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Comparison of neuroimaging modalities for the prediction of conversion from mild cognitive impairment to Alzheimer's dementia

Paula T. Trzepacz [a,b,*], Peng Yu [a], Jia Sun [c], Kory Schuh [a], Michael Case [a], Michael M. Witte [d], Helen Hochstetler [d], Ann Hake [b,d], for the Alzheimer's Disease Neuroimaging Initiative [1]

[a] Eli Lilly and Company, Indianapolis, IN, USA
[b] Indiana University School of Medicine, Indianapolis, IN, USA
[c] Bucher & Christian Consulting, Inc, Indianapolis, IN, USA
[d] Lilly USA, LLC, Indianapolis, IN, USA

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ABSTRACT

In this study we compared Pittsburgh compound-B (PIB) positron emission tomography (PET) amyloid imaging, fluorodeoxyglucose PET for metabolism, and magnetic resonance imaging (MRI) for structure to predict conversion from amnestic mild cognitive impairment (MCI) to Alzheimer's dementia using data from the Alzheimer's Disease Neuroimaging Initiative cohort. Numeric neuroimaging variables generated by the Alzheimer's Disease Neuroimaging Initiative-funded laboratories for each neuroimaging modality along with apolipoprotein-E genotype ($n = 29$) were analyzed. Performance of these biomarkers for predicting conversion from MCI to Alzheimer's dementia at 2 years was evaluated in 50 late amnestic MCI subjects, 20 of whom converted. Multivariate modeling found that among individual modalities, MRI had the highest predictive accuracy (67%) which increased by 9% to 76% when combined with PIB-PET, producing the highest accuracy among any biomarker combination. Individually, PIB-PET generated the best sensitivity, and fluorodeoxyglucose PET had the lowest. Among individual brain regions, the temporal cortex was found to be most predictive for MRI and PIB-PET.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the most common form of dementia, accounting for approximately 60%–80% of cases (Alzheimer's Association, 2012). Mild cognitive impairment (MCI) attributed to AD refers to the symptomatic predementia phase of AD (Albert et al., 2011). Individuals with MCI experience a progressive cognitive decline that is greater than expected for their age and education level. When the cognitive impairment worsens and interferes with activities of daily living, the patient is diagnosed with dementia (Albert et al., 2011). In general, individuals with MCI convert to dementia at a rate of 10%–25% per year, though some will never convert to dementia or might revert to normal cognitive status (Grand et al., 2011).

Because not all MCI is caused by AD, being able to identify phenotypic and endophenotypic characteristics of persons with MCI who will go on to develop dementia would be important prognostic information to allow patients and families to plan and manage treatments including future neuroprotective therapies (Gelosa and Brooks, 2012). "Value of knowing" research suggests that patients and families can benefit from early disclosure of MCI and AD diagnoses (Smith et al., 1998) but there is some question as to patient benefit from knowing the diagnosis (Maguire et al., 1996; Monaghan and Begley, 2004; Pinner, 2000), in part related to level of insight.

AD pathology involves cortical and subcortical atrophy, beta amyloid (Aβ) plaques, and tau neurofibrillary tangles. The 5 most

* Corresponding author at: Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA. Tel.: +1 317 433 5391; fax: +1 317 276 7100.
E-mail address: trzepacz_paula_t@lilly.com (P.T. Trzepacz).

[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.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.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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commonly studied biomarkers of AD are Aβ plaque positron emission tomography (PET) neuroimaging, cerebrospinal fluid (CSF) $A\beta_{42}$ levels, CSF total (t-tau) and phosphorylated (p-tau) tau levels, fluorodeoxyglucose (FDG) PET, and structural magnetic resonance imaging (MRI), especially of hippocampal volume (Gelosa and Brooks, 2012; Jack et al., 2011). There is a growing literature investigating the use of these biomarkers alone, or in combination, to predict conversion from MCI to dementia.

Pittsburgh compound-B (PIB), a carbon 11-labeled derivative of the thioflavin-T amyloid dye that binds with high affinity to Aβ plaques, is a PET neuroimaging ligand used in clinical research (Klunk et al., 2004; Pike et al., 2007). PIB-positive MCI patients are significantly more likely to convert to Alzheimer's dementia than PIB-negative (Forsberg et al., 2008), in whom higher initial PIB retention levels were associated with faster rates of conversion (Okello et al., 2009). Conversion rates of MCI to dementia were consistently found to be much greater in those who had evidence of positive or high retention on PIB PET: 67% versus 5% in a 20-month study (Villemagne et al., 2011), 38% versus 0% in an average of 21-month follow-up in another study (Wolk et al., 2009), and 50% versus 19% in a 2-year study (Jack et al., 2010b). A low level of CSF $A\beta_{42}$ is a biomarker for plaque formation in the brain. CSF $A\beta_{42}$ levels are inversely correlated with the presence of brain amyloid imaged using PIB (Fagan et al., 2006). In a study by Shaw et al. (2009), $A\beta_{42}$ was the most sensitive CSF biomarker for dementia in the autopsy-confirmed AD cohort ($n = 56$) with a sensitivity for dementia detection (patients accurately identified as converters among all converters) of 96.4% and specificity (patients accurately identified as nonconverters among all nonconverters) of 76.9%.

Increased levels of CSF t-tau and p-tau occur after release from damaged and dying neurons and are constituents of neurofibrillary tangles (Shaw et al., 2009). As with $A\beta_{42}$, CSF levels of t-tau and p-tau are used to predict MCI conversion to Alzheimer's dementia with sensitivities of 69.6% and 67.9%, respectively (Shaw et al., 2009).

FDG-PET measures uptake of labeled glucose which reflects metabolism in brain structures and might be used to distinguish frontotemporal dementia with its anterior functional defects from Alzheimer's dementia with its temporoparietal cortex defects (Albert et al., 2011). Using FDG-PET to predict which patients with MCI would convert to dementia at 18 months, Chételat et al. (2003) found that converters had lower FDG uptake in the right temporoparietal cortex. Drzezga et al. (2005) found that 11 of 13 MCI patients with baseline FDG-PET suggestive for AD converted to dementia by 16 months versus 16 of 17 FDG-PET-negative patients who remained stable at the end of the study.

Whitwell et al. (2007) demonstrated that MRI can detect patterns of cerebral atrophy in patients with MCI and identify early region of interest (ROI) changes associated with dementia. Atrophy of medial temporal structures was noted in MCI 3 years before Alzheimer's dementia was diagnosed. At 1 year before dementia was diagnosed, the extent and magnitude of the atrophy had progressed and spread to the middle temporal gyrus and more posterior temporal regions including the hippocampus, and into the parietal lobe. Dementia had more widespread atrophy especially of medial temporal, frontal, and temporoparietal association cortices. Using Alzheimer's Disease Neuroimaging Initiative (ADNI) data, Risacher et al. (2009) compared MCI converters to Alzheimer's dementia versus MCI-stable patients and found that the degree of neurodegeneration of the medial temporal structures was the best antecedent MRI marker of imminent conversion, with decreased hippocampal volume being the most robust.

Some studies (e.g., Brys et al., 2009; Galluzzi et al., 2010; Jack et al., 2010b; Mattsson et al., 2009; Shaw et al., 2009; Yu et al., 2012) evaluated combinations of biomarkers for their relative or combined predictive value for dementia conversion. Brys et al. (2009) found that adding CSF p-tau to MRI significantly increased overall prediction accuracy of dementia conversion from 74% to 84%. Medial temporal atrophy on MRI scans and abnormal CSF are the single most robust predictors of conversion to Alzheimer's dementia in MCI in which their combination enhances prediction (accuracy of medial temporal atrophy, area under the curve = 0.73, abnormal CSF = 0.74, combination = 0.82) (Galluzzi et al., 2010). Yuan et al. (2009) compared FDG-PET, single-photon emission tomography, and structural MRI to predict conversion to Alzheimer's dementia from MCI ($n = 1112$). For FDG-PET, single-photon emission tomography, and MRI, sensitivity and specificity were 88.8% and 84.9%, 83.8% and 70.4%, and 72.8% and 81.0%, respectively. Yu et al. (2012) compared MRI, FDG-PET, and CSF biomarkers and their combinations to assess which best predicted MCI conversion to Alzheimer's dementia within 2 years. The results indicated that MRI had the best individual predictive power (78% accuracy) but the combination of all 3 biomarkers provided the most accurate prediction (81% accuracy).

In the current study, we compared 3 neuroimaging methods (PIB-PET, FDG-PET, and volumetric MRI) to predict conversion from MCI to Alzheimer's dementia using 2-year follow-up clinical data from the ADNI cohort. We first evaluated each individual biomarker including the ROIs and composite measures from different imaging modalities. Using a variable selection algorithm, we then compared the performance of these biomarkers in a multivariate analysis using all imaging modalities. Finally, we compared individual modalities and their combinations for their prediction performance. To the best of our knowledge, there are no published prediction reports comparing these 3 imaging methods.

2. Methods

2.1. Subjects and design

We analyzed ADNI 1 data available as of August 2011 (http://www.loni.ucla.edu/ADNI). ADNI 1 is a 5-year multisite program funded by a public-private partnership including the National Institute on Aging, Food and Drug Administration, pharmaceutical companies, and nonprofit organizations to investigate the relationship of neuroimaging, biological, clinical, and neuropsychological assessments to disease progression in AD. Recruitment included approximately 800 subjects—200 elderly control subjects, 400 with MCI, and 200 with mild Alzheimer's dementia. Written informed consent was obtained for participation in these studies, approved by the institutional review board at each participating center. Subjects were followed for 2–3 years and assessed every 6–12 months. MCI subjects had Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive), a memory complaint, objective memory loss measured according to education-adjusted scores on Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. Mild AD subjects had MMSE scores between 20 and 26 (inclusive), Clinical Dementia Rating of 0.5 or 1.0, and met National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD.

At each visit, subjects were evaluated using cognitive tests including the MMSE (range, 0–30 points), in which lower MMSE scores indicate more cognitive impairment, and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); ADAS-Cog 11-item (range, 0–70 points) and ADAS-Cog 13-item (range, 0–85), in which higher scores indicate worse cognitive function. For MCI subjects, the site clinician also assessed whether the subject progressed to Alzheimer's dementia, remained as MCI, or returned

to normal using all cognitive and clinical data available at the day of visit.

Using baseline data of MCI patients, we evaluated the ability of neuroimaging, including PIB—PET, MRI, and FDG-PET, to predict conversion from MCI to a clinical diagnosis of Alzheimer's dementia within 2 years. In addition to demographic data (e.g., age and education), apolipoprotein E (ApoE) genotype is the only laboratory test included in this analysis.

For this study, we selected MCI subjects who had a PIB-PET scan and 2-year follow-up clinical evaluation. In ADNI 1, most of the subjects had MRI scans, and approximately half of the subjects had FDG-PET scans. Because the PIB-PET study was initiated as an add-on project toward the end of the first year, only 103 participants at 14 participating ADNI PET centers were recruited for PIB-PET imaging and the first PIB-PET scan was acquired at month 12 or later instead of at the baseline visit for some participants. Therefore, in this study, the baseline visit for each subject was defined as the time of the first PIB-PET scan. This resulted in 60 MCI subjects with a baseline PIB-PET measurement, 50 of whom had a 2-year clinical follow-up. Of these 50, all subjects also had FDG-PET and ApoE genotype at the visit that included the first PIB-PET scan, and only 49 subjects had MRI scans at that visit. This study was conducted on these 50 MCI subjects; 20 of them converted to AD and the others remained stable at the 2-year follow-up. (A list of subjects used in this study can be found in Supplementary Table 1.)

2.2. Biomarker variables

We considered a total of 29 numeric variables, comprising ROI and composite imaging measures generated by the ADNI-funded laboratories for PIB-PET, structural MRI, and FDG-PET, along with ApoE genotype (see Table 1 for the variable list and descriptions).

The PIB-PET data were analyzed at the University of Pittsburgh, which reported standardized uptake value ratios (SUVRs) for 14 ROIs, and SUVR was calculated as the ratio of ROI uptake value to that of the whole cerebellum. Out of the 14 variables provided by ADNI, we selected 12 measurements because cerebellum and sensory motor cortex are not considered specific regions related to AD pathology. In addition, we generated a PIB-PET composite measure using the average of SUVR values across right and left sides for 5 ROIs in which PIB uptake is known to predominate, including prefrontal, lateral temporal, anterior cingulate gyrus, parietal, and posterior cingulate/precuneus.

Several research laboratories were funded to analyze the structural MRI data in the ADNI study and some generated closely related measures (e.g., hippocampal volume, cortical parcellation). We used volumetric MRI measurements generated by the University of California, San Diego, because of its good performance in power analysis (Holland et al., 2009), which yielded 14 volumetric MRI variables, in addition to intracranial volume. We condensed these measurements to 7 variables by averaging the symmetrical ROIs across the left and right hemispheres (Table 1).

Three laboratories analyzed the ADNI FDG-PET images using different methods, resulting in several recommended summary statistics (Chen et al., 2010; Landau et al., 2009). In this study, we included 5 variables generated by 2 ADNI-funded analysis laboratories as listed in Table 1. The measurements in the cross-validated regions generated by Banner Alzheimer's Institute were excluded because of missing data.

Information about the acquisition and measurements of PIB-PET, MRI, FDG-PET, and ApoE genotype can be found in the ADNI procedure manual (http://www.adni-info.org/Scientists/

Table 1
Description of biomarker variables

Modality	Laboratory	Variable	Annotation
MRI	University of California, San Diego	TEMPORAL	Sum of middle and inferior temporal cortex
		FUSIFORM	Fusiform cortex
		ENTORHINAL	Entorhinal cortex
		BRAIN	Whole brain
		VENTRICLES	Ventricle
		HIPPOCAMPUS	Hippocampus
		INFLATVEN	Inferior lateral ventricles
		ICV	Intracranial volume
PIB-PET	University of Pittsburgh	ACG	Anterior cingulate
		AVS	Anterior ventral striatum
		FRC	Frontal cortex
		LTC	Lateral temporal cortex
		MTC	Mesial temporal cortex
		OCC	Occipital cortex
		OCP	Occipital pole
		PAR	Parietal cortex
		PRC	Precuneus cortex
		PON	Pons
		SWM	Sub-cortical white matter
		THL	Thalamus
		Composite SUVR	Average of ACG, LTC, PAR, FRC, and PRC
FDG-PET	University of Utah	AVEASSOC	Average cerebral metabolic rate of glucose (CMRglc) in frontal parietal and temporal cortices
		AVEFRONT	Average CMRglc in frontal cortex
		X2SDSIGPXL	Number of pixels with hypometabolic activity two standard deviations below normal mean
		X3SDSIGPXL	Number of pixels with hypometabolic activity three standard deviations below normal mean
	University of California, Berkeley	ROI-avg	The average signal from the right/left angular, right/left temporal, and bilateral posterior cingulate
ApoE	UPENN	ApoE 24	ApoE Genotype 24
		ApoE 33	ApoE Genotype 33
		ApoE 34	ApoE Genotype 34
		ApoE 44	ApoE Genotype 44

Key: ADNI, Alzheimer's Disease Neuroimaging Initiative; ApoE, apolipoprotein E; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; PIB, Pittsburgh compound-B; ROI, region of interest; SUVR, standardized uptake value ratio.

Pdfs/adniproceduresmanual12.pdf). A summary (mean and SD) of these biomarkers in MCI converter and nonconverter groups is reported in Supplementary Table 2.

2.3. Statistical analyses

In this study, subjects' description and demographic data were expressed as mean and SD or frequencies as relevant to the variable. Elastic net logistic regression (Zou and Hastie, 2005) was used for conversion prediction and biomarker selection.

Considering that there are 29 biomarker measures across multiple modalities, it is crucial to select the biomarkers that best separate the converters from the nonconverters to obtain a parsimonious model that avoids overfitting to noise in the data. For that purpose, we used the elastic net logistic regression method to jointly select measurements that are predictive of MCI progression and to train the classifier. Elastic net logistic regression is a regularized version of logistic regression designed to deliver good prediction performance while conducting automatic variable selection. In addition, when there are strongly correlated predictors, the elastic net method encourages selecting the group of variables together if they are predictive. This grouping effect was considered to be useful, particularly in biomedical data analysis, for discovering the relationship among all of the input variables (Zou and Hastie, 2005). Additional technical details on the elastic net method can be found in the original technical report (Zou and Hastie, 2005).

Because each variable has a different range and unit, we standardized each variable to have a 0 mean and variance of 1 across all subjects. After applying the elastic net logistic regression to the input variables, we can obtain a classification model, in which only variables relevant to separating converters from nonconverters have nonzero weights. In other words, only input variables that are determined to be predictive of conversion are selected in the output model. Moreover, we can rank the importance of these selected variables by using their corresponding weights in the classifier. The larger the magnitude of the weight, the more important the variable is for distinguishing MCI converters from nonconverters. Finally, we can use the resulting classification model to directly predict the conversion for a new patient. Specifically, a default probability threshold of 50% was used when we applied the predictive model to the test subject in this work (i.e., the test subject is classified as a converter if the predicted conversion probability is larger than 50%, and a nonconverter otherwise).

Because of the limited number of subjects in this study, we used the 'leave one out' (LOO) cross-validation to calculate the prediction accuracy of these biomarkers. That is, we built n classification models using $n-1$ subject each time, and used the resulting classifier to classify the nth (left out) subject as a converter or nonconverter. The average LOO prediction accuracy across all subjects was then reported for all tests shown in this work.

We first evaluated neuroimaging and ApoE biomarkers individually to estimate the predictive power of each for conversion. In this step, we built the classification model individually for each biomarker variable by turning off the variable selection function in the elastic net algorithm. In this step, we used the ApoE ε4 carrier status (0 = no ApoE ε4 allele, 1 = at least 1 ApoE ε4 allele) instead of genotype. For comparison with these biomarkers, we also randomly generated 10 variables drawn from a uniform distribution (on the closed interval [0, 1]) and calculated their classification accuracies.

We then tested the prediction performance combining all biomarkers together. We applied the elastic net logistical regression method to all 28 variables (PIB-PET (excluding the composite SUVR score), MRI, FDG-PET, and ApoE). For comparison, we also generated 10 sets of 28 random variables and calculated their prediction performance. These tests on random variables provided a comparison to evaluate if the biomarkers indeed provided better predictive value.

Finally, we evaluated the prediction accuracies using different combinations of neuroimaging modalities to understand the added value contributed by each modality (i.e., gain in classification accuracy). In this step, we used results from the individual biomarker analyses to filter out less predictive variables. Therefore, only ROI or composite neuroimaging variables whose prediction accuracy was better than that for the random variables from the individual biomarker test analyses were included. Combinations of MRI with either PET modality were tested but not both PET types together, because it is uncommon to use both types of PET imaging in clinical practice.

Tests involving MRI measurements were based on 49 subjects to accommodate 1 missing subject, and all the other tests were based on 50 subjects.

3. Results

3.1. Description of subjects

Of the 50 MCI subjects included in this study, 20 (40%) converted to Alzheimer's dementia within 2 years (converters) and 30 did not (nonconverters). As shown in Table 2, demographic and baseline clinical profiles of the MCI cohort according to converter and nonconverter groups were similar except that baseline MMSE and ADAS-Cog scores were significantly worse in the converter group (2-sided Student t test, $p < 0.05$). Both groups were well-educated (12–20 years) and had MMSE scores from 22 to 30.

3.2. Conversion prediction accuracy based on single biomarker variables

We first evaluated the performance of each biomarker alone for prediction of conversion. Fig. 1 shows the LOO classification accuracy and rank of individual biomarkers according to prediction accuracy that exceeded 50%. Only 9 biomarker variables outperformed the best prediction accuracy generated from the 10 random variables, which was 60%. At 72%, MRI temporal lobe volume had the highest accuracy followed at 68% by PIB-PET SUVR of the lateral temporal cortex, and MRI hippocampus and entorhinal cortex volumes. PIB-PET composite and frontal cortex SUVRs were next at 64% accuracy. The highest accuracy achieved with any FDG-PET variable was 62% and the other FDG-PET measures had 60% or less accuracy and no better than the random variables. ApoE ε4

Table 2
Demographic and clinical profile for MCI subjects ($n = 50$) reported as mean ± SD and range unless otherwise specified

Variable	MCI converters, $n = 20$	MCI nonconverters, $n = 30$
Age (range), years	75.4 ± 6.6 (59.6–83.9)	74.2 ± 8.4 (56.4–87.7)
Sex (% female)	40	30
Education (range), years	16.3 ± 2.8 (12–20)	15.9 ± 2.6 (12–20)
MMSE (range)	26.2 ± 2.1 (22–30)	28.3 ± 1.6 (24–30)[a]
ADAS-Cog 11 (range)	15.1 ± 3.4 (7.67–21.33)	7.3 ± 3.4 (0.67–15.33)[a]
ApoE		
ε3/ε3	$n = 7$ (35%)	$n = 15$ (50%)
ε3/ε4	$n = 10$ (50%)	$n = 11$ (36.7%)
ε4/ε4	$n = 2$ (10%)	$n = 2$ (6.7%)
ε2/ε4	$n = 1$ (5%)	$n = 2$ (6.7%)

Key: ApoE, apolipoprotein E; ADAS-Cog 11, Alzheimer's Disease Assessment Scale-Cognitive Subscale 11-item; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation.
[a] $p \leq 0.05$, 2-sided Student t test.

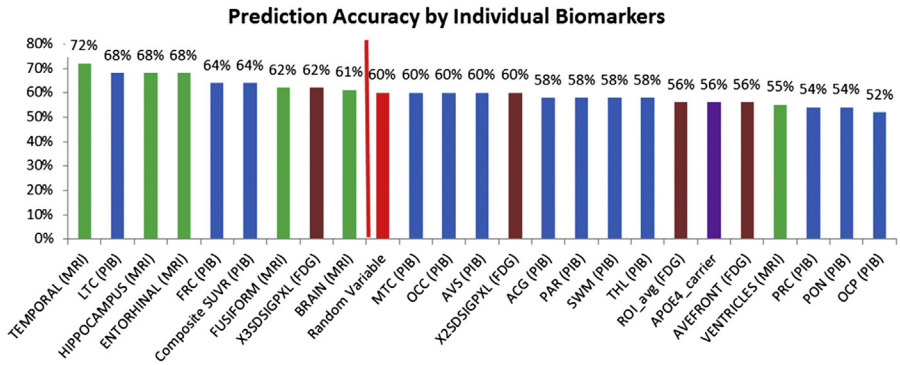


Fig. 1. Prediction accuracy for each individual biomarker (univariate analysis) including ROIs and composite measures. Only biomarkers with prediction accuracy >50% are shown in this graph. Color indicates different modalities (modality also noted in parentheses after variable names) where green = MRI, blue = PIB-PET, brown = FDG-PET, purple = ApoE, and red = random variable. Note the best prediction accuracy by the random variables was 60%. Abbreviations: ACG, anterior cingulate; ApoE, apolipoprotein E; APOE4, apolipoprotein E ε4 allele; AVEFRONT, Average CMRglc in frontal cortex; AVS, anterior ventral striatum; FDG, fluorodeoxyglucose; FRC, frontal cortex; LTC, lateral temporal cortex; MRI, magnetic resonance imaging; MTC, mesial temporal cortex; OCC, occipital cortex; OCP, occipital pole; PAR, parietal cortex; PET, positron emission tomography; PIB, Pittsburgh compound-B; PON, pons; PRC, precuneus cortex; ROI_avg, average from right/left angular, right/left temporal, and bilateral posterior cingulate; SUVR, standardized uptake value ratio; SWM, sub-cortical white matter; THL, thalamus; X2SDSIGPXL, number of pixels with hypometabolic activity 2 SD below normal mean; X3SDSIGPXL, number of pixels with hypometabolic activity 3 SD below normal mean.

carrier status did not outperform the random variable (accuracy = 56%).

Although not shown in Fig. 1, we also evaluated accuracy of demographic variables including age (56%) and education (60%), neither outperforming the random variables. Therefore, age and education were excluded from subsequent analyses.

3.3. Conversion prediction accuracy using all biomarkers

We then tested the prediction performance using all 28 neuroimaging and ApoE biomarker variables together (excluding the composite SUVR score). The elastic net method chose a combination of 7 variables that together best predicted conversion (Table 3). These were: 3 MRI, 3 PIB-PET, and 1 FDG-PET variable which predominantly represented areas of the temporal cortex and, to some extent, prefrontal and/or association cortices. Again, ApoE was not selected. Taken together, these 7 variables provided a conversion prediction accuracy of 69% (sensitivity = 45%, specificity = 86%) using the LOO cross-validation. The best prediction performance by random variables was approximately 56%, a value considerably lower than that provided by the biomarker combination.

Next, we ranked these 7 selected variables according to their predictive power (see weights in the second column of Table 3). Hippocampus volume based on MRI at baseline was ranked the highest among all the input variables, indicating a smaller hippocampus volume was the most predictive among these variables. Also, MRI atrophy of the temporal lobe and entorhinal cortex were each associated with a higher risk of conversion. Ranked after these MRI variables, a higher PIB-PET SUVR in the medial temporal lobe corresponded to higher risk of conversion. The average cerebral metabolic rate of glucose in frontal, parietal, and temporal cortices was the only FDG-PET variable that was selected, in which a higher metabolic rate corresponded to a lower risk of conversion. Finally, ApoE genotype was not selected, which is consistent with the less optimal performance in the individual test.

In summary, in this analysis we found that converters have more atrophy in the hippocampus, temporal lobe, and entorhinal cortex; more amyloid deposition in the mesial temporal cortex, lateral temporal cortex, and anterior ventral striatum; and lower metabolic rate in the (combined) frontal, parietal, and temporal cortices. Ranked according to modality, MRI measurements had the most predictive power, followed by PIB-PET and FDG-PET measurements. Ranking of selected variables was consistent with the results of the individual biomarker prediction test shown in the previous section.

3.4. Conversion prediction accuracy based on selected neuroimaging variables

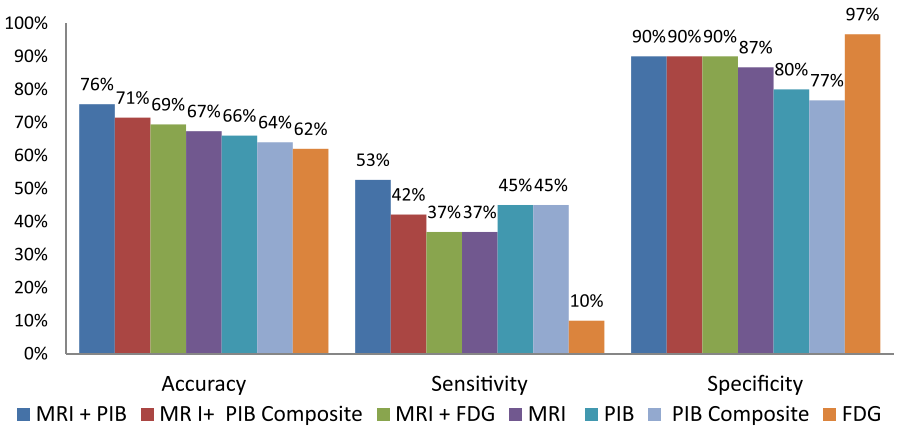
Finally, we performed 7 analyses that tested the prediction performance of individual neuroimaging modalities and combinations of MRI with PET by analyzing the 9 variables obtained from the univariate analyses (Fig. 1) in which accuracy had exceeded that for the random variables. Results from these 7 sets of analyses are shown in Fig. 2, which displays bars for accuracy, sensitivity, and specificity values. Variables selected for each analysis are also listed in descending predictive power in Fig. 2. We found that the prediction accuracy for individual neuroimaging modalities were as follows: 67% (MRI), 66% (PIB-PET), 64% (PIB-PET composite), and 62% (FDG-PET). However, their sensitivities were relatively low (range, 10%–45%), compared with their specificities (range, 77%–97%). The best sensitivity among individual modalities was obtained with PIB-PET (45%) followed by MRI (37%), with the lowest for FDG-PET (10%). When PET modalities were each combined with MRI, accuracy improved for these combinations, with PIB-PET (76%)

Table 3
Variables selected using the elastic net method for predicting MCI converters in 2 years using all biomarkers (classification accuracy 69.39%, sensitivity 45.00%, specificity 86.21%)

Variable according to ranking	Weight, mean[a]	Modality
Hippocampus	−0.35	MRI
Temporal	−0.28	MRI
Entorhinal	−0.21	MRI
MTC	0.18	PIB-PET
AVEASSOC	−0.15	FDG-PET
AVS	0.12	PIB-PET
LTC	0.08	PIB-PET

Key: AVEASSOC, average cerebral metabolic rate of glucose in frontal, parietal, and temporal cortices; AVS, anterior ventral striatum; FDG, fluorodeoxyglucose; LTC, lateral temporal cortex; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MTC, mesial temporal cortex; PET, positron emission tomography; PIB, Pittsburgh compound-B.

[a] Positive/negative weight indicates increased value in biomarker corresponds to a higher/lower risk for conversion, respectively.



Predictive variables selected by the model for each combination tested:
MRI+PIB: Temporal, Fusiform, Hippocampus, Entorhinal, LTC, Brain
MRI+PIB Composite: Temporal, Fusiform, Hippocampus , Entorhinal, Composite SUVR, Brain
MRI+FDG: Hippocampus,Temporal, Entorhinal
MRI: Hippocampus,Temporal, Entorhinal
PIB: LTC
PIB Composite: Composite SUVR
FDG: X3SDSIGPXL
Variables from different modalities are color-coded by: MRI, PIB-PET, FDG-PET

Fig. 2. Prediction accuracy, sensitivity, and specificity are graphed for 7 different analyses using either individual or combinations of neuroimaging modalities. Each color bar represents a separate analysis using relevant biomarker variables. For these analyses only the 9 biomarkers with prediction accuracy better than that of random variables in the univariate analyses (see Fig. 1) were used as input biomarkers. Subsets of these variables were selected using the elastic net method as the output biomarker variables and are noted below the graph (color-coded according to imaging modality) and in descending order according to their prediction power for each analysis. Abbreviations: FDG, fluorodeoxyglucose positron emission tomography; LTC, lateral temporal cortex; MRI, magnetic resonance imaging; PIB, Pittsburgh compound-B positron emission tomography; SUVR, standardized uptake value ratio; X3SDSIGPXL, number of pixels with hypometabolic activity 3 SD below normal mean.

being the best, followed by PIB-PET composite (71%), and FDG-PET (69%). The improvements in accuracy when adding PIB-PET and composite modalities to MRI were mainly driven by increased sensitivity (from 37% to 53% and 37% to 42%, respectively). Conversely, the increased accuracy when combining FDG-PET with MRI was related to an increased specificity (from 87% to 90%).

4. Discussion

To the best of our knowledge, we describe the first analyses using 3 neuroimaging modalities (PIB-PET, MRI, and FDG-PET) to predict conversion from a clinical diagnosis of MCI to Alzheimer's dementia within a 2-year follow-up. We studied patients from the ADNI cohort with late amnestic MCI and high education. We performed univariate and multivariate modeling methods to first select the most predictive variables and then analyzed those for accuracy, sensitivity, and specificity values alone and in various combinations. The best prediction performance involved MRI plus PIB-PET. Their combined advantage might be additive and complementary because these modalities provide different types of information about the brain. In clinical settings, MRI is performed to identify structural conditions that could be causative of cognitive impairment and might reveal patterns of atrophy that might be associated with AD, and amyloid PET detects pathology more specific to AD not measurable by other types of neuroimaging. This is in accordance with the latest model of dynamic biomarkers proposed by Jack et al. (2013), in which amyloid accumulation occurs much earlier in the disease and generally plateaus, whereas atrophy and metabolic changes increase with disease progression. It is unclear why MRI outperformed FDG-PET for prediction of conversion to dementia.

In univariate analyses, MRI scan of the temporal cortex had the highest (72%) accuracy followed by PIB-PET scan of lateral temporal cortex and MRI scan of entorhinal and hippocampus (each 68%). In the multivariate analysis, among individual neuroimaging modalities, MRI had the highest accuracy (67%). When combined with PIB-PET, its accuracy increased by an additional 9% to 76% resulting in the highest accuracy among any comparison. The brain regions selected by these analyses for MRI and PIB-PET were largely represented by the temporal cortex. The accuracy for MRI plus PIB-composite was second best (71%) in the multivariate analyses with identical MRI regions selected except that the PIB-PET composite was substituted for PIB-PET lateral temporal cortex. Thus, in later-stage amnestic MCI patients who have higher cognitive reserve, as found in this ADNI cohort (Whitwell et al., 2012), temporal cortex volume on MRI or a combination of MRI and PIB-PET indices offers good predictive information about conversion to dementia. Although MRI had higher accuracy than PIB-PET, this is probably because this ADNI sample is comprised of late MCI patients. It is believed that MRI is the last biomarker to become abnormal, and MRI has the closest relationship to cognitive performance later in the disease (Jack et al., 2010a). Because amyloid accumulates before volume changes on MRI in the progression of Alzheimer's pathological changes, one might find the opposite in an early MCI sample.

Of the 3 neuroimaging modalities, MRI and PIB-PET were more accurate in predicting conversion within 2 years than FDG-PET, individually and when combined. Several ROIs or composite measures from each of the MRI and PIB-PET modalities had higher predictive value than the random variable, as compared with only 1 for FDG-PET. When combined with MRI, none of the FDG-PET variables were selected as contributing beyond the MRI regions. Interestingly, a recent congress report revealed that florbetapir PET distinguished early MCI and FDG-PET distinguished late MCI from healthy control subjects (Wu et al., 2012). In 2012, the Food and Drug Administration approved florbetapir as a commercially available PET ligand to detect amyloid neuritic plaques for use in clinical settings. Florbetapir PET has a high correlation with PIB-PET

(Wolk et al., 2012). More studies directly comparing different neuroimaging modalities need to be conducted to further understand their relevance in disease progression.

Across univariate and multivariate analyses, temporal cortex areas predominated for MRI and PIB-PET, although the PIB-PET composite was also useful for predicting conversion. MRI temporal lobe volume had the highest accuracy followed by PIB-PET SUVR of the lateral temporal cortex and hippocampus and entorhinal cortex volumes based on MRI. These results are supported by recent findings from Ossenkoppele et al. (2012). These investigators found a significant increase in PIB binding in MCI patients over a 2- to 4-year follow-up period, which was most prominent in the lateral temporal lobe.

The conversion rate in our ADNI MCI cohort was 40% in 2 years, which is consistent with the overall conversion rate of 44% in the whole ADNI MCI population in the August 2011 download. However, the ADNI MCI conversion rate was higher than what has been reported in other studies (e.g., 12% per year; Petersen, 2004) and so might not reflect the general population.

In our study, we found that neither age, education, nor ApoE allele status was predictive of conversion. In other studies, the effect of ApoE $\varepsilon 4$ carrier status and conversion from MCI to dementia has been inconsistent (Fei and Jianhua, 2013; Winblad et al., 2004).

In this study, we found low biomarker sensitivity, alone and in combination, using the default probability threshold of 50% in the logistic regression model as described in section 2. Methods. When changing the threshold probability from 0% to 100%, we can appreciate the balance between sensitivity and specificity under different thresholds. However, because the focus of this work was to compare different imaging modalities, we did not focus on fine-tuning the classification model to achieve the best accuracy, sensitivity, or specificity. In this default setting, we found that specificity was greater than sensitivity for these neuroimaging biomarkers, with FDG-PET having the lowest value for sensitivity and highest for specificity. In clinical settings, specificity is important and all of these modalities had specificities $\geq$77%. However, sensitivity is desired to detect patients at higher risk for conversion. PIB-PET had the highest sensitivity (45%), MRI had 37%, and FDG-PET had only 10%. When PIB-PET and MRI were combined, sensitivity increased to 53% and, when considered together, had a specificity of 90%, which suggests that combining these 2 modalities provides promising clinical conversion prediction ability in late MCI.

Strengths of this study include comparing the predictive value of 3 different neuroimaging methods in the same cohort, including analyses of different ROIs. We also used the elastic net logistical regression method, which simultaneously selected variables and built the classification model, and then used cross-validation to test the prediction performance.

Results from this study must be considered in light of several limitations. Patients were from ADNI 1, which might limit generalizability to the broader MCI population. ADNI represents a highly selected convenience sample which differs from population-based studies, and largely includes those with higher education and cognitive reserve who were diagnosed with later amnestic MCI (Whitwell et al., 2012). Based on rates of decline in hippocampal volume, Whitwell et al. (2012) suggested that ADNI subjects have a more aggressive brain pathologic process than subjects in a population-based sample (the Mayo Clinic Study of Aging) and that findings on imaging biomarkers from the ADNI subjects might not perfectly translate to the general population. This study also had a relatively small sample size because PIB-PET was only conducted in a small portion of the subjects, being a later addition to ADNI 1. Because we wanted to preserve as many PIB-PET cases as possible for analyses using only PIB-PET biomarkers, we were willing to have 1 fewer MRI for our analysis. Considering the strength and importance of some of the MRI biomarkers in predicting conversion, we do not believe that this would have had a meaningful effect on our findings. Although recent studies have reported that neuropsychological measures can have equal or greater predictive value than biomarkers (Cui et al., 2011; Ewers et al., 2012; Gomar et al., 2011), we chose not to analyze neuropsychological and cognitive measures because those are relied on to determine a dementia diagnosis and could be considered circular. Because study clinicians use ADAS-Cog and MMSE scores to help determine a dementia diagnosis and these measures are therefore, by definition, predictive of conversion, they were not used in our biomarker modeling. Certain biomarkers might be useful adjuncts to cognitive status in predicting conversion to dementia. In our study, the converters have significantly worse cognition, measured using the MMSE and ADAS-Cog, suggesting the converters were later in the MCI stage than the nonconverters, even though they all met the threshold for MCI diagnosis using study criteria. Additionally, this cognitive severity variability is reflective of the timing of PET scans being performed as the basis for determining the baseline visit for our analysis.

The clinical relevance of this study is that MRI (structural evidence) plus PIB-PET (amyloid deposition) was shown to be the best combination of biomarker modalities for predicting conversion. Our study suggests that use of both MRI and amyloid PET neuroimaging modalities could provide additional clinical information over that of MRI alone, including about clinical course, at least in late amnestic MCI. Future research should validate these findings with a larger data set and with cases evaluated earlier in the disease process. It would also be important to explore the temporal relationship between disease stage and imaging modality because amyloid deposition is thought to precede atrophy.

Disclosure statement

Drs Trzepacz, Yu, Schuh, Witte, Hochstetler, and Hake, and Mr Case are full-time employees and minor shareholders of Eli Lilly and Company and/or one of its wholly owned subsidiaries. Mr Sun is an employee with Bucher and Christian Consulting, Inc. and under contract to work with Eli Lilly and Company.

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Appendix A

The Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, and lessen the time and cost of clinical trials. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California - San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from more than 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 adults, ages 55 to 90, to participate in the research—approximately 200 cognitively normal older individuals to be followed for 3 years, 400 people with amnestic MCI to be followed for 3 years, and 200 people with early AD to be followed for 2 years. For up-to-date information see www.adni-info.org.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2013.06.018.

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