several other issues that deserve comment. First, our new predictive model did not include any brain morphometry measure. Although left middle temporal lobe thickness and left hippocampus volume were significant predictors in the individual MRI model, they did not reach statistical significance when combined with the rest of the markers. One possible reason for this might be related to the inclusion of a glucose metabolism measure (FDG-PET) because when this biomarker was not modeled, left middle temporal lobe thickness and left hippocampus volume (plus episodic memory) were significant predictors of conversion in the combined model (data not shown). Furthermore, a complementary analysis showed that middle temporal thickness and FDG-PET had greater decline along 4 years than the rest of the brain morphometric measures (see Figure 2). Hence, collinearity and sample size issues (subjects with valid measures on all of the variables changed as a different set of variables were fitted together) may have forced the exclusion of MRI measures in the final model.

A second issue relates to our CSF findings. When modeling only CSF measures, the p-tau/$A\beta_{1\text{-}42}$ ratio was found to be predictive of AD conversion; however, this ratio did not demonstrate predictive significance when combined with other measures (MRI, FDG-PET, and cognitive measures) in the final regression model. Therefore, in this MCI sample, CSF biomarkers at baseline did not have independent predictive utility when combined with other predictors, and they did not show significant decline through follow-up. It might be possible that this result is related to the stage in the progression of the underlying neuropathology in this particular MCI population [32] (i.e., CSF biomarkers have been proposed as more informative in very early preclinical states) or increased utility in longer follow-ups [33], making these measures perhaps more suitable to identify healthy subjects at risk of future AD development. However, our results suggest that cognitive markers may be equally if not more effective as predictors in our study. As opposed to our methods, preclinical CSF studies generally do not directly compare CSF and cognitive markers. In addition, it has also been claimed that Aβ-associated brain volume loss [15] and clinical decline [9] occur only in the presence of elevated p-tau. However, our findings do not point

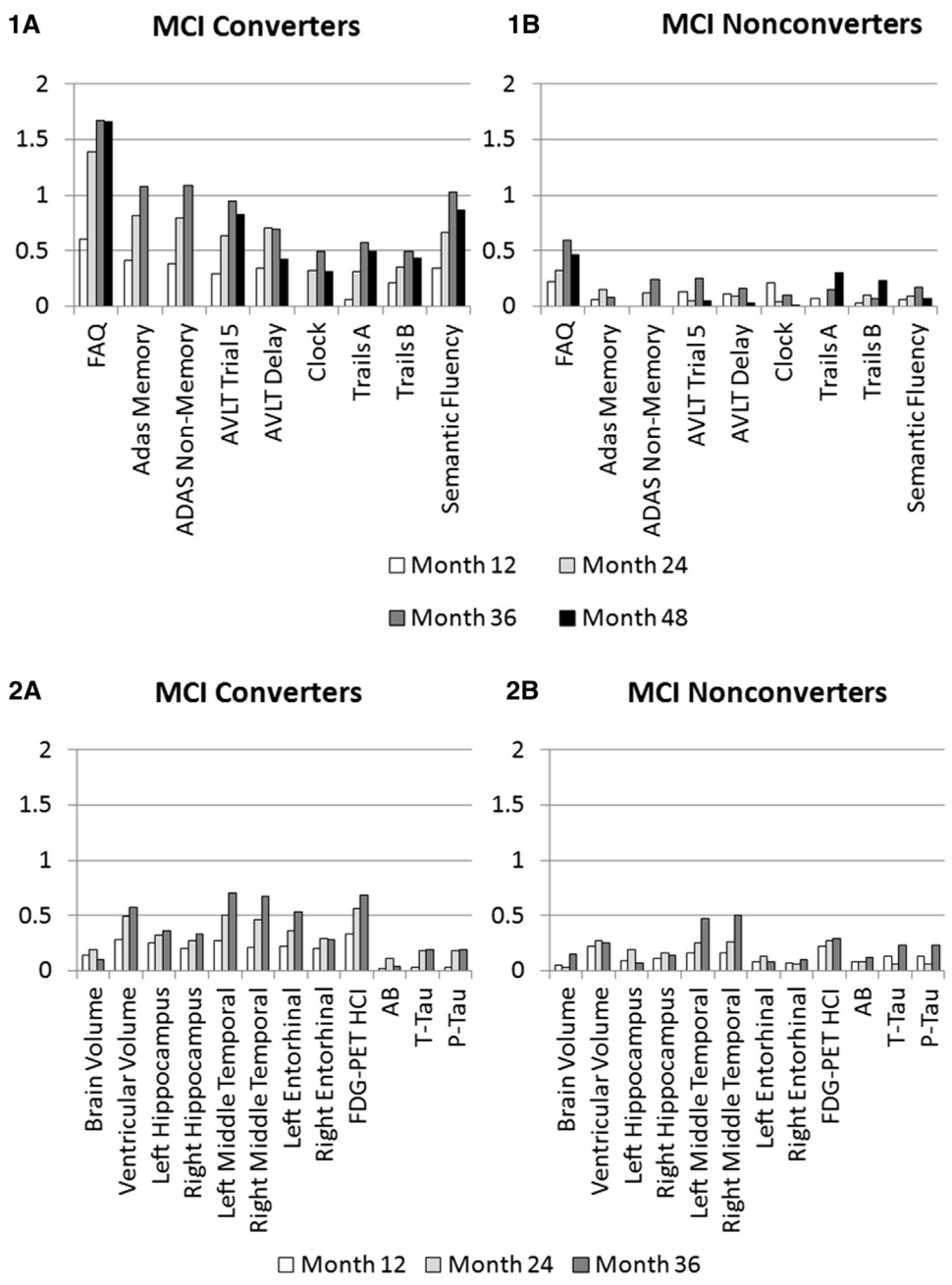

Fig. 2. Patterns of decline of the different classes of markers. Panel 1 shows the effect sizes for the difference in cognitive and functioning measures between baseline and each one of the follow-ups from months 12 to 48 (except for the ADAS-Cog test from month 12 to 36): (1A) the MCI group that converted to AD and (1B) the MCI group that remained stable. Panel 2 shows effect sizes in MRI morphometry, FDG-PET HCI, and CSF biomarkers between baseline and each one of the follow-ups from months 12 to 36 (measures at month 48 were not available): (2A) the MCI group that converted to AD and (2B) the MCI group that remained stable. Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive; MCI, mild cognitive impairment; AD, Alzheimer's disease; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose–positron emission tomography; HCI, hypometabolic convergence index; CSF, cerebrospinal fluid.

toward a strong predictive ability of a p-tau/Aβ linear combination on AD progression in MCI.

Third, it is important to note that the number of subjects included in our regression models decreased when predictive variables were progressively estimated together given that fewer subjects underwent lumbar punctures compared with MRI or cognitive assessment; this fact may have restricted our ability to adequately compare different clusters of markers in simultaneous combination. Our approach to overcome this issue was clustering set of similar markers into separate regression analyses, hence maximizing sample size on each model, and finally aggregating the resulting significant measures ("winners") into a final predictive model. Also, we acknowledge that our

findings may not be fully generalizable to other studies outside of ADNI.

Fourth, another factor that could have influenced our findings is related to the age of the subjects studied. MRI and cognition have been found to remain informative in older and younger patients (as subjects included in our study), unlike CSF biomarkers, which are only predictive of subsequent AD development in younger individuals [34]. As such, biological and cognitive markers may have different roles at various points in the development of AD (i.e., they can be differentially sensitive to changes at different stages of the disease) [35].

Finally, as our complementary ES analysis indicated, function as measured by the FAQ showed the highest decline through 4 years in the MCI converters subgroup. However, we did not include it in the predictive models because doing so would create a tautology (i.e., function is used to distinguish the MCI and AD diagnoses). Nevertheless, it is empirically a strong predictor of conversion.

In summary, cognitive markers were still predictive of conversion to AD in a MCI population at 4 years of follow-up as they were found to be at 2 years of follow-up. This set of findings highlights the importance of cognitive measures, even those derived from basic clinical neuropsychological tests, in their predictive utility for MCI to AD progression.

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RESEARCH IN CONTEXT

1. Systematic review: Few studies combining several clinical, cognitive, and biological markers in the progression of MCI to AD have been performed. We searched PubMed for published studies of combined predictive utility of different markers on the progression from MCI to AD and conducted our analyses in ADNI.
2. Interpretation: Our findings highlight the importance of cognitive measures on the detection of preclinical AD and prediction of progression from MCI to AD over shorter and longer time periods. Cognitive markers perform as robustly, if not more so, than biomarkers in unbiased predictive models of the development of AD.
3. Future directions: Future studies should compare all classes of markers on integrative models of prediction comprising longer follow-ups in at risk groups. Development of novel and sensitive measures of episodic memory may be an economical, safe, and empirically promising approach to capture changes in prodromal AD and perhaps preclinical AD.

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