

Neuropsychological Testing Predicts Cerebrospinal Fluid Amyloid- β in Mild Cognitive Impairment

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Abstract.

Background: Psychometric tests predict conversion of mild cognitive impairment (MCI) to probable Alzheimer's disease (AD). Because the definition of clinical AD relies on those same psychometric tests, the ability of these tests to identify underlying AD pathology remains unclear.

Objective: To determine the degree to which psychometric testing predicts molecular evidence of AD amyloid pathology, as indicated by cerebrospinal fluid (CSF) amyloid- β ($A\beta$)₁₋₄₂, in patients with MCI, as compared to neuroimaging biomarkers.

Methods: We identified 408 MCI subjects with CSF $A\beta$ levels, psychometric test data, FDG-PET scans, and acceptable volumetric MR scans from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We used psychometric tests and imaging biomarkers in univariate and multivariate models to predict $A\beta$ status.

Results: The 30-min delayed recall score of the Rey Auditory Verbal Learning Test was the best predictor of $A\beta$ status among the psychometric tests, achieving an AUC of 0.67 ± 0.02 and odds ratio of 2.5 ± 0.4 . FDG-PET was the best imaging-based biomarker (AUC 0.67 ± 0.03 , OR 3.2 ± 1.2), followed by hippocampal volume (AUC 0.64 ± 0.02 , OR 2.4 ± 0.3). A multivariate analysis based on the psychometric tests improved on the univariate predictors, achieving an AUC of 0.68 ± 0.03 (OR 3.38 ± 1.2). Adding imaging biomarkers to the multivariate analysis did not improve the AUC.

Conclusion: Psychometric tests perform as well as imaging biomarkers to predict presence of molecular markers of AD pathology in MCI patients and should be considered in the determination of the likelihood that MCI is due to AD.

Keywords: Alzheimer's disease, magnetic resonance imaging, mild cognitive impairment, positron emission tomography

¹Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: <http://adni.loni.usc.edu/>

wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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INTRODUCTION

Recent guidelines for diagnosing mild cognitive impairment (MCI) due to Alzheimer's disease (AD) have emphasized the importance of psychometric testing for establishing the existence of MCI, and subsequently relying on biomarkers based on imaging and biofluids to assess the likelihood that the existing cognitive impairment is "due to AD" relative to a different cause [1]. In particular, cognitive testing is a component of the "core clinical criteria" for MCI, which requires that impairment greater than expected for age must be present in at least one cognitive domain. Once clinical categorization of MCI is established, the guidelines suggest that the likelihood that the cognitive phenotype is "due to AD" should rely on various imaging and molecular biomarkers (each classified as either a biomarker of neurodegeneration or cerebral amyloid), without specifically taking into account the severity of the cognitive deficit within the MCI category.

Although imaging-derived biomarkers for diagnosis of AD and prediction of conversion from MCI to AD have been the subject of intensive research [2–4], how these biomarkers can be used most effectively in the presence of alternative sources of clinical information about a subject's status, such as cognitive testing, is still not settled. Several recent studies have examined the relative utility of cognitive testing, imaging, or molecular biomarkers for predicting conversion from MCI to AD [5–9]. These studies have generally found that cognitive testing performs similarly to other biomarkers, but a potential criticism of these study designs is that using psychometric measurements to predict conversion to AD is circular, as the diagnosis of AD is itself determined in large part based on psychometric tests that are the same as or similar to those used to predict conversion.

To avoid this circularity, we sought to determine if cognitive testing with standard psychometric measures can predict the presence of cerebral amyloid based on a well-established cerebrospinal fluid (CSF) molecular biomarker, the detection of which is independent of cognitive scores, unlike clinical diagnosis of conversion to AD. Although postmortem histology remains the gold standard for establishing AD pathology, measures of CSF $A\beta_{1-42}$ and amyloid positron emission tomography (PET) imaging are the closest currently available surrogate [10, 11]. For the present study, we used CSF $A\beta$ as a marker for AD pathology given its higher uniform availability in the studied cohort. We choose CSF $A\beta$ in isolation, as opposed to

tau/ $A\beta$ ratio, because we were specifically comparing the relationship between cognitive and neuroimaging neurodegenerative biomarkers and evidence of AD molecular pathology; thus, incorporating a molecular neurodegenerative marker like tau may confound the results. Moreover, we wanted to determine the relative and combined predictive value of psychometric testing with neuroimaging biomarkers of neuronal injury or neurodegeneration.

In particular, we examined several cognitive measures, including verbal memory, given their putative sensitivity to prodromal AD. We used diverse imaging-derived biomarkers to accurately represent both standard and developing measurement approaches. Further, we chose structural magnetic resonance imaging (MRI) and FDG-PET measures given their emphasis in the MCI guidelines. For MRI data, we used an automated hippocampal volume measurement, several cortical-thickness measurements including a summary measure of several regions associated with AD-related tissue loss [12, 13], and multivariate analysis of voxelwise measurements of cortical thickness [14, 15]. Hippocampal volume is considered to be one of the most established biomarkers of AD with numerous studies demonstrating its predictive value in MCI. We also used FDG-PET data from a set of regions (meta-region of interest, ROI) previously determined to be sensitive to early AD and prediction of clinical conversion to AD in MCI cohorts [16]. To obtain such a wide variety of clinical data in a sufficiently large population, we utilized the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. If cognitive measures perform similarly to both more standard and developing imaging biomarkers in prediction of AD pathology with MCI patients, they can provide a cost-effective and easily accessible method for assessing the likelihood of prodromal AD in patients with MCI.

METHODS

Clinical data

Subjects

This study was a retrospective analysis of data obtained from the ADNI database (<http://adni.loni.usc.edu>). The ADNI was launched 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, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has

130 been to test whether serial MRI, PET, other biological
131 markers, and clinical and neuropsychological assess-
132 ment can be combined to measure the progression of
133 MCI and early AD. Determination of sensitive and spe-
134 cific markers of very early AD progression is intended
135 to aid researchers and clinicians to develop new treat-
136 ments and monitor their effectiveness, as well as lessen
137 the time and cost of clinical trials.

138 Data used in this article were downloaded from the
139 ADNI website in January 2014. We included only
140 MCI subjects with complete datasets for the current
141 analysis, including CSF A β levels, all neuropsycho-
142 logical tests examined, and FDG-PET. Only those
143 subjects with Freesurfer cortical and hippocampal seg-
144 mentations of acceptable quality, as determined by the
145 publicly available Freesurfer dataset available through
146 ADNI, were included.

147 In the ADNI study, MCI is split into two groups,
148 early MCI (EMCI) and late MCI (LMCI). Diagnos-
149 tic criteria for both EMCI and LMCI subjects were
150 as follows: Mini-Mental State Examination (MMSE)
151 scores between 24–30 (inclusive), a subjective memory
152 concern reported by subject, informant, or clinician, a
153 Clinical Dementia Rating of 0.5, absence of signifi-
154 cant levels of impairment in other cognitive domains,
155 essentially preserved activities of daily living, and an
156 absence of dementia. They also were required to have
157 objective memory loss measured by education adjusted
158 scores on delayed recall of one paragraph from
159 Wechsler Memory Scale Logical Memory II, which
160 further determined EMCI (≥ 16 years: 9–11; 8–15
161 years: 5–9; 0–7 years: 3–6) or LMCI (≥ 16 years: ≤ 8 ;
162 8–15 years: ≤ 4 ; 0–7 years: ≤ 2) status. In this
163 manuscript, MCI refers to both EMCI and LMCI.

164 The ADNI study includes a variety of collection sites
165 around the United States and Canada, and a full list
166 is available at <http://adni.loni.usc.edu/about/centers-cores/study-sites/>. Recruitment for the ADNI study
167 aimed to achieve a balance of normal controls, MCI,
168 and AD subjects. For ADNI 1, a random subsample
169 of subjects was selected for FDG imaging; in ADNI
170 2/GO, all subjects enrolled received FDG imaging.
171 For up-to-date information on specific inclusion and
172 exclusion criteria, please see <http://www.adni-info.org>.
173

174 *Psychometric testing*

175 We aimed to include a battery of psychometric tests
176 that would cover a broad range of cognitive domains,
177 with special focus on memory due to its importance in
178 AD. For memory, we included components of the Rey
179 Auditory Verbal Learning Test (AVLT) [17] given its

180 richness of measures for various aspects of mnemonic
181 processing (e.g., immediate versus delayed recall ver-
182 sus delayed recognition); for assessment of cognitive
183 speed, sequencing, and executive function, the Trail
184 Making Test [18] (Trails A and Trails B) was used; for
185 language/semantics, category fluency [19] (Animals)
186 and the Boston Naming Test [20] were examined; and
187 as a measure of global cognition, the MMMSE was
188 utilized [21]. We examined several of the AVLT mea-
189 sures, which depend on differential aspects of episodic
190 and working memory [22]. The AVLT consists of five
191 learning trials in which a list of 15 words is read and the
192 subject is asked to immediately recall as many items as
193 possible. After an interference list of 15 novel words
194 is read and recalled, subjects are then asked to recall
195 words from the initial list (5-min delayed recall). A 30-
196 min delayed recall trial and recognition test follow. For
197 the recognition test, subjects are presented with a list
198 of the 15 studied words and 15 nonstudied foils and
199 are asked to circle all words previously studied. To
200 account for false alarms (FA) to nonstudied items, we
201 calculated a measure of discriminability, d' (d'),
202 in a standard fashion based on classic signal detection
203 theory [23]. Because d' is undefined when either pro-
204 portion is 0 or 1, we used standard formulas to convert
205 these values: Hits = (no. of hits + 0.5)/(no. of studied
206 items + 1) and FA = (no. of FA + 0.5)/(no. of unstudied
207 items + 1). For the current study, we analyzed perfor-
208 mance on the fifth immediate memory trial (AVLT Trial
209 5 Recall), 5- and 30-min delayed recall (AVLT 5-min
210 Recall, AVLT 30-min Recall), and recognition memory
211 discrimination (AVLT Recognition Discrimination). In
212 addition, we calculated a retention score, which is the
213 number of items remembered after a 30-min delay
214 (AVLT 30-min Recall) divided by the number of items
215 remembered during the last immediate memory trial
216 (AVLT Trial 5 Recall).

217 *Determination of amyloid and ApoE status*

218 CSF-based molecular biomarkers were processed
219 by the University of Pennsylvania/ADNI Biomarker
220 Core Laboratory as previously described [10, 24].
221 An A β_{1-42} value of less than or equal to 191 pg/ml
222 was considered to be “positive” for the presence of
223 amyloid pathology based on a prior autopsy-based
224 study performed at the University of Pennsylvania
225 [10]. For analyses involving ApoE status, subjects
226 were dichotomized into ApoE $\epsilon 4$ positive and negative
227 groups. ApoE $\epsilon 4$ positive status is defined as having at
228 least one ApoE $\epsilon 4$ allele.

229 *Neuroimaging measures*

230 Processing of neuroimaging data included both anal- 279
 231 yses made publicly available by ADNI and in-house 280
 232 image processing. The following analyses were based 281
 233 on preprocessed data downloaded from the ADNI web- 282
 234 site: FDG-PET scans were acquired and analyzed in 283
 235 accordance with a standard protocol [16]. Mean FDG 284
 236 uptake was averaged over 5 ROIs that are sensitive 285
 237 to AD-related changes in metabolism, including right 286
 238 and left angular gyri, right and left inferior tempo- 287
 239 ral regions, and bilateral posterior cingulate. These 288
 240 regions were averaged into a meta-ROI and normalized 289
 241 to an ROI focused on the pons and cerebellar vermis to 290
 242 give a summary FDG PET measure. Cortical thickness 291
 243 and hippocampal measurement of the MRI scans were 292
 244 performed according to the standard ADNI Freesurfer 293
 245 [25] processing pipeline, and downloaded from the 294
 246 ADNI website. Only images that passed ADNI quality 295
 247 control for the temporal, occipital, temporal, and pari- 296
 248 etal lobe were included. Cortical thickness in the caudal 297
 249 portion of the middle frontal gyrus, medial portion of 298
 250 the orbital frontal cortex, inferior parietal lobule, lat- 299
 251 eral portion of the occipital cortex, inferior temporal 300
 252 gyrus, entorhinal cortex, temporal pole, and the isth-
 253 mus of the cingulate cortex were averaged to form a
 254 meta-ROI thought sensitive to early AD related neu-
 255 rodegeneration, as previously suggested [26].

256 *Image analysis*

257 In addition to the image analysis performed by var- 301
 258 ious ADNI investigators, we ran additional analyses 302
 259 of MR images to supplement standard approaches 303
 260 with a state of the art multivariate analysis techni- 304
 261 que. 1.5T and 3T non-accelerated T1-weighted 305
 262 MPRAGE and SPGR MRI scans of all MCI subjects 306
 263 from ADNI1 and ADNI2/GO were downloaded from 307
 264 <http://adni.loni.usc.edu>. We computed an alternative 308
 265 measure of cortical thickness using DiReCT [12, 13], 309
 266 and used the AAL label set [27] to define medial tem- 310
 267 poral and precuneal ROIs, as these areas are known to 311
 268 atrophy in early AD. We performed a singular value 312
 269 decomposition (SVD) analysis of the whole-brain cor- 313
 270 tical thickness data, as this analysis has proven useful 314
 271 in differentiating AD from frontotemporal dementia 315
 272 and predicting CSF-based biomarkers in this popula- 316
 273 tion [28, 29]. The SVD was performed using the prin- 317
 274 comp function in R, and we retained the top 10 com- 318
 275 ponents. A grid search strategy using bootstrapping 319
 276 with 100 repetitions, with half the subjects left out 320
 277 for a validation cohort, was used to determine the 321
 optimal number of components to retain. 322

278 *Statistical analysis*

279 All statistical analysis was performed using the R 280
 281 programming language, version 3.1.0. For predictive 282
 283 studies, we randomly split the subjects 5 times into 284
 285 training and testing cohorts, retaining half the subjects 286
 287 for training and using the other half for testing in a 288
 289 5×2 cross-validation scheme [30]. All area under the 290
 291 curve (AUC), odds ratios, and positive and negative 291
 292 predictive values are on the testing cohorts. Two-tail 292
 293 t -tests were used to compare AUC values between 293
 294 testing cohorts of different models to calculate a 294
 295 p -value for differences in mean AUC; false discovery 295
 296 rate (FDR) correction was applied to correct for multi- 296
 297 ple comparisons. For all analyses, patient age, gender, 297
 298 and education were used as additional predictors; for 298
 299 all MR-based imaging analyses, magnet field strength 299
 300 (1.5 or 3T) was included as a covariate. In addition to 300
 univariate predictions of A β status from psychometrics 301
 and imaging modalities, we performed principal com- 302
 ponent regression, using three principal components, 303
 on all the psychometric scores, as well as the psycho- 304
 metric and imaging values combined. AUC analysis 305
 was performed using the ROC package in R [31]. 306

307 **RESULTS**308 *Subject demographics*

309 Subject data was collected between January 2006 310
 311 and January 2013. A total of 622 MCI subjects with 311
 312 CSF-derived A β values were identified, and 407 of 312
 313 those were A β positive. Of these, 547 (350 A β posi- 313
 314 tive) had FDG scans; 450 (286 A β positive) had 314
 315 complete Freesurfer segmentations without failures; 315
 316 433 (273 A β positive) had intracranial volume avail- 316
 317 able; and 408 subjects (257 A β positive) had complete 317
 318 psychometric scores available. There was a mean dif- 318
 319 ference of 15 days between the psychometric tests 319
 320 and imaging studies, with 95% of subjects having 320
 321 the imaging and psychometric tests done within 55 321
 322 days of each other. The maximum time difference 322
 323 was 138 days. A total of 62 adverse events were 323
 324 reported from the lumbar punctures, most of which 324
 325 were headaches (25 cases) or pain (23 cases), with 325
 two subjects reporting nausea and a few reporting a 326
 variety of other effects, including bruising, tenderness, 327
 and swelling. One adverse event, transient procedural 328
 anxiety, occurred during the imaging. 329

330 A summary of the demographics of the study 331
 332 population, including the psychometric and imag- 332
 333 ing information, is given in Table 1. We computed 333

Table 1
Summary of demographics, psychometric scores, and imaging data for subjects

	All subjects (mean \pm standard deviation)	A β +	A β -
Number of subjects	408	257	151
Number of males	232	151	81
Number of ApoE ϵ 4+	207	178	29
Age	71.61 \pm 7.16	72.66 \pm 6.76	69.79 \pm 7.47
Education	16.24 \pm 2.71	16.14 \pm 2.79	16.41 \pm 2.59
Mini-Mental Status Examination	28.0 \pm 1.74	27.7 \pm 1.80	28.4 \pm 1.54
AVLT Trial 5 Recall	9.03 \pm 3.00	8.35 \pm 2.85	10.19 \pm 2.90
AVLT 5-min Recall	5.65 \pm 3.74	4.82 \pm 3.42	7.05 \pm 3.87
AVLT 30-min Recall	4.27 \pm 3.92	3.30 \pm 3.33	5.92 \pm 4.29
AVLT Recognition Discrimination	2.31 \pm 1.21	2.07 \pm 1.18	2.72 \pm 1.14
Retention	0.41 \pm 0.31	0.34 \pm 0.29	0.53 \pm 0.31
Trail Making Test A	39.00 \pm 16.71	41.64 \pm 18.21	34.50 \pm 12.63
Trail Making Test B	105.70 \pm 57.60	116.30 \pm 62.47	87.66 \pm 42.69
Boston Naming Test	26.92 \pm 3.28	26.73 \pm 3.20	27.26 \pm 3.39
Category fluency (animals)	18.05 \pm 4.93	17.44 \pm 4.88	19.08 \pm 4.84
Hippocampal volume	3497.62 \pm 577.07	3386.02 \pm 537.17	3687.56 \pm 537.17
Medial Temporal Thickness	3.83 \pm 0.60	3.78 \pm 0.61	3.93 \pm 0.57
Precuneus Thickness	1.54 \pm 0.39	1.52 \pm 0.39	1.58 \pm 0.37
Mean Cortical Thickness of AD Meta-ROI	2.64 \pm 0.17	2.61 \pm 0.17	2.68 \pm 0.16
Mean FDG-PET SUVR of AD Meta-ROI	1.26 \pm 0.14	1.23 \pm 0.15	1.31 \pm 0.11

Table 2
Summary of univariate logistic regressions predicting A β status from each psychometric test and imaging biomarker. Age, gender, and education level (in years) were included as covariates. All data were scaled before regression to facilitate inspection of regression coefficients

	β Estimate	Std. Error	Zval	p val
Mini-Mental State Examination	-0.36	0.12	-3.11	1.9E-3
AVLT Trial 5 Recall	-0.57	0.12	-4.946	7.6E-7
AVLT 5-min Recall	-0.55	0.11	-4.83	1.3E-6
AVLT 30-min Recall	-0.63	0.11	-5.47	4.4E-8
Trail Making Test A	0.44	0.14	3.18	1.5E-3
AVLT Recognition Discrimination	-0.50	0.11	-4.45	8.7E-6
Retention	-0.59	0.11	-5.25	1.5E-7
Trail Making Test B	0.52	0.15	3.57	3.6E-4
Boston Naming Test	-0.08	0.11	-0.76	4.5E-1
Category fluency (animals)	-0.26	0.11	-2.39	1.7E-2
Hippocampal volume	-0.43	0.13	-3.44	5.9E-4
Medial Temporal Thickness	-0.12	0.11	-1.01	3.1E-1
Precuneal Thickness	-0.01	0.12	-0.05	9.6E-1
Mean Cortical Thickness of AD Meta-ROI	-0.23	0.12	-1.88	6.1E-2
Mean FDG-PET SUVR of AD Meta-ROI	-0.54	0.12	-4.57	4.9E-6

326 a logistic regression relating each psychometric
327 test and modality with A β status, while covary-
328 ing for age, gender, and education (Table 2). The
329 logistic regression results indicated that the psycho-
330 metric tests and imaging modalities were predictive
331 of A β status, even when included in a univariate
332 model.

333 Predictive models

334 The associations between the various psychometric
335 scores and A β status were strong enough to predict
336 A β status when the data used to train the model was
337 separate from the data used for evaluation. While

338 many of the psychometric measures displayed pre-
339 dictive value, varying in range of AUCs from 0.59
340 to 0.67, immediate and delayed recall measures per-
341 formed particularly well, reaching an AUC of 0.65 and
342 0.67 respectively, corresponding to odds ratios of 3.0
343 and 2.5 (Fig. 1, Table 3). The 30-min delayed recall
344 test was significantly better than both Trails tests, the
345 Boston Naming Test, category fluency, and MMSE.
346 The standard imaging modalities were similar to each
347 other and the individual psychometric tests in predic-
348 tion of A β status with FDG-PET displaying the highest
349 AUC at 0.67, followed by hippocampal volume at 0.64.
350 Delayed recall performed significantly better than all of
351 the cortical thickness-based measurements and trended

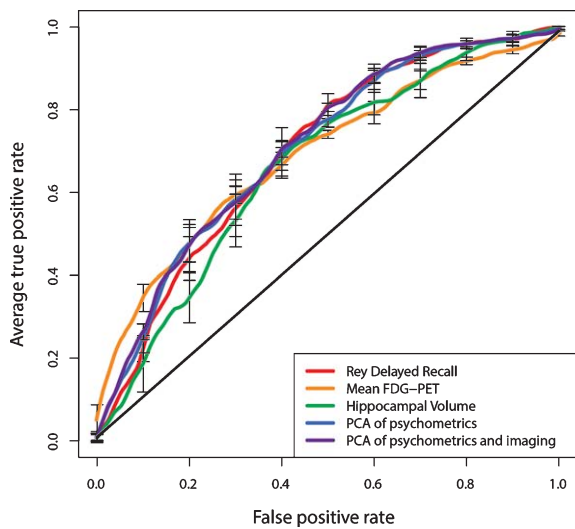


Fig. 1. ROC curves for predicting A β status from psychometric scores, imaging biomarkers, and principal components analysis of a collection of psychometric scores, and principal components of psychometric and imaging biomarkers.

352 better, but was not statistically significantly better, than
 353 hippocampal volume. Delayed recall performed simi-
 354 larly to FDG-PET. Despite the prior evidence of SVD
 355 analysis of the whole-brain cortical thickness data in
 356 prediction of CSF A β measures in a cohort of AD
 357 and FTD patients, this approach did not appear to
 358 enhance prediction (AUC = 0.59) versus more standard
 359 structural MRI measures. Performing a principal com-
 360 ponents analysis on the psychometric scores and using
 361 the resulting components boosted the AUC slightly to

0.68 with an odds ratio of 3.38; adding the imaging
 362 modalities to that model increased the AUC to 0.69,
 363 but the increase was not significant (Table 4). The mul-
 364 tivariate analysis of the cognitive tests, however, was
 365 statistically significantly better than hippocampal vol-
 366 ume, which was not true for any individual cognitive
 367 test. Repeating the analysis using only subjects with
 368 3T MR scans did not significantly change the results.
 369

Effect of ApoE allele

370
 371 Because of the tight link between ApoE ϵ 4 and A β
 372 pathology, we sought to determine, as a secondary
 373 analysis, whether the observed effects are modulated
 374 by ϵ 4 status. We divided the subjects into ϵ 4 positive
 375 and ϵ 4 negative groups and performed the analyses in
 376 the same way as before (Table 5). The results were
 377 broadly the same in that imaging did not significantly
 378 improve diagnostic accuracy over psychometric tests.
 379 Nearly all psychometric and neuroimaging biomark-
 380 ers were more predictive of A β status in ϵ 4 negative as
 381 compared to ϵ 4 positive subjects. This trend was highly
 382 statistically significant ($p < 0.001$ using a paired t -test).

DISCUSSION

Impact

385 The results shown here indicate that a psycho-
 386 metric evaluation can be as useful as FDG-PET or
 387 quantitative MR imaging in predicting whether or not
 388 a given amnesic MCI patient likely has underlying

Table 3
 Area under the curve (AUC), odds ratios, and positive (PPV) and negative predictive values (NPV) predicting A β status from biomarkers

	AUC	Odds Ratio	PPV	NPV
Mini-Mental Status Examination	0.61 \pm 0.03	1.94 \pm 0.60	0.71 \pm 0.05	0.43 \pm 0.05
AVLT Trial 5 Recall	0.65 \pm 0.03	3.01 \pm 0.36	0.75 \pm 0.04	0.50 \pm 0.05
AVLT 5-min Recall	0.65 \pm 0.02	2.50 \pm 0.44	0.73 \pm 0.05	0.47 \pm 0.04
AVLT 30-min Recall	0.67 \pm 0.02	2.46 \pm 0.52	0.73 \pm 0.05	0.48 \pm 0.06
AVLT Recognition Discrimination	0.64 \pm 0.03	2.44 \pm 0.55	0.73 \pm 0.02	0.48 \pm 0.07
Retention	0.67 \pm 0.03	2.48 \pm 0.48	0.73 \pm 0.03	0.47 \pm 0.06
Trail Making Test A	0.62 \pm 0.02	2.13 \pm 0.46	0.73 \pm 0.04	0.44 \pm 0.05
Trail Making Test B	0.63 \pm 0.02	2.49 \pm 0.48	0.75 \pm 0.05	0.45 \pm 0.05
Boston Naming Test	0.59 \pm 0.02	1.66 \pm 0.17	0.70 \pm 0.03	0.42 \pm 0.04
Category fluency (animals)	0.60 \pm 0.02	1.88 \pm 0.43	0.71 \pm 0.05	0.42 \pm 0.03
Hippocampal volume	0.64 \pm 0.02	2.41 \pm 0.34	0.74 \pm 0.04	0.46 \pm 0.04
Medial Temporal Thickness	0.59 \pm 0.01	1.67 \pm 0.07	0.70 \pm 0.04	0.42 \pm 0.04
Precuneal Thickness	0.59 \pm 0.02	1.83 \pm 0.25	0.71 \pm 0.03	0.43 \pm 0.05
Mean Cortical Thickness of AD Meta-ROI	0.61 \pm 0.02	1.90 \pm 0.31	0.71 \pm 0.04	0.43 \pm 0.04
Mean FDG-PET SUVR of AD Meta-ROI	0.67 \pm 0.03	3.19 \pm 1.22	0.76 \pm 0.05	0.49 \pm 0.08
PCA of psychometric scores	0.68 \pm 0.02	3.38 \pm 1.16	0.71 \pm 0.03	0.56 \pm 0.10
PCA of psychometric scores and imaging biomarkers	0.69 \pm 0.02	3.18 \pm 0.76	0.71 \pm 0.03	0.55 \pm 0.08
PCA of cortex-wide cortical thickness	0.59 \pm 0.03	1.57 \pm 0.21	0.67 \pm 0.04	0.43 \pm 0.02

PCA, principal components analysis.

Table 4

Table of *p*-values of AUC's for each variable compared with every other variable (FDR corrected). *p*-values of less than 0.05 are color-coded to indicate which measure is better: Blue indicates that the test indicated in the row name is better, whereas green indicates that the test indicated in the column name is better

AVLT Trial 5 recall	AVLT 5-min recall	AVLT 30-min recall	Trails A	Trails B	Boston Naming Test	Category Fluency (animals)	MMSE	Discrimination	Retention	Medial Temporal Thickness	Precuneus Thickness	Mean FDG	Hippocampal Volume	Thickness of Meta-ROI	PCA of psychometrics	PCA of psychometrics and imaging
	1.00	0.37	0.23	0.39	0.02	0.04	0.12	0.77	0.25	0.02	0.02	0.29	0.54	0.05	0.12	0.10
1.00		0.24	0.17	0.33	0.01	0.03	0.10	0.77	0.12	0.00	0.01	0.23	0.50	0.03	0.07	0.05
0.37	0.24		0.03	0.05	0.00	0.01	0.03	0.23	0.82	0.00	0.00	0.76	0.10	0.01	0.38	0.28
0.23	0.17	0.03		0.62	0.07	0.24	0.62	0.44	0.02	0.05	0.08	0.04	0.52	0.38	0.01	0.01
0.39	0.33	0.05	0.62		0.03	0.09	0.31	0.73	0.03	0.01	0.03	0.07	0.87	0.12	0.02	0.02
0.02	0.01	0.00	0.07	0.03		0.50	0.25	0.03	0.00	1.00	0.86	0.01	0.03	0.23	0.00	0.00
0.04	0.03	0.01	0.24	0.09	0.50		0.62	0.09	0.01	0.38	0.62	0.01	0.08	0.69	0.00	0.00
0.12	0.10	0.03	0.62	0.31	0.25	0.62		0.24	0.02	0.20	0.30	0.03	0.27	0.87	0.01	0.01
0.77	0.77	0.23	0.44	0.73	0.03	0.09	0.24		0.16	0.03	0.04	0.19	0.86	0.13	0.09	0.07
0.25	0.12	0.82	0.02	0.03	0.00	0.01	0.02	0.16		0.00	0.00	0.87	0.06	0.00	0.50	0.35
0.02	0.00	0.00	0.05	0.01	1.00	0.38	0.20	0.03	0.00		0.78	0.01	0.02	0.11	0.00	0.00
0.02	0.01	0.00	0.08	0.03	0.86	0.62	0.30	0.04	0.00	0.78		0.01	0.03	0.27	0.00	0.00
0.29	0.23	0.76	0.04	0.07	0.01	0.01	0.03	0.19	0.87	0.01	0.01		0.10	0.02	0.79	0.65
0.54	0.50	0.10	0.52	0.87	0.03	0.08	0.27	0.86	0.06	0.02	0.03	0.10		0.12	0.03	0.03
0.05	0.03	0.01	0.38	0.12	0.23	0.69	0.87	0.13	0.00	0.11	0.27	0.02	0.12		0.00	0.00
0.12	0.07	0.38	0.01	0.02	0.00	0.00	0.01	0.09	0.50	0.00	0.00	0.79	0.03	0.00		0.86
0.10	0.05	0.28	0.01	0.02	0.00	0.00	0.01	0.07	0.35	0.00	0.00	0.65	0.03	0.00	0.86	

Table 5

AUC values for prediction of A β status from cognitive tests when stratifying patients by ApoE ϵ 4 status. Cognitive tests were overall more predictive of A β status in ϵ 4 negative subjects than ϵ 4 positive subjects.

	AUC	
	ϵ 4+	ϵ 4-
AVLT Trial 5 recall	0.72 \pm 0.03	0.71 \pm 0.04
AVLT 5-min recall	0.70 \pm 0.04	0.72 \pm 0.04
AVLT 30-min recall	0.70 \pm 0.03	0.74 \pm 0.03
Trails A	0.68 \pm 0.03	0.75 \pm 0.03
Trails B	0.67 \pm 0.02	0.76 \pm 0.03
Boston Naming Test	0.67 \pm 0.02	0.72 \pm 0.06
Category Fluency (animals)	0.70 \pm 0.03	0.72 \pm 0.05
MMSE	0.68 \pm 0.03	0.73 \pm 0.02
Discrimination	0.69 \pm 0.04	0.72 \pm 0.02
Retention	0.70 \pm 0.03	0.73 \pm 0.03
Medial Temporal Thickness	0.68 \pm 0.03	0.72 \pm 0.04
Precuneus Thickness	0.68 \pm 0.03	0.70 \pm 0.05
Mean FDG	0.70 \pm 0.02	0.75 \pm 0.03
Hippocampal Volume	0.70 \pm 0.04	0.74 \pm 0.04
Thickness of Meta-ROI	0.67 \pm 0.03	0.69 \pm 0.03
PCA of psychometrics	0.69 \pm 0.03	0.74 \pm 0.03
PCA of psychometrics and imaging	0.69 \pm 0.03	0.73 \pm 0.04

PCA, principal components analysis.

AD pathology. The low cost and ready availability of psychometric batteries as compared to imaging studies makes them an attractive and useful alternative to specialized imaging techniques in clinical evaluation. Although the psychometric batteries do not approach perfect classification between A β -positive and A β -negative subjects, they can be useful in clinical practice to broadly estimate risk of prodromal AD and, perhaps, guide the process of obtaining additional studies, including molecular biomarkers. For situations in which obtaining an accurate measure of A β is paramount, such as evaluating appropriateness of a future anti-amyloid therapy, direct molecular imaging or CSF measurement of A β is still necessary, perhaps after initial screening with psychometrics to enrich with amyloid positive patients.

One intriguing finding of this study is that multivariate analysis using principal components analysis of the psychometric scores only marginally improved on the single best psychometric test, and the difference in AUC was not statistically significant at the $p < 0.05$ level. At the same time, the modest boost in AUC achieved by a multivariate analysis was sufficient to give a statistically significant improvement over hippocampal volume, but not over FDG-PET. These results suggest that improvements in diagnostic capability by using a multivariate cognitive profile as opposed to a single test offer only marginal improvements while at the same time suffering from less interpretability than a single test. Adding the imaging

biomarkers to the multivariate analysis did not significantly improve the AUC, suggesting that imaging offers little added value over a cognitive profile when screening for underlying AD pathology.

Further, the fact that even the “standard” cognitive measures examined here displayed some success in determining the likelihood of AD pathology suggests that more research is warranted on designing and evaluating psychometric tests optimized for detection of early AD-related cognitive decline. In particular, measures guided by the cognitive neuroscience literature may be particularly useful in this regard [32]. Finally, the results here indicate that the ability of psychometric scores to identify patients who will progress to AD is not due solely to the fact that those same scores are used to establish presence of probable AD. Instead, it appears that the predictive value of psychometric tests are due, at least in part, to their ability to separate MCI patients into sub-populations with higher and lower prevalence of AD pathology.

Limitations

Although this study does indicate that a psychometric battery should be an important component of the evaluation of MCI subjects beyond initial categorization to the MCI designation, there are several factors that may influence the relative ability of imaging to predict AD pathology. First, this study focused exclusively on cross-sectional imaging studies. Longitudinal imaging may provide a more reliable representation of disease progression. Nevertheless, longitudinal imaging may not be feasible for many care settings, so evaluating the diagnostic power of cross-sectional imaging is also important. It is worth noting that this study is meant to help guide providers caring for patients with MCI, not to detect AD pathology in presymptomatic patients. By the time cognitive scores become clearly abnormal, significant neurodegeneration has likely already occurred while this may be more variable in the preclinical phase. Thus, it is unclear whether the same relative predictive value of cognitive versus neuroimaging methods would hold in that context. The patient selection criteria also may limit the applicability of the findings presented here to a broader range of patients. This study focused on amnesic MCI subjects. It is possible that in a broader selection of MCI subjects, the memory tests proposed may provide even greater capability in prediction of amyloid status. On the other hand, in non-amnesic MCI populations, these tests may be less predictive due to differences in the loci of neurodegenerative change in amnesic

versus non-amnesic prodromal AD. In addition, the ADNI study population is enriched in AD or AD-like pathology. In a more general clinical setting, providers must also consider the possibility of other sources of cognitive impairment, such as depression or stroke. It is uncertain how this greater heterogeneity would impact the predictive value of both cognitive and neuroimaging measures. Another drawback to the current study is the sampling procedure. We excluded subjects who did not have all the biomarkers examined here, including those for whom the automated hippocampal segmentation failed. As such, the subset in this study would, if anything, overestimate the ability of hippocampal segmentation to track AD pathology; had we not excluded patients with unreliable segmentations, the predictive ability of hippocampal volumes would likely be lower.

It is also possible that advances in image processing techniques may improve the diagnostic capability of neuroimaging data. Although it is impossible to rule out such advances, the variety of imaging modalities and image processing techniques used here make it less likely that new analytic approaches would improve the predictive power of imaging data enough to supplant psychometric measures as a key method for characterization of MCI patients. Indeed, the current work did use a promising analytic approach involving singular value decomposition across the entire cortical mantle, which had previously demonstrated good predictive value of CSF t-tau/ A β in patients with AD and frontotemporal dementia [28]. Nonetheless, this approach did not display significant advantages over more traditional measures (e.g., hippocampal volume) or psychometric tests. In any case, psychometric tests are more accessible than sophisticated image processing techniques, especially to physicians who do not work in academic medical centers.

An obvious limitation of this study is the use of CSF-derived A β status as a gold standard in the prediction models, as CSF A β does not perfectly reflect brain AD pathology. While we took this approach to avoid the circularity of longitudinal studies of conversion, a better design would have autopsy-confirmed AD pathology for comparison with the other biomarkers. Nonetheless, CSF A β , along with amyloid PET, are the closest surrogates to histopathologic evaluation presently available and have displayed high sensitivity in autopsy studies [10, 11].

Finally, the limited accuracy for prediction of amyloid status of even the most accurate models indicates that caution should be exercised when using values from these models to guide clinical decision-making and, at most, they should be considered another piece

in the overall assessment of risk in MCI patients. Fundamentally, the main conclusion of this study is that psychometric scores provide as much information as neurodegenerative imaging biomarkers in prediction of underlying amyloid pathology, not that either imaging or cognitive biomarkers should be regarded as having perfect diagnostic accuracy. This conclusion strengthens the argument made in previous studies that cognitive tests are a crucial component in multivariate predictive models for conversion from MCI to AD by demonstrating that cognitive scores predict molecular AD pathology, not just cognition-based diagnoses of AD. Therefore, cognitive tests should be considered just as important a biomarker for AD pathology as other neurodegenerative biomarkers, which have already been recognized by the National Institute on Aging – Alzheimer’s Association (NIA-AA) work group for MCI diagnosis. Finally, while the AUC values are relatively modest, the odds ratios suggest that poorer performance on the best cognitive predictors are associated with approximately a three-fold risk of underlying AD pathology, which may influence counseling of patients.

Effect of ApoE

One intriguing result in this study is the marked difference in prediction accuracy in ApoE ϵ 4 positive versus ϵ 4 negative subjects. This finding is consistent with previous work showing that cognitive function is more closely linked to A β status within ϵ 4 negative than within ϵ 4 positive subjects [33, 34]. The mechanism behind this effect is not clear, but may be that the effects of A β on cognitive function are modulated by ApoE isoforms. However, an important confounding factor is the highly unbalanced nature of the samples: The ϵ 4 negative group had 79 A β + and 120 A β - subjects, whereas the ϵ 4 positive group had 178 A β + and only 29 A β - subjects. The relative paucity of ϵ 4 positive but A β - subjects may contribute to the lower performance of the predictive model in the ϵ 4 positive group. Thus, it is possible that the strong association of A β with ϵ 4 status obscures the association with cognitive measures.

Psychometric scores as functional biomarkers

It is worth pointing out that the current algorithm for determining the likelihood of “MCI due to AD” in the recently proposed criteria treats neurodegenerative and molecular markers as dissociable modalities of evidence. In a sense, psychometric tests can be considered

569 another type of downstream neurodegenerative measure. Thus, it may seem somewhat odd to use one type
570 of biomarker (neurodegenerative) to predict another (molecular) in this context if these measures provide
571 orthogonal information. However, these measures are obviously related and multiple studies have demon-
572 strated the significant predictive value for conversion to clinical AD in patients either with “positive” CSF
573 or PET amyloid studies or neurodegenerative markers [1, 35, 36].

574 Nonetheless, one reason for the modest ability of cognitive measures to predict amyloid status is that
575 MCI A β +likely is associated with variable levels of impairment. This is almost certainly an issue for
576 any neurodegenerative biomarker given the range of disease severity within the MCI category. Indeed, neu-
577 rodegenerative biomarkers, in addition to providing some currency on the underlying pathology (e.g., cere-
578 bral amyloid), also are informative on disease stage and enhance prediction of the timing of transitions
579 to dementia, as has been suggested in the literature [37–39]. Thus, relatively poor performance on cog-
580 nitive measures within the MCI category increases both the likelihood that the underlying process is AD
581 and that progression to dementia is more likely to occur in the near future, which may help provide addi-
582 tional context for clinicians in their assessment of these patients.

583 The choice of CSF A β as the proxy or standard for AD pathology in the present analysis also reflects
584 the notion that it is a more specific measure of AD pathology than neurodegenerative markers given the
585 defining nature of cerebral amyloid in the pathologic criteria for AD. Indeed, more and more therapeutic
586 trials, including in MCI, are using a positive amyloid study as inclusion criteria [40]. Thus, examination of
587 psychometric measures within the MCI category may contribute to increasing the likelihood that a given
588 patient may qualify for such a study on that basis.

608 CONCLUSION

609 In an MCI population, psychometric scores predict presence of CSF-based amyloid pathology that over-
610 laps with predictions obtainable from FDG-PET and structural MR images. Thus, psychometric measures
611 may be preferable in the cross-sectional context to provide initial screening on the likelihood of prodromal
612 AD. The ability of cognitive scores to predict the existence of underlying AD pathology indicates that
613 in addition to using cognitive test cutoffs to establish

618 the existence of MCI, the severity of the test scores is as reliable an indicator as imaging biomarkers of neu-
619 rodegeneration that the cognitive impairment is due to AD pathology. Thus, these measures could be included
620 in the MCI algorithm as a type of neurodegenerative marker that could further help clinicians prognosticate
621 in the clinical setting.

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