ApoE4 effects on automated diagnostic classifiers for mild cognitive impairment and Alzheimer's disease

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ABSTRACT

Biomarkers are the only feasible way to detect and monitor presymptomatic Alzheimer's disease (AD). No single biomarker can predict future cognitive decline with an acceptable level of accuracy. In addition to designing powerful multimodal diagnostic platforms, a careful investigation of the major sources of disease heterogeneity and their influence on biomarker changes is needed. Here we investigated the accuracy of a novel multimodal biomarker classifier for differentiating cognitively normal (NC), mild cognitive impairment (MCI) and AD subjects with and without stratification by ApoE4 genotype. 111 NC, 182 MCI and 95 AD ADNI participants provided both structural MRI and CSF data at baseline. We used an automated machine-learning classifier to test the ability of hippocampal volume and CSF Aβ, t-tau and p-tau levels, both separately and in combination, to differentiate NC, MCI and AD subjects, and predict conversion. We hypothesized that the combined hippocampal/CSF biomarker classifier model would achieve the highest accuracy in differentiating between the three diagnostic groups and that ApoE4 genotype will affect both diagnostic accuracy and biomarker selection. The combined hippocampal/CSF classifier performed better than hippocampus-only classifier in differentiating NC from MCI and NC from AD. It also outperformed the CSF-only classifier in differentiating NC vs. AD. Our amyloid marker played a role in discriminating NC from MCI or AD but not for MCI vs. AD. Neurodegenerative markers contributed to accurate discrimination of AD from NC and MCI but not NC from MCI. Classifiers predicting MCI conversion performed well only after ApoE4 stratification. Hippocampal volume and sex achieved AUC = 0.68 for predicting conversion in the ApoE4-positive MCI, while CSF p-tau, education and sex achieved AUC = 0.89 for predicting conversion in ApoE4-negative MCI. These observations support the proposed biomarker trajectory in AD, which postulates that amyloid markers become abnormal early in the disease course while markers of neurodegeneration become abnormal later in the disease course and suggests that ApoE4 could be at least partially responsible for some of the observed disease heterogeneity.

1. Introduction

Alzheimer's disease (AD), the most common neurodegenerative disorder, is increasingly prevalent among those aged 65 years and over. AD prevalence is projected to triple by the year 2050 (Hebert et al., 2001) making it vital to achieve early and accurate diagnosis and to discover disease-modifying therapies. The only feasible approach for presymptomatic diagnosis to date is through the use of biomarkers.

Hippocampal atrophy is the most established AD structural imaging biomarker. Hippocampal atrophy is seen in normal aging, yet in the latent AD stages hippocampal atrophy becomes greatly accelerated (Apostolova et al., 2006, in press, 2010a; Jack et al., 1997, 1998, 2000). Hippocampal atrophy shows strong correlation with cognitive decline (de Toledo-Morrell et al., 2000; Fleischman et al., 2005; Mortimer et al., 2004) and with AD pathologic markers such as neuronal and neurofibrillary tangle counts and Braak and Braak pathological stages (Apostolova et al., 2010b; Bobinski et al., 1995, 1997; Schonheit et al., 2004; Zarow et al., 2005).

Cerebrospinal fluid (CSF) measures of amyloid beta protein ($A\beta$) and tau are the most established AD fluid biomarkers. Pathologic $A\beta$ deposition in the brain tissue is thought to occur early in the disease course and is associated with low CSF $A\beta_{42}$ levels (Blennow and Hampel, 2003). CSF total tau (t-tau) and phosphorylated tau (p-tau) are significantly elevated in subjects with AD (Andreasen et al., 2001; Blennow et al., 1995; Clark et al., 2003; Galasko et al., 1998) and are thought to reflect neurodegeneration of tau-containing neurons. Unlike CSF $A\beta_{42}$ (Wallin et al., 2006), CSF t-tau and p-tau changes occur later in the disease course and are associated with cognitive decline (Buerger et al., 2002, 2005; Riemenschneider et al., 2002; Wallin et al., 2006).

Several research groups have independently investigated the individual accuracy of these biomarkers to differentiate cognitively normal elderly, MCI and AD subjects (Andreasen et al., 2001; Brys et al., 2009; de Leon et al., 2006; Frisoni et al., 2009; Galasko et al., 1998; Hampel et al., 2004; Mattsson et al., 2009; Shaw et al., 2009). Yet while biomarker changes are clearly present years before AD is diagnosed, no single biomarker can adequately predict conversion to AD or serve as a diagnostic tool with an acceptable level of accuracy.

Many groups including ours have made important strides towards multimodal biomarker diagnostic discrimination (Cui et al., 2011; Davatzikos et al., 2011; Ewers et al., 2012; Kohannim et al., 2010; Vos et al., 2012; Walhovd et al., 2010; Westman et al., 2012). Here we combined imaging and CSF biomarker data from the Alzheimer's Disease Neuroimaging Initiative-1 (ADNI-1) dataset to compare the performance of unimodal (hippocampal atrophy or CSF biomarkers alone) and multimodal (hippocampal atrophy, CSF variables and ApoE genotype combined) biomarker classifiers for differentiating NC, MCI and AD. We also examined to what extent the amyloid (i.e., CSF $A\beta_{42}$) and the neurodegenerative biomarkers (CSF tau, CSF p-tau and hippocampal atrophy) play a role for differentiating different disease stages from each other and for predestining conversion to AD. In addition we sought to determine the effect of ApoE4 genotype on diagnostic accuracy and biomarker selection.

2. Materials and methods

2.1. Subjects

Data used preparing this article were obtained from the ADNI database (www.loni.ucla.edu/ADNI). ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations; subjects have been recruited from over 50 sites across the U.S. and Canada. For up-to-date information, please see www.adni-info.org.

ADNI-1 enrolled approximately 400 amnestic MCI, 200 mild AD and 200 NC subjects, aged 55–90. Written informed consent was obtained from all participants. The clinical description of the ADNI-1 cohort was recently published (Petersen et al., 2010). The full list of inclusion/exclusion criteria may be accessed online at http://www.adni-info.org/Scientists/ADNIGrant.aspx.

As all ADNI subjects had serial 1.5T MRI images, their inclusion in our analyses was largely determined by the availability of CSF data. CSF measures were performed in only a subset of the ADNI subjects. 111 NC, 182 MCI and 95 AD ADNI participants had both structural MRI and CSF assessment at baseline. 191 subjects (49%; 27 NC, 99 MCI, 65 AD) were apolipoprotein E4 (ApoE4) carriers and 197 (51%; 84 NC, 83 MCI, 30 AD) were noncarriers. Additionally 21 NC, 14 MCI and 3 AD subjects were ApoE2 carriers.

As one of the main goals of ADNI is to carefully track biomarker changes in NC and MCI predestined to convert to AD, we also analyzed which combination of biomarkers can predict conversion to AD. We used all available MCI subjects who had either converted to AD at any point between baseline and month 36 (MCI converters, N = 80) or remained stable all the way to month 36 (MCI nonconverters, N = 80). 22 MCI subjects dropped out before month 36 without converting to AD and were excluded from our analyses.

2.2. CSF biomarker data

We downloaded the baseline CSF $A\beta_{42}$, t-tau and the tau phosphorylated at threonine at position 181 (p-tau$_{181}$) data from the ADNI website (http://www.loni.ucla.edu/ADNI) in October 2008. CSF collection and transportation protocols, and procedural details on CSF $A\beta_{42}$, t-tau and the p-tau$_{181}$ measurements are provided in the ADNI procedural manual posted at http://www.adni-info.org and in a recent publication by Shaw et al. (Shaw et al., 2009).

2.3. MRI preprocessing

All subjects were scanned with a standardized high-resolution MRI protocol (http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml) on scanners developed by one of three manufacturers (General Electric Healthcare, Siemens Medical Solutions and Philips Medical Systems) with a protocol optimized for best contrast to noise in a feasible acquisition time (Jack et al., 2008; Leow et al., 2006). Raw data with an acquisition matrix of $192 \times 192 \times 166$ and voxel size $1.25 \times 1.25 \times 1.2$ mm^3 in the x-, y-, and z-dimensions was subjected to in-plane, zero-filled reconstruction (i.e., sinc interpolation) resulting in a 256×256 matrix and voxel size of $0.9375 \times 0.9375 \times 1.2$ mm^3. Image quality was inspected at the ADNI MRI quality control center at the Mayo Clinic (in Rochester, MN, USA) (Jack et al., 2008). Phantom-based geometric corrections, image non-uniformity and bias field corrections were applied (Gunter et al., 2006; Jack et al., 2008; Jovich et al., 2006; Sled et al., 1998). Both the uncorrected and corrected image files are freely available to interested researchers at http://www.loni.ucla.edu/ADNI.

2.4. Hippocampal segmentation

The preprocessed baseline 1.5T 3D T1-weighted scans were downloaded and linearly registered to the International Consortium for Brain Mapping (ICBM-53) brain template (Mazziotta et al., 2001) using the Minctracc algorithm and 9-parameter (9P) transformation (3 translations, 3 rotations, 3 scales) (Collins et al., 1994). The aligned images were resampled in an isotropic space of 220 voxels along each axis (x, y, and z) resulting in a final voxel size of 1 mm^3. The hippocampi were segmented with our recently developed and validated automated machine-learning hippocampal segmentation technique (AdaBoost) which uses the adaptive boosting approach originally proposed by Freund and Shapire (1997) as previously described (Apostolova et al., 2010d; Morra et al., 2008a,b,2009a,b). Hippocampal volumes were extracted.

Table 1
Mean demographic and biomarker data.

Variable at baseline	NC N = 111	MCI N = 182	AD N = 95	One-way ANOVA/chi squared test, p-value
Age, years	75.5 (5.2)	74.2 (7.4)	74.6 (7.9)	0.3
Gender, M:F	56:55	121:61	55:40	**0.023**
Education, years	15.8 (2.8)	15.8 (3.0)	15.3 (3.0)	0.3
MMSE	29.1 (1.0)	26.9 (1.8)	23.6 (1.9)	**<0.001**
CSF $A\beta_{42}$ level, pg/ml	206 (55)	163 (55)	143 (40)	**<0.001**
CSF t-tau level, pg/ml	69 (30)	103 (61)	124 (58)	**<0.001**
CSF p-tau$_{181}$ level, pg/ml	25 (15)	35 (18)	43 (20)	**<0.001**
Mean hippocampal volume, mm^3	4100 (586)	3779 (631)	3518 (604)	**<0.001**
ApoE4 positive subjects				
Variable at baseline	NC N = 27	MCI N = 99	AD N = 65	One-way ANOVA/chi squared test, p-value
Age, years	75.8 (5.8)	73.5 (6.6)	74.0 (7.4)	0.3
Gender, M:F	18:9	60:39	39:26	0.8
Education, years	15.6 (2.8)	15.7 (2.8)	14.8 (3.0)	0.2
MMSE	28.9 (1.1)	27.0 (1.8)	23.6 (1.9)	**<0.001**
CSF $A\beta_{42}$ level, pg/ml	157(49)	143 (41)	131 (27)	**0.012**
CSF t-tau level, pg/ml	80 (40)	117 (67)	122 (53)	**0.007**
CSF p-tau$_{181}$ level, pg/ml	32 (21)	40 (18)	43 (19)	**0.05**
Mean hippocampal volume, mm^3	4175 (443)	3708 (608)	3476 (608)	**<0.001**
ApoE4 negative subjects				
Variable at baseline	NC N = 84	MCI N = 83	AD N = 30	One-way ANOVA/chi squared test, p-value
Age, years	75.4 (5.0)	74.9 (8.2)	75.9 (8.9)	0.8
Gender, M:F	38:46	61:22	14:16	**0.001**
Education, years	15.8 (2.7)	16.0 (3.2)	16.3 (2.8)	0.7
MMSE	29.1 (1.0)	26.8 (1.8)	23.5 (1.9)	**<0.001**
CSF $A\beta_{42}$ level, pg/ml	222 (48)	187 (60)	168 (52)	**<0.001**
CSF t-tau level, pg/ml	65 (25)	85 (48)	127 (69)	**<0.001**
CSF p-tau$_{181}$ level, pg/ml	22 (11)	30 (16)	42 (22)	**<0.001**
Mean hippocampal volume, mm^3	4077 (625)	3731 (573)	3610 (564)	**<0.001**

Bold values indicate significance at p<0.05.

2.5. Statistical methods

2.5.1. Demographic comparisons

We used one-way Analyses of Variance (ANOVA) with post hoc Bonferroni correction for multiple comparisons to examine diagnostic differences in age, education, MMSE, CSF biomarker levels and hippocampal volume at baseline, and chi-squared test to determine differences in sex distribution between each diagnostic group. For comparison of baseline demographic and biomarker measures between ApoE4-positive and negative subjects and MCI converters (MCIc) and MCI nonconverters (MCInc) we used a two-tailed Student's t-test for continuous variables, and a chi-squared test for categorical variables.

2.5.2. Support vector machines classifier

SVMs are popular machine learning algorithms, formulated to learn patterns in training data and classify new testing data. The mathematical principle by which SVM performs pattern recognition is by finding a multidimensional plane that maximizes the margin between data points in different classes (Vapnik, 1995). SVMs have been particularly successful in biological classification problems, as non-linear kernels can be introduced to the algorithm so that non-planar, multidimensional surfaces can instead be used to classify patterns of data. In our study, we implemented the radial basis function (RBF) kernel and optimized its width or γ parameter (as well as the SVM cost or C parameter) through grid search using the e1071 package (Dimitriadou et al., 2006) in R (http://cran.r-project.org). Often, addition of non-contributory features can reduce classification performance. For this reason, we ranked our features based on the elements of a linear SVM's normal vector (i.e., $|w_i|$; (Guyon et al., 2002)) and iteratively removed those with lower weights to find sets of features that yield maximal classification accuracies.

We trained the SVM algorithm with CSF, ApoE4 and imaging measures for subjects with known diagnoses and used the leave-one-out approach to predict each new subject's diagnostic category. This process was repeated n times and the machine's predictive accuracy was measured by summing up the correct and incorrect classifications. All classifiers included age, sex, and educational level (in years). Next, we obtained receiver operating characteristic (ROC)

Table 2
Demographic and biomarker comparisons by ApoE genotype using a two-tailed t-test for continuous and a chi-squared test for categorical variables (p-values are shown; for mean and SD for each variable, please see Table 1).

Variable at baseline	MCI ApoE4+ vs ApoE4-	MCI ApoE4+ vs. ApoE4-	AD ApoE4+ vs ApoE4-
Age, years	0.7	0.2	0.3
Gender, M:F	0.053	0.07	0.5
Education, years	0.8	0.5	**0.02**
MMSE	0.4	0.6	0.8
CSF $A\beta_{42}$ level, pg/ml	**<0.001**	**<0.001**	**0.001**
CSF t-tau level, pg/ml	0.07	**<0.001**	0.8
CSF p-tau$_{181}$ level, pg/ml	**0.024**	**<0.001**	0.9
Mean hippocampal volume, mm^3	0.5	0.8	0.3

Bold values indicate significance at p<0.05.

Table 3

Baseline demographic and biomarker comparisons of MCI converters vs. nonconverters using a two-tailed t-test for continuous and a chi-squared test for categorical variables.

Variable at baseline	MCI converters	MCI nonconverters	Two-tailed t-test/chi squared test, p-value
Age, years	74.8 (7.1)	73.6 (7.5)	0.3
Gender, M:F	48:32	55:25	0.3
Education, years	15.5 (3.0)	16.3 (2.8)	0.1
ApoE4 positive:negative	53:27	35:45	**0.004**
MMSE	26.6 (1.8)	27.3 (1.7)	**0.014**
CSF $A\beta_{42}$ level, pg/ml	145 (40)	172 (60)	**0.001**
CSF t-tau level, pg/ml	113 (51)	88 (47)	**0.002**
CSF p-tau$_{181}$ level, pg/ml	40 (16)	31 (17)	**0.001**
Mean hippocampal volume, mm^3	3600 (569)	3803 (542)	**0.022**

Bold values indicate significance at p<0.05.

curves for the predictions to additionally assess the classifier's sensitivity, specificity and area under the curve (AUC) characteristics.

Our classifier results were further subjected to multiple comparisons correction by permutation analyses. We ran 10,000 permutations of the dependent variable (clinical diagnosis) against the sets of individual biomarker characteristics for each individual classifier and defined a final single corrected *p*-value for each ROC.

3. Results

3.1. Demographic characteristics

The demographic characteristics of the diagnostic groups are shown in Tables 1–3. There were no significant age or educational differences between the diagnostic groups. The MCI group had significantly more males relative to both the NC and the AD groups (p = 0.023). As expected, AD subjects had the lowest mean MMSE and CSF $A\beta_{42}$ and NC the highest (p < 0.001). The opposite was seen for CSF t-tau and p-tau (both p < 0.001). The MCI group was intermediate on these variables (Table 1).

ApoE4-positive NC subjects had significantly lower CSF $A\beta_{42}$ (p < 0.001) and higher CSF p-tau levels (p = 0.024) relative to ApoE4-negative NC. ApoE4-positive MCI subjects also showed significantly lower CSF $A\beta_{42}$ (p < 0.001), higher CSF tau and p-tau (both p < 0.001) relative to ApoE4-negative MCI subjects. ApoE4-positive AD subjects were significantly less educated (p = 0.02) and had lower CSF $A\beta_{42}$ levels (p = 0.001) relative to ApoE4-negative AD subjects (Table 2).

Relative to MCI nonconverters, MCI converters had significantly lower MMSE (p = 0.014), higher proportion of ApoE4 carriers (p = 0.004), lower hippocampal volume (p = 0.022) and CSF $A\beta_{42}$ (p = 0.001), and higher CSF tau (p = 0.002) and p-tau (p = 0.001, Table 3).

3.2. Classifier results

3.2.1. Cross-sectional classifiers

Fig. 1 and Table 4 show the cross-sectional classifier ROCs, classifier performance metrics, ranking of variables selected by each classifier and permutation corrected classifier significance.

3.2.1.1. NC vs. MCI classifiers (Fig. 1 top portion first row). The hippocampal NC vs. MCI classifier achieved an AUC of 0.68. The features selected by the classifier included hippocampal volume, age and sex. The permutation corrected classifier significance was p$_{corrected}$ < 0.0001.

The CSF NC vs. MCI classifier achieved an AUC of 0.77. The features selected by the classifier included CSF $A\beta_{42}$, CSF tau, sex and age. The permutation corrected classifier significance was p$_{corrected}$ < 0.0001.

ApoE4 genotype performed as well as hippocampal volume and CSF biomarkers regardless of whether ApoE2 carriers were excluded or not (all subjects AUC = 0.7, p$_{corrected}$ < 0.0001, without ApoE2 carriers AUC = 0.71, p$_{corrected}$ < 0.0001). Substituting the binary ApoE4-positive vs. negative predictor variable with a variable reflecting the number of

ApoE4 alleles (0, 1 or 2) did not result in overall improvement in classifier performance (AUC = 0.67, p$_{corrected}$ < 0.0001).

The multimodal NC vs. MCI classifier presented with all three CSF variables, hippocampal volume, age, sex and education achieved an AUC of 0.78. The variables selected by the classifier included CSF $A\beta_{42}$, CSF tau, hippocampal volume, sex, and age. The permutation corrected classifier significance was p$_{corrected}$ < 0.0001. The addition of ApoE4 genotype did not seem to affect the overall multimodal classifier results (AUC = 0.79, p$_{corrected}$ < 0.0001, Table 6).

Direct statistical comparison showed that the CSF NC vs. MCI classifier performed significantly better than the hippocampal NC vs. MCI classifier (p = 0.01). The hippocampal + CSF classifier performed better than the hippocampal-only (p = 0.0044) but not the CSF-only (p = 0.65) classifiers. Adding ApoE4 genotype to the multimodal hippocampal + CSF classifier did not result in a statistically significant difference (p = 0.56).

3.2.1.2. NC vs. AD classifier (Fig. 1 top portion second row). The hippocampal NC vs. AD classifier achieved an AUC of 0.78. The features selected by the classifier included hippocampal volume, age, and education. The permutation corrected classifier significance was p$_{corrected}$ < 0.0001.

The CSF NC vs. AD classifier achieved an AUC of 0.85. The features selected by the classifier included CSF $A\beta_{42}$, CSF tau and p-tau, sex, education and age. The permutation corrected classifier significance was p$_{corrected}$ < 0.0001.

ApoE4 genotype performed about the same as the hippocampal volume and worse than CSF regardless of whether ApoE2 carriers were excluded or not (all subjects AUC = 0.76, p$_{corrected}$ < 0.0001, without ApoE2 carriers AUC = 0.74, p$_{corrected}$ < 0.0001). Substituting the binary ApoE4-positive vs. negative predictor variable with a variable reflecting the number of ApoE4 alleles (0, 1 or 2) did not result in overall improvement in classifier performance (AUC = 0.78, p$_{corrected}$ < 0.0001).

The multimodal NC vs. AD classifier presented with all CSF variables, hippocampal volume, age, sex and education achieved an AUC of 0.90. The variables selected by the classifier included CSF tau, CSF $A\beta_{42}$, hippocampal volume, age, CSF p-tau and sex. The permutation corrected classifier significance was p$_{corrected}$ < 0.0001. The addition of ApoE4 genotype did not affect the overall multimodal classifier results (AUC = 0.88, permutation corrected significance p$_{corrected}$ < 0.0001, Table 6).

Direct statistical comparison showed that CSF NC vs. AD classifier performed significantly better than the hippocampal NC vs. AD classifier (p = 0.04), and the hippocampal + CSF classifier performed better than the hippocampal-only (p = 0.0001) and the CSF-only (p = 0.03) classifiers. Adding ApoE4 genotype to the multimodal hippocampal + CSF classifier did not result in a statistically significant difference (p = 0.43).

3.2.1.3. MCI vs. AD classifier (Fig. 1 top portion bottom row). The hippocampal MCI vs. AD classifier achieved an AUC of 0.53. The features selected by the classifier included education and hippocampal volume. The permutation corrected classifier significance was p$_{corrected}$ = 0.024.
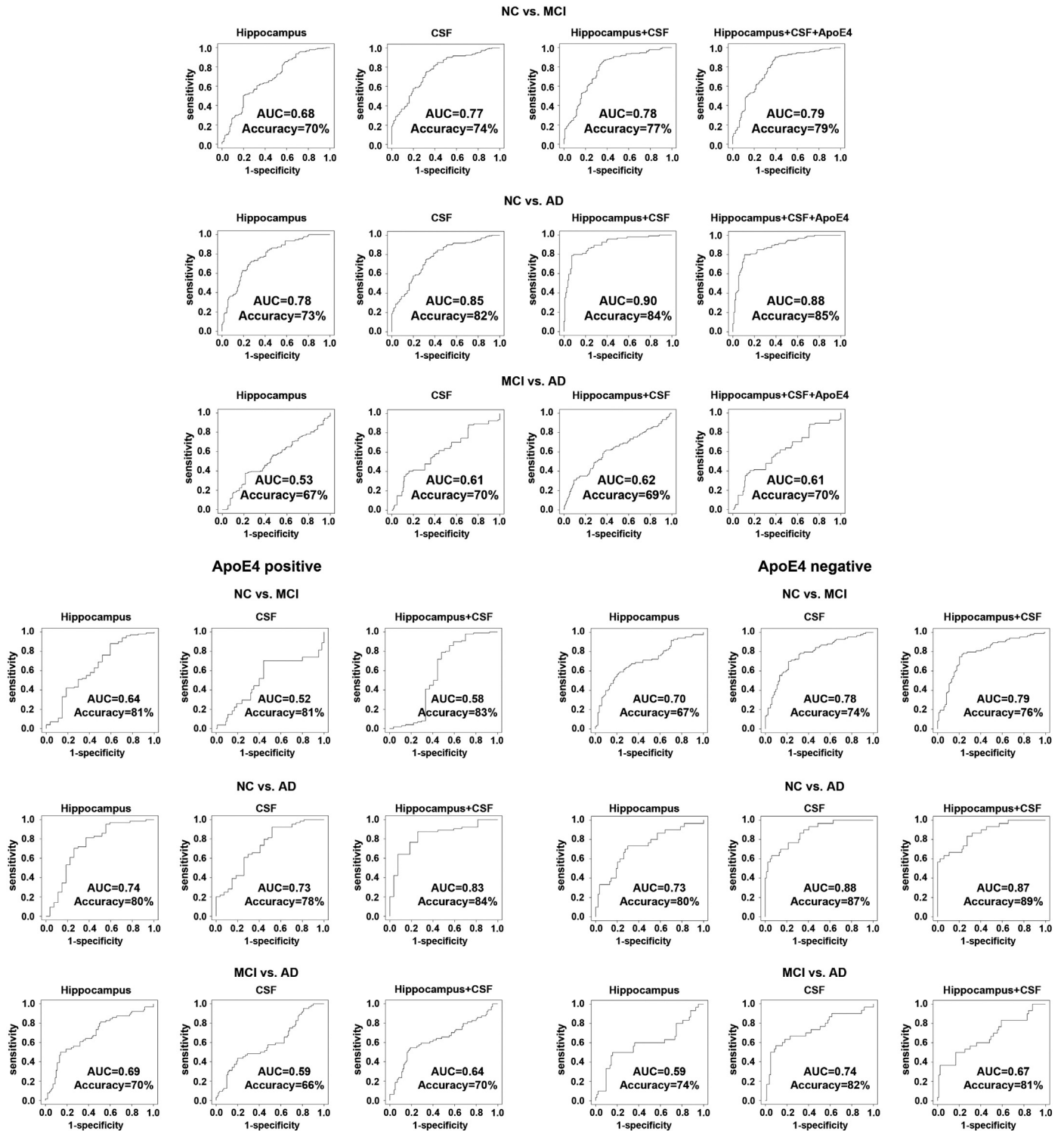
Fig. 1. Receiver Operation Characteristic (ROC) for the cross-sectional classifiers.

The CSF MCI vs. AD classifier achieved an AUC of 0.61. The single feature selected by the classifier was CSF p-tau. The permutation corrected classifier significance was $p_{corrected} < 0.001$.

ApoE4 genotype performed about the same as the hippocampal volume and worse than CSF regardless of whether ApoE2 carriers were excluded or not (all subjects AUC = 0.52, $p_{corrected} < 0.0001$, without ApoE2 carriers AUC = 0.51, $p_{corrected} < 0.0001$). Substituting the binary ApoE4-positive vs. negative predictor variable with a variable reflecting the number of ApoE4 alleles (0, 1 or 2) did not result in overall improvement in classifier performance (AUC = 0.53, $p_{corrected} < 0.0001$).

The multimodal MCI vs. AD classifier presented with all CSF variables, hippocampal volume age, sex and education achieved an AUC of 0.62. The variables selected by the classifier included hippocampal volume, CSF p-tau, sex and CSF tau. The permutation corrected classifier significance was $p_{corrected} < 0.001$. The addition of ApoE4 genotype did not seem to affect the overall multimodal classifier results (AUC = 0.61, permutation corrected significance $p_{corrected} = 0.0011$, Table 6).

Direct statistical comparison showed no statistically significant improvement in performance between the various classifiers.

Table 4
Classifier performance metrics, ranking of variables selected by each classifier, and permutation corrected classifier significance.

Diagnostic comparison	Hippocampal classifier		CSF classifier		Hippocampal + CSF classifier		Hippocampal + CSF + ApoE classifier	
	Selected variables (ranked)	Accuracy AUC p-value	Selected variables (ranked)	Accuracy AUC p-value	Selected variables (ranked)	Accuracy AUC p-value	Selected variables (ranked)	Accuracy AUC p-value
NC vs. MCI	Hippocampal volume Age Sex	Accuracy 70% AUC 0.68 p<0.0001	CSF $A\beta_{42}$ CSF tau Sex Age	Accuracy 74% AUC 0.77 p<0.0001	CSF $A\beta_{42}$ CSF tau Hippocampal volume Sex Age	Accuracy 77% AUC 0.78 p<0.0001	CSF $A\beta_{42}$ Hippocampal volume CSF tau Sex ApoE Age	Accuracy 79% AUC 0.79 p<0.0001
NC vs. AD	Hippocampal volume Age Education	Accuracy 73% AUC 0.78 p<0.0001	CSF $A\beta_{42}$ CSF tau CSF p-tau Sex Age Education	Accuracy 82% AUC 0.85 p<0.0001	CSF tau CSF $A\beta_{42}$ Hippocampal volume Age CSF p-tau Sex	Accuracy 84% AUC 0.90 p<0.0001	CSF tau Hippocampal volume CSF $A\beta_{42}$ ApoE Age Sex CSF p-tau	Accuracy 85% AUC 0.88 p<0.0001
MCI vs. AD	Education Hippocampal volume	Accuracy 67% AUC 0.53 p=0.024	CSF p-tau	Accuracy 70% AUC 0.61 p<0.001	Hippocampal volume CSF p-tau Sex CSF $A\beta_{42}$	Accuracy 70% AUC 0.6 p<0.001	CSF p-tau	Accuracy 70% AUC 0.61 p=0.0011

ApoE4-positive subjects						
Diagnostic comparison	Hippocampal classifier		CSF classifier		Hippocampal + CSF classifier	
	Selected variables	Accuracy AUC p-value	Selected variables	Accuracy AUC p-value	Selected variables	Accuracy AUC p-value
NC vs. MCI	Hippocampal volume Education Age Sex	Accuracy 81% AUC 0.64 p=0.005	CSF tau CSF p-tau Education Age	Accuracy 81% AUC 0.52 p=0.01	Age CSF p-tau	Accuracy 83% AUC 0.58 p=0.0006
NC vs. AD	Hippocampal volume	Accuracy 80% AUC 0.74 p<0.0001	CSF $A\beta_{42}$ CSF tau CSF p-tau Age	Accuracy 78% AUC 0.73 p<0.0005	Hippocampal volume CSF tau	Accuracy 84% AUC 0.83 p<0.0001
MCI vs. AD	Hippocampal volume	Accuracy 70% AUC 0.69 p=0.0006	CSF p-tau Education CSF tau CSF $A\beta_{42}$	Accuracy 66% AUC 0.59 p=0.003	Education Hippocampal volume CSF $A\beta_{42}$ CSF tau	Accuracy 70% AUC 0.64 p=0.0002

ApoE4-negative subjects						
Diagnostic comparison	Hippocampal classifier		CSF classifier		Hippocampal + CSF classifier	
	Selected variables	Accuracy AUC p-value	Selected variables	Accuracy AUC p-value	Selected variables	Accuracy AUC p-value
NC vs. MCI	Sex Hippocampal volume Age Education	Accuracy 67% AUC 0.7 p=0.008	CSF $A\beta_{42}$ Sex CSF p-tau CSF tau Age	Accuracy 74% AUC 0.78 p=0.0008	CSF $A\beta_{42}$ Hippocampal volume Sex CSF tau Education Age	Accuracy 76% AUC 0.79 p=0.003
NC vs. AD	Education Hippocampal volume Age	Accuracy 80% AUC 0.73 p=0.0002	CSF tau CSF p-tau CSF $A\beta_{42}$ Sex Age	Accuracy 87% AUC 0.88 p<0.0001	CSF tau CSF p-tau CSF $A\beta_{42}$ Hippocampal volume Age Sex	Accuracy 89% AUC 0.87 p<0.0001
MCI vs. AD	Hippocampal volume	Accuracy 74% AUC 0.59 p=0.008	CSF tau Education CSF $A\beta_{42}$ Sex CSF p-tau Age	Accuracy 82% AUC 0.74 p<0.0001	CSF tau Sex	Accuracy 81% AUC 0.67 p<0.0001

3.2.1.4. ApoE4 stratified analyses (Fig. 1 bottom portion). Hippocampal volume and CSF biomarkers both separately and in combination performed well in discriminating NC vs. AD regardless of ApoE4 genotype (ApoE4-positive subjects: hippocampal classifier AUC = 0.74 $p_{corrected}$ < 0.0001, CSF classifier AUC = 0.73 $p_{corrected}$ = 0.0005 and combined classifier AUC = 0.83 $p_{corrected}$ < 0.0001; ApoE4-negative subjects: hippocampal classifier AUC = 0.73 $p_{corrected}$ = 0.0002,

CSF classifier AUC = 0.88 $p_{corrected}$ < 0.0001 and combined classifier AUC = 0.87 $p_{corrected}$ < 0.0001).

In the NC vs. MCI analyses CSF biomarkers alone and the combination of hippocampus and CSF biomarkers achieved reasonable AUCs in the ApoE4-negative sample only (ApoE4-negative subjects: hippocampal lassifier AUC = 0.70 $p_{corrected}$ = 0.008, CSF classifier AUC = 0.78 $p_{corrected}$ = 0.0008 and combined classifier AUC = 0.79

$p_{corrected} = 0.003$; ApoE4-positive subjects: hippocampal classifier AUC = 0.64 $p_{corrected} = 0.005$, CSF classifier AUC = 0.52 $p_{corrected} = 0.01$ and combined classifier AUC = 0.58 $p_{corrected} = 0.0006$).

In the MCI vs. AD analyses the hippocampal classifier performed best in ApoE4-positive subjects (AUC = 0.69, $p_{corrected} = 0.0006$) and the CSF classifier performed best in the ApoE4-negative subjects (AUC = 0.74, $p_{corrected} < 0.0001$).

Among ApoE4-positive subjects classifiers did not prove to be statistically significant from each other. Among ApoE4-negative subjects the hippocampal + CSF classifier was significantly better than the hippocampal-only classifier when discriminating NC vs. MCI ($p = 0.012$) and NC vs. AD ($p = 0.008$, Table 6). The CSF-only classifier performed significantly better than the hippocampal-only classifier when discriminating Apoe4-negative NC vs. AD subjects ($p = 0.012$, Table 6).

3.2.2. Predicting conversion

Fig. 2 and Table 5 show the SVM classifier ROCs, classifier performance metrics, ranking of variables selected by each classifier and permutation corrected classifier significance for the MCI conversion classifier analyses.

In the classifier model including both ApoE4-positive and negative subjects the hippocampal-only classifier selected hippocampal volume, sex and education and achieved an AUC = 0.64 ($p_{corrected} = 0.048$). The CSF-only classifier selected only CSF Aβ_{42} and achieved an AUC = 0.63 ($p_{corrected} = 0.008$). The combined hippocampal-CSF classifier selected hippocampal volume, CSF Aβ_{42}, CSF p-tau, education, sex and CSF tau and achieved an AUC = 0.64 ($p_{corrected} = 0.042$). The addition of ApoE4 genotype did not seem to affect the overall multimodal classifier results (AUC = 0.68, $p_{corrected} = 0.019$). ApoE4 genotype performed about the same as hippocampal volume and CSF regardless of whether ApoE2 carriers were excluded or not (all subjects AUC = 0.64, $p_{corrected} = 0.002$, without ApoE2 carriers AUC = 0.61, $p_{corrected} = 0.004$). Substituting the binary ApoE4-positive vs. negative predictor variable with a variable reflecting the number of ApoE4 alleles (0, 1 or 2) did not result in overall improvement in classifier performance (AUC = 0.61, $p_{corrected} = 0.0026$).

Once stratified by ApoE4 genotype the best results for predicting conversion to AD were achieved by the hippocampus-only classifier in ApoE4-positive (predictors: hippocampal volume and sex; AUC = 0.68, $p_{corrected} < 0.0001$) and CSF-only classifier for ApoE4-negative subjects (predictors: CSF p-tau, education and sex; AUC = 0.89, $p_{corrected} < 0.0001$).

4. Discussion

All classifier models performed very well in discriminating NC from AD and moderately well in discriminating NC from MCI. The MCI vs. AD ascertainment, as expected, proved to be more challenging for unimodal and multimodal classifiers alike presumably due to the fact that the MCI biomarker pattern is rather similar to the one seen in AD. The multimodal biomarker classifier approach had better diagnostic and predictive power than any unimodal classifier.

Several important observations can be made from the discriminative classifier performance. CSF Aβ_{42} played a significant role in discriminating NC from MCI and AD but was not selected by the MCI vs. AD classifiers while CSF p-tau contributed to accurate discrimination of AD from both NC and MCI, yet played no role in differentiating NC from MCI. These observations are in agreement with the proposed biomarker trajectory in AD where amyloid markers become abnormal early in the disease course and neurodegenerative markers (here CSF p-tau) become abnormal later in the disease course. Interestingly hippocampal atrophy and CSF t-tau seemed quite ubiquitously used by most classifiers including the NC vs. MCI classifiers, suggesting that these neurodegenerative biomarkers are becoming abnormal somewhere between the CSF Aβ_{42} and the CSF p-tau changes.

CSF Aβ_{42} proved to be useful for differentiating NC from MCI only among ApoE4-negative but not ApoE4-positive subjects. This is likely due to the fact that many ApoE4-positive cognitively normal elderly already have significant brain amyloidosis and low CSF Aβ_{42} rendering amyloid biomarkers insensitive for differentiating NC and MCI. At the same time neurodegenerative biomarkers (CSF tau, CSF p-tau and/or hippocampal atrophy) were readily chosen in both ApoE4-positive and ApoE4-negative NC vs. MCI classifiers establishing their discriminative role for patients with either genotype.

Both amyloid and neurodegenerative biomarkers were readily chosen by the conversion classifiers. Similar to the observations of others (Cui et al., 2011; Davatzikos et al., 2011; Ewers et al., 2012; Vos et al., 2012; Westman et al., 2012) the classifier accuracies in the full sample were marginal at best. However once split by ApoE4 genotype we observed that hippocampal volume and sex were helpful for predicting conversion to AD among ApoE4-positive MCI, while CSF p-tau was helpful for the prediction of conversion to AD among ApoE4-negative MCI subjects. Both classifier algorithms chose only markers of neurodegeneration as one might expect to be the case in the symptomatic MCI stage. These conclusions are well supported by data from a recent paper by Jack et al. showing that among amyloid positive MCI subjects hippocampal atrophy, and not amyloid burden, predicted shorter time to progression to dementia (Jack et al., 2010) because amyloid load plateaus (Jack et al., 2013) while hippocampal volume does not (Jack et al., 2010).

The CSF outperformed the hippocampal metrics in discriminating NC from MCI and AD. Low CSF Aβ_{42} is tightly linked to the presence of amyloid pathology in the brain while hippocampal atrophy is criticized for being a nonspecific measure observed in many disease states and in normal aging (Apostolova and Thompson, 2008). Techniques capable of detecting hippocampal atrophy in selected subfields are being developed (Apostolova et al., 2010a,c; Csernansky et al., 2000; Mueller and Weiner, 2009) and some have even demonstrated ability to detect hippocampal atrophy in the presymptomatic disease stages (Apostolova et al., 2010c). Alternatively more sophisticated MRI measures such as for instance the Structural Abnormality Index (STAND), which captures hippocampal and cortical atrophy, can also improve the ability of MRI for predicting future decline (Vemuri et al., 2009a,b).

In contrast to other groups that have published multimodal diagnostic classification papers using ADNI data (Cui et al., 2011; Davatzikos et al., 2011; Ewers et al., 2012; Kohannim et al., 2010; Vos et al., 2012; Walhovd et al., 2010; Westman et al., 2012) we also investigated classifier performance after ApoE4-stratification (i.e., investigated the classifier performance separately in carriers and noncarriers). This led to some interesting observations in respect to the modulatory effect of ApoE4 genotype on biomarker trajectory in AD. It is fascinating that support vector machine classifiers can help uncover interesting observations in respect to AD pathophysiology. This is a novel way of utilization of a statistical methodology thought by many to be only capable of diagnostic discrimination and outcome prediction.

Although multicollinearity can be a problem for multiple linear regression, it is standard for SVMs to be provided with thousands of correlated predictors, and still perform very well. Only certain kinds of machine learning methods, such as naive Bayes methods, assume that the inputs of the classifier are statistically independent. Even when inputs considered to be an n-dimensional vector by SVM, are highly correlated, the SVM will find the optimal hyperplane for separating the samples and making decisions to categorize or classify future data.

Correlation among inputs is less of an issue when making predictions. Redundancy among predictors is common and does not undermine the predictive accuracy of the classifier. However correlated inputs do tend to complicate the interpretation of which predictor variables are driving the effects. This is more of an issue if the classifier is considered as a "descriptive" model — telling us the relative
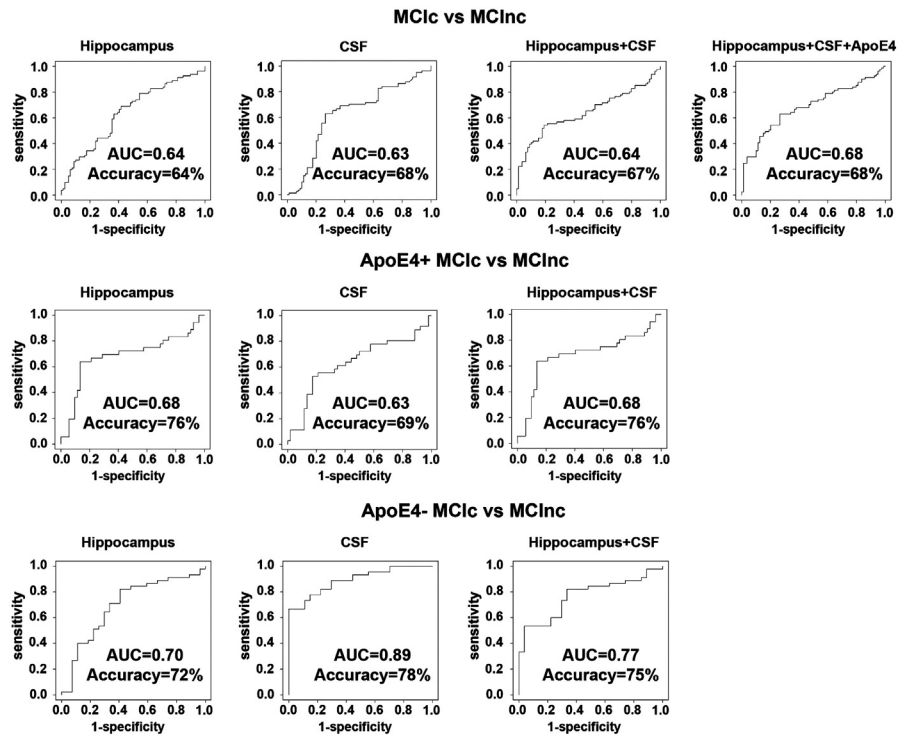
Fig. 2. Receiver Operation Characteristic (ROC) for the conversion classifier.

importance of variables for the prediction, but it is less of an issue for predictive accuracy as many of the redundant predictors can be used.

When one fits an SVM with multiple predictors, if the predictors are correlated, SVM might pick some predictors on one occasion and may do equally well on another occasion using other predictors. SVM will always pick the one that minimizes the error. Sometimes the accuracies of certain feature combinations are very close, yet SVM will pick the one with the lowest error. It does not mean that the other dropped variables might not be predictive, only that they are sufficiently redundant with the ones that were used that they were not chosen.

This study has several strengths and limitations. The strengths of ADNI lie in its large size, its detailed cognitive assessment protocol and careful diagnostic ascertainment, as well as in the implementation of unified MRI and CSF collection and processing strategies across multiple sites and the meticulous data quality control. Yet ADNI was designed to inform decisions about future disease modifying clinical trials and as such it employs the rigorous inclusion and exclusion criteria typical of clinical trials. As such, the ADNI cohort is not a complete representation of the elderly population and its findings should be generalized with caution; for example, the classification accuracies may be poorer in populations with a great mix of conditions and co-morbidities. Another relative weakness of our study is the etiologic/pathologic uncertainty in the MCI stage as at least 30% of amnestic MCI subjects have been found to harbor non-AD pathology (Jicha et al., 2006). Even so, etiologic heterogeneity should not be expected to invalidate the biomarker-to-biomarker correlations across the pooled sample.

Another important limitation of our study is the classifiers' exclusive reliance on biomarkers for diagnostic categorization. By doing so we inadvertently compromise our ability to accurately classify AD vs. MCI subjects as the diagnostic distinction between these categories is determined by the presence or absence of functional decline which cannot be ascertained from biomarker data. Thus it is not surprising that our biomarker-based classifier models failed to discriminate between MCI and AD. However we must acknowledge that providing our classifiers with functional or cognitive variables would have introduced a circularity argument, as cognitive variables were used for diagnostic ascertainment of ADNI subjects.

One must also take under consideration that CSF tau and p-tau changes do not accurately reflect (i.e., lag behind) the severity and extent of tau pathology in the AD brain. CSF biomarkers are just peripheral surrogates of actual tau pathology. Several tau-imaging ligands are currently under development. Such technology might provide a much more accurate metric of tau pathology and contribute meaningfully to an improved understanding and staging of the early and presymptomatic stages of AD. Last but not least, our classifier results will benefit from independent validation in a different cohort with similar longitudinal follow-up and biomarker data availability.

Table 5
Classifier performance metrics, ranking of variables selected by each classifier and permutation corrected classifier significance in predicting conversion from MCI to AD with and without stratification by ApoE4 genotype.

Diagnostic comparison	Hippocampal classifier		CSF classifier		Hippocampal + CSF classifier		Hippocampal + CSF + ApoE classifier	
	Selected variables (ranked)	Accuracy AUC p-value	Selected variables (ranked)	Accuracy AUC p-value	Selected variables (ranked)	Accuracy AUC p-value	Selected variables (ranked)	Accuracy AUC p-value
MCIc vs MCInc	Hippocampal volume, Sex, Education	Accuracy 64% AUC 0.64 p = 0.048	CSF Aβ_{42}	Accuracy 68% AUC 0.63 p = 0.008	Hippocampal volume, CSF Aβ_{42}, CSF p-tau, Education, Sex, CSF tau	Accuracy 67% AUC 0.64 p = 0.042	ApoE CSF p-tau, Hippocampal volume, CSF Aβ_{42}, CSF tau, Education	Accuracy 68% AUC 0.68 p = 0.019

ApoE4 stratified MCIc vs. MCInc classifier

Diagnostic comparison	Hippocampal classifier		CSF classifier		Hippocampal + CSF classifier	
	Selected variables	Accuracy AUC p-value	Selected variables	Accuracy AUC p-value	Selected variables	Accuracy AUC p-value
ApoE4+ MCIc vs. ApoE4 + MCInc	Hippocampal volume, Sex	Accuracy 76% AUC 0.68 p < 0.0001	Age, Sex	Accuracy 69% AUC 0.63 p = 0.002	Hippocampal volume, Sex	Accuracy 76% AUC 0.68 p < 0.0001
ApoE4− MCIc vs. ApoE4− MCInc	Sex, Age	Accuracy 72% AUC 0.70 p = 0.005	CSF p-tau, Education, Sex	Accuracy 78% AUC 0.89 p < 0.0001	CSF p-tau	Accuracy 75% AUC 0.77 p < 0.001

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Dr. Apostolova serves on the Speakers Bureau for Lilly Pharmaceuticals. She receives research funding from the National Institutes of Health and the Easton Consortium for Alzheimer's Drug Development and Biomarker Discovery. Dr. Apostolova receives research funding from the NIH. Dr. Apostolova had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Apostolova was responsible for design and conduct of the study; collection, management, analysis, and interpretation of the data, and preparation, review and approval of the manuscript.

Ms. Hwang has no disclosures. Ms. Hwang was responsible for data management, analysis, and interpretation of the data, preparation, review and approval of the manuscript.

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Dr. Trojanowski may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein he is co-Inventor and he received revenue from the sale of Avid to Eli Lily as co-inventor on imaging related patents submitted by the University of Pennsylvania. He receives research support from the NIH, Bristol Myer Squib, Astra Zeneca and several non-profits. Dr. Trojanowski receives research funding from the NIH. Dr. Trojanowski was responsible for the interpretation of the data, review and approval of the manuscript.

Dr. Weiner has served in the past three years on the Scientific Advisory Boards of Lilly, Biogen Idec, Pfizer, Araclon and Institut Catala de Neurociencies Aplicades, Gulf War Veterans Illnesses Advisory

Table 6
Statistical comparisons of classifiers (p-values).

Diagnostic comparison	Classifier Comparison	p-value
NC vs. MCI	Hippocampal vs. CSF classifier	0.01
	Hippocampus + CSF vs. hippocampal classifier	0.0044
	Hippocampus + CSF vs. CSF classifier	NS
	Hippocampus + CSF + ApoE vs. hippocampus + CSF classifier	NS
NC vs. AD	Hippocampal vs. CSF classifier	0.04
	Hippocampus + CSF vs. hippocampal classifier	0.0001
	Hippocampus + CSF vs. CSF classifier	0.03
	Hippocampus + CSF + ApoE vs. hippocampus + CSF	NS
MCI vs. AD	Hippocampal vs. CSF classifier	NS
	Hippocampus + CSF vs. hippocampal classifier	NS
	Hippocampus + CSF vs. CSF classifier	NS
	Hippocampus + CSF + ApoE vs. hippocampus + CSF classifier	NS
ApoE4+ NC vs. MCI	Hippocampal vs. CSF classifier	NS
	Hippocampus + CSF vs. hippocampal classifier	NS
	Hippocampus + CSF vs. CSF classifier	NS
	Hippocampus + CSF + ApoE vs. hippocampus + CSF classifier	NS
ApoE4+ NC vs. AD	Hippocampal vs. CSF classifier	NS
	Hippocampus + CSF vs. hippocampal classifier	NS
	Hippocampus + CSF vs. CSF classifier	NS
	Hippocampus + CSF + ApoE vs. hippocampus + CSF classifier	NS
ApoE4+ MCI vs. AD	Hippocampal vs. CSF classifier	NS
	Hippocampus + CSF vs. hippocampal classifier	NS
	Hippocampus + CSF vs. CSF classifier	NS
	Hippocampus + CSF + ApoE vs. hippocampus + CSF classifier	NS
ApoE4− NC vs. MCI	Hippocampal vs. CSF classifier	NS
	Hippocampus + CSF vs. hippocampal classifier	0.012
	Hippocampus + CSF vs. CSF classifier	NS
	Hippocampus + CSF + ApoE vs. hippocampus + CSF classifier	NS
ApoE4− NC vs. AD	Hippocampal vs. CSF classifier	0.012
	Hippocampus + CSF vs. hippocampal classifier	0.008
	Hippocampus + CSF vs. CSF classifier	NS
	Hippocampus + CSF + ApoE vs. hippocampus + CSF classifier	NS
ApoE4− MCI vs. AD	Hippocampal vs. CSF classifier	NS
	Hippocampus + CSF vs. hippocampal classifier	NS
	Hippocampus + CSF vs. CSF classifier	NS
	Hippocampus + CSF + ApoE vs. hippocampus + CSF classifier	NS

NS—not significant.

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