Journal of Alzheimer's Disease 39 (2014) 49–61
DOI 10.3233/JAD-130359
IOS Press

Quantitative Evaluation of Disease Progression in a Longitudinal Mild Cognitive Impairment Cohort

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Handling Associate Editor: Javier Escudero

Accepted 20 August 2013

Abstract. Several neuropsychological tests and biomarkers of Alzheimer's disease (AD) have been validated and their evolution over time has been explored. In this study, multiple heterogeneous predictors of AD were combined using a supervised learning method called Disease State Index (DSI). The behavior of DSI values over time was examined to study disease progression quantitatively in a mild cognitive impairment (MCI) cohort. The DSI method was applied to longitudinal data from 140 MCI cases that progressed to AD and 149 MCI cases that did not progress to AD during the follow-up. The data included neuropsychological tests, brain volumes from magnetic resonance imaging, cerebrospinal fluid samples, and apolipoprotein E from the Alzheimer's Disease Neuroimaging Initiative database. Linear regression of the longitudinal DSI values (including the DSI value at the point of MCI to AD conversion) was performed for each subject having at least three DSI values available (147 non-converters, 126 converters). Converters had five times higher slopes and almost three times higher intercepts than non-converters. Two subgroups were found in the group of non-converters: one group with stable DSI values over time and another group with clearly increasing DSI values suggesting possible progression to AD in the future. The regression parameters differentiated between the converters and the non-converters with classification accuracy of 76.9% for the slopes and 74.6% for the intercepts. In conclusion, this study demonstrated that quantifying longitudinal patient data using the DSI method provides valid information for follow-up of disease progression and support for decision making.

Keywords: Alzheimer's disease, biomarkers, data mining, decision support techniques, early diagnosis, mild cognitive impairment

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that develops gradually over the years and finally results in loss of cognitive function and dementia [1]. Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia. Patients with MCI have cognitive problems that are not normal for their age and do not yet interfere with their daily activities [2–4]. MCI with memory dysfunction is a risk factor for AD, however, not all MCI patients will progress to AD [2, 3].

There is no cure for AD, but it has been modeled that delaying the onset of the disease would reduce its prevalence considerably, and slowing down its progression would allow more cases to remain as mild AD instead of progressing to moderate or severe AD which

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causes huge costs to society [5]. Different treatments to modify disease progression have been studied [6, 7] and it has been shown that they should be started as early as possible to be effective [7, 8]. To make earlier AD diagnosis and interventions feasible, different neuropsychological tests and biomarkers from laboratory tests and imaging have been studied extensively [9–12].

In 2010, Jack et al. [13] proposed a model describing temporal evolution of major AD biomarkers. The model was recently updated on the basis of gained knowledge, and according to it, different biomarkers of AD become abnormal in a certain temporal order and their longitudinal behavior is non-linear [14]. Biomarkers measuring deposition of amyloid-β plaques become abnormal first, years before the clinical symptoms appear. They are followed by indicators of neurodegeneration, and the last biomarkers to become abnormal are structural changes visible in magnetic resonance imaging (MRI) and changes in cerebral metabolism revealed by fluorodeoxyglucose positron emission tomography (FDG-PET). The updated model also takes into account that the severity of cognitive impairment due to pathophysiological load of AD is individual depending on, e.g., genetics, lifestyle, and other brain diseases.

New guidelines, incorporating both cognitive assessment and biomarkers for diagnosing different stages of AD, were recently published as a result of these research findings [15–18]. They state that the detection of preclinical stages of AD in research subjects should be based on biomarkers and that MCI and AD are diagnosed using clinical and cognitive evaluation and biomarkers can provide complementary information.

All the different tests and investigations done in modern diagnostics produce large amounts of data that clinicians need to explore carefully. Assessing the heterogeneous data and measuring longitudinal changes in them may be difficult. Several studies have successfully combined multimodal data to classify subjects into classes of healthy, MCI, or AD using established classification methods, e.g., logistic regression or support vector machines [19–24]. There also exists a statistical Disease State Index (DSI) method which estimates the state of a patient in the continuum from healthy to disease on the basis of measured data. The DSI method has been developed and extensively studied by most of the authors of this manuscript. Mattila et al. [22] demonstrated that it discriminated well between healthy cases, MCI cases that do not convert to AD, MCI cases that convert to AD, and AD cases. A recent study, also by Mattila et al. [25], showed that approximately half of the MCI patients who developed into AD could have been classified with a high accuracy already a year before receiving the clinical diagnoses using the DSI. However, it has not been studied yet how DSI values develop over time in subjects with MCI.

DSI values can be visualized with a Disease State Fingerprint (DSF) technique which shows how results from different tests contribute to the disease state of a patient. The DSF allows rapid interpretation of large amounts of patient data and helps clinicians to discern relevant information from irrelevant [22]. Until now, only data from a single time point have been visualized using the DSF.

The objective of this work was to study disease progression quantitatively using heterogeneous longitudinal data in an MCI cohort. First, it was studied whether it is possible to discern significant trends in the severity of AD as reflected by the DSI and whether subjects that convert from MCI to AD have a different longitudinal DSI behavior than subjects that do not convert. Second, classification of MCI subjects to converters and non-converters on the basis of the trend parameters from longitudinal DSI values was tested. Third, to facilitate interpretation of data, the DSF visualization was developed further for the presentation of longitudinal data.

MATERIALS AND METHODS

Study population

Data used in the analyses were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [26]. ADNI is a 5-year study aiming at developing and testing methods for acquiring and analyzing biological markers that measure the progression of MCI and AD [27]. ADNI was launched in 2004, and approximately 800 subjects of age 50 to 90 years have been recruited at around 50 sites in the United States and Canada. The enrolled subjects included 200 healthy elderly controls, 400 subjects with MCI, and 200 subjects with early AD. The subjects underwent cognitive assessment, neuropsychological testing, and MRI at intervals of six or twelve months for two to four years. Other tests, such as FDG-PET and blood and cerebrospinal fluid samples (CSF), were performed less frequently [28].

In the present study, MCI cases with at least 24 months of follow-up data were included. The selected MCI cases were divided into two groups: a stable

Table 1
Demographics of the study population at the baseline

	Stable MCI	Progressive MCI	*p*
Subjects	149 (51.6%)	140 (48.4%)	
Gender			0.373
Female	51 (34.2%)	55 (39.3%)	
Male	98 (65.8%)	85 (60.7%)	
Age (years)	75.1 ± 7.4	75.4 ± 6.7	0.916
Education (years)	15.9 ± 3.0	15.6 ± 3.0	0.239

Data presented as number of subjects (percentage of subjects %) or mean ± standard deviation. p: Group differences were examined using appropriate tests based on whether their distribution was normal or not as determined by the Kolmogorov-Smirnov test: Pearson χ^2 test (gender) and Mann-Whitney U test (age and education).

MCI group (SMCI, $n = 149$), who did not obtain the diagnosis of AD during the follow-up period, and a progressive MCI group (PMCI, $n = 140$), whose diagnosis changed from MCI to AD during the follow-up. Subjects whose diagnosis changed from MCI to healthy or from MCI to AD and then back to MCI were excluded from the study. Demographics of these two groups are presented in Table 1.

The data were downloaded from the ADNI website (http://adni.loni.ucla.edu) in September 2011. The data used in the analyses comprised Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS), Neuropsychological Battery (NeuroBat), brain volume measures based on MRI, amyloid-β and total tau in CSF, and apolipoprotein E (APOE). Details of the included variables are presented in the Supplementary Material. MRI brain volume measures provided to ADNI by Anders Dale Lab (University of California, San Diego) were used. They performed volumetric segmentation of MRI with the FreeSurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Technical details of the segmentation are described in [29].

Diagnosis of MCI and AD in the ADNI is based on evaluation of memory, cognition, and functional performance (memory complaints by a subject or a study partner, Logical Memory II, MMSE, and Clinical Dementia Rating) [28]. In addition, diagnosis of probable AD requires fulfillment of the AD criteria defined by the NINCDS-ADRDA (the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) [30, 31]. Although the diagnosis is partly based on MMSE and Logical Memory II, they were included in the data analyses in this study because 1) MMSE is widely used making it interesting in clinical sense, 2) the diagnosis is not based only on the MMSE and Logical Memory II, and 3) the ADNI criteria to decide between MCI versus AD does allow overlap in MMSE score and Logical Memory II score.

Variables summarizing the tests, e.g., total MMSE score and ADAS 13 point total, were excluded as independent variables from the analysis because the subscores and the individual items contain the same information as the total scores. Justification for the use of individual items instead of total scores is that some items may differentiate between SMCI and PMCI cases better than others and part of the available information is lost if only the total scores are used. For example, Llano et al. [32] weighted individual items of ADAS with coefficients derived using data-driven approach and constructed a new composite ADAS score. Their composite score differentiated normal controls, MCI, and AD cases better than the ADAS total score and the composite score also predicted conversion to AD slightly better than the ADAS total score.

Disease State Index

The DSI is a statistical method for deriving a scalar value that estimates the state of a disease in a patient [22]. The DSI method is based on the computation of two different values: DSI values and relevance values. The DSI value of an individual variable is computed by comparing a measurement value from a patient to the distributions of known healthy and diseased cases using a so-called fitness function. DSI values are between zero and one, with higher values indicating that the patient fits better to the disease than to the control population on the basis of the measured data. The relevance value describes how well the variable differentiates between the known healthy and diseased cases. In other words, relevance is a measure of the differences in the data measured from healthy and diseased cases. Relevance values, like the DSI values, are also between zero and one, with higher values representing better discrimination. A composite DSI combining different variables is computed as a weighted arithmetic mean of the individual DSI values weighted by the relevance values. This averaging is done several times recursively to yield a hierarchy of DSI values that reveals the overall position or rank in relation to the disease, i.e., quantifies the progression of a disease based on available patient data. In this work, the study population consisted of SMCIs as control cases and PMCIs as disease cases.

The DSI method is robust against overfitting by its design. Estimation of the DSI and relevance values

Table 2
Number of available patient visits at different time points

	Baseline	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48
Total	289	287	287	279	281	0	233	0	51
SMCI	149	148	147	143	142	0	121	0	19
PMCI	140	139	140	136	139	0	112	0	32

SMCI, stable mild cognitive impairment; PMCI, progressive mild cognitive impairment.

for individual variables is done independently from other variables, thus, there is no over-dimensionality at the variable level because only two parameters are estimated for each variable (the DSI value and the relevance value). In addition, weighting of features and the use of the hierarchy lead in practice to feature selection. As a result, any few values alone will not determine the resulting composite DSI value, but it is an amalgam of all relevant data sources. Mathematical details of the computation of the DSI and relevance values are explained in [22].

The DSI values can be calculated on the basis of a single variable or multiple variables together. In this study, it was investigated whether combining different data modalities would yield better results than utilizing data from a single modality alone. Thus, DSI values were calculated using two different approaches: 1) using all available variables together (MMSE, ADAS, NeuroBat, MRI, CSF, and APOE) and 2) using data from individual data modalities independently (MMSE, ADAS, NeuroBat, and MRI). CSF was measured less frequently so it was not analyzed individually and neither was APOE genetics, which do not change with disease progression. For the calculation of the DSI values, subjects were divided into ten training and test sets for stratified 10-fold cross-validation in which each fold contains the same proportions of class labels. The training data used for building the model of AD progression included actual measurement values from SMCI baseline visits and actual measurement values from the time of receiving AD diagnosis for PMCI cases. This kind of selection of training data sets the dynamic range of the DSI method between SMCIs at the baseline and early AD, i.e., the dynamic range of the DSI method was optimized for the purposes of the study and clinical problem at the hand. The test sets included data from the complete series of visits of the remaining SMCI and PMCI cases. The number of patient visits available at the different time points is shown in Table 2. Missing values in the raw data (e.g., a missing result in MMSE) were replaced with the values from the patient's previous available visit. This allowed having complete data sets for the analysis at each patient visit. Although using previous data can result in slightly outdated data and conservative disease progression estimates for some patient visits, that data were known to have been available at those time points.

Disease State Fingerprint

The DSF is a method for visualizing the patient data and the hierarchy of the DSI values [22]. Example visualizations are shown in the left panel of Fig. 1. DSF consists of a tree with nodes of different sizes and colors. The size of the node indicates the relevance value, i.e., how well a variable or a test differentiates between SMCI and PMCI, and color indicates the DSI value. Higher DSI values refer to PMCI and result in shades of red. Lower values represent SMCI and result in shades of blue. In this study, the progression of AD was visualized using the DSF technique extended with support for longitudinal data.

Synchronization of the time stamps

The initial visits of MCI patients to a memory clinic occurred in different phases of the disease. For example, some PMCI cases converted from MCI to AD at follow-up month 6 and others at month 36. To take this into account, the time stamps of the patient visits were synchronized. The moment of receiving AD diagnosis was set as the zero time point (Z) of PMCIs. For SMCIs, the last available time point up to month 36 was set as their Z. The time points preceding the zero point were labeled as Z-6, Z-12, etc. DSI values from Z-42 and Z-48 months were excluded from the analysis because they contained only a few cases. Thus, DSI values computed from visit data at Z, Z-6, Z-12, Z-18, Z-24, Z-30, and Z-36 months were used in the analysis. Only those subjects who had at least three DSI values available in all approaches (DSI calculated using all variables, MMSE, ADAS, NeuroBat, or MRI), were included for further analysis. The purpose was to perform linear regression (see below) and using only two points would have yielded in perfect regression, making the comparison of goodness of fit values between the different datasets unfair. The number of available

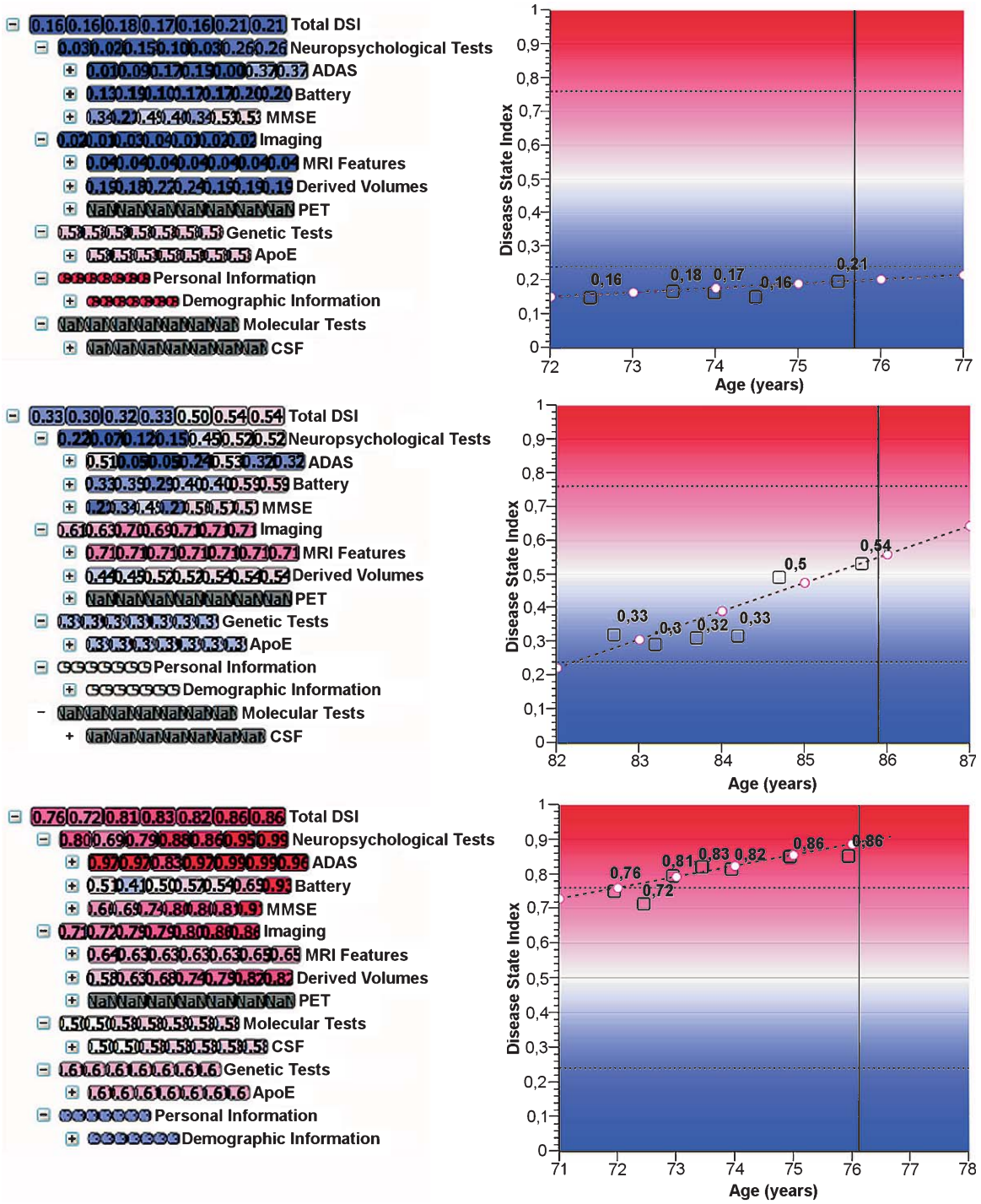

Fig. 1. Visualizations of three sets of longitudinal patient data. Left panel: Disease State Fingerprints (DSF) in which Disease State Index (DSI) values of the individual tests at different time points are shown on the rows. Total DSI values (the topmost rows of the DSFs) combines the results from the individual tests. Sizes of the boxes indicate how well the variable discriminates between the stable (SMCI) and progressive (PMCI) mild cognitive impairment cases. Color indicates to which group the data fits the best. Blue corresponds to SMCI and red to PMCI. Right panel: linear regression of the total DSI values (red dashed line with white circles). Black squares present the total DSI values of a patient. The horizontal lines indicate a threshold where the classification accuracy of 85% is achieved. The vertical line shows the current age of a patient. Data from two SMCI cases are presented in the topmost panels and data from a PMCI case is presented in the lowest panel.

Table 3
Number of Disease State Index values of the SMCI and PMCI cases at synchronized time points. The last available time point up to month 36 was selected as the zero time point (Z) of SMCI. The moment of receiving Alzheimer's disease diagnosis was set as the Z of PMCI. The time points preceding the Z were labeled as Z-6 etc

	Z-36	Z-30	Z-24	Z-18	Z-12	Z-6	Z
SMCI	147	147	147	147	147	147	147
PMCI	29	29	64	90	126	126	126

SMCI, stable mild cognitive impairment; PMCI, progressive mild cognitive impairment. The number of SMCI cases stays the same because the visit Z-36 is their baseline visit and any missing values have been replaced with the values from the previous available visit. The number of PMCI cases changes over time because some have converted in an early phase of the study. Only the cases having at least three available DSI values were included.

DSI values of the included SMCI and PMCI cases at the synchronized time points is presented in Table 3.

Modeling progression of AD

In this work, it was assumed that the change of the DSI values over time, and thus the progression of AD, can be modeled linearly:

$$DSI = a * t + b \quad (1)$$

where a is the slope of regression (rate of change for DSI values), b is the intercept of regression (DSI value at the time point zero), and t is time measured in months. A linear model was selected because it is the simplest method to model the progression of AD and it is also the simplest to interpret. Another reason was that due to the synchronization of the time stamps some subjects had only few DSI values available for the regression. Thus, there were not enough data points for more complicated models. The third reason supporting the linear model was that the follow-up times were relatively short compared with the time span of disease progression in AD in overall. Linear regression was performed for each subject separately to model each individual's disease progression.

Differentiation using the trend parameters

Classification of subjects as SMCI or PMCI cases on the basis of their regression parameters (slope, intercept) was studied as follows. First, optimal classification thresholds for the regression parameters were defined on the basis of the receiver operating characteristic (ROC) curves. Then, the regression parameters were compared to the threshold value and if it was exceeded the subject was classified as PMCI. Otherwise he or she was classified as SMCI. The thresholds and classification performance measures (classification accuracy, sensitivity, and specificity) were calculated using the stratified 10-fold cross-validation.

Statistical methods

Normality of the continuous demographic variables was studied using Kolmogorov-Smirnov test. Group differences in demographics between SMCI and PMCI groups were examined using non-parametric Mann-Whitney U test for continuous variables and Pearson χ^2 test for categorical variables.

Linear regression was performed using the longitudinal DSI values which were derived using 1) all available variables together (total) and 2) data from individual tests separately. Goodness of fit of the linear regression using 1) and 2) was compared using R^2, adjusted R^2, and mean square errors. Residuals of the regression were also examined using histograms and by plotting residuals versus predicted values. The regression parameters of the SMCI and PMCI groups were compared to zero using one-sample Wilcoxon Signed Rank test and the differences between the groups were studied using Mann-Whitney U test.

Normality of the regression parameters was studied using histograms. On the basis of the initial histogram analysis, it appeared that the slopes of the SMCI group may have a bimodal distribution. Fits of unimodal and bimodal distributions were compared and details of these analyses are explained in the Supplementary Material.

Subjects were classified as SMCIs or PMCIs on the basis of their regression parameters. Classification performance was measured using the area under the ROC curve (AUC), classification accuracies, sensitivities, and specificities. To study whether using all data modalities together would yield in significantly greater classification performance than using only a single data modality, classification accuracies of the individual tests were compared to the classification accuracies derived using all data. Thus, four comparisons with both the slopes and the intercepts (total-MMSE, total-ADAS, total-NeuroBat, total-MRI) were performed. The classification accuracies of the slopes and the intercepts derived using all data were also compared. Paired samples t-test was used if the classification accuracies were normally distributed according to Kolmogorov-Smirnov test, otherwise, related-samples Wilcoxon Signed Rank test was performed. In all analyses, $p < 0.05$ was considered significant. In pairwise comparisons of classification accuracies, Bonferroni

Table 4
Goodness of fit for the linear regression of longitudinal Disease State Index values derived using different data modalities

Dataset	R^2	Adjusted R^2	Mean square error
Total	0.553 ± 0.289	0.422 ± 0.369	0.006 ± 0.008
MMSE	0.364 ± 0.295	0.172 ± 0.390	0.014 ± 0.016
ADAS	0.388 ± 0.298	0.196 ± 0.413	0.024 ± 0.026
NeuroBat	0.475 ± 0.318	0.315 ± 0.426	0.005 ± 0.004
MRI	0.721 ± 0.259	0.642 ± 0.321	0.001 ± 0.001

Total, All available variables included when calculating DSI values; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale-cognitive subscale; NeuroBat, Neuropsychological Battery; MRI, brain volumes derived from magnetic resonance imaging. The values are mean ± standard deviation because the linear regression was performed for each subject independently.

correction was applied and $p < 0.0056$ was considered significant (number of comparisons was nine).

All analyses were performed in Matlab R2012a (The Mathworks, Natick, MA) and IBM SPSS Statistics 19 (IBM, Armonk, NY). Visualizations were processed in GNU Image Manipulation Program 2.0 (GIMP 2.0, freely available at http://www.gimp.org/).

RESULTS

Modeling progression of AD

Goodness of fit for linear regression of the longitudinal DSI values is shown in Table 4. On the basis of R^2, adjusted R^2, and mean square error, the linear association was the strongest when DSI values were calculated using only MRI-derived volumes. The linear model fitted the second best when all available variables were used together. The longitudinal DSI values derived on the basis of cognitive and neuropsychological tests had the smallest association values. Plots of residuals versus predicted values supported the interpretation that the DSI values calculated on the basis of ADAS and MMSE were the least linear over time: points in the plots were not as randomly distributed as they were when the DSI values were based on all available data, MRI, or NeuroBat (results not shown here).

The linear regression of the DSI values over time was performed for each subject independently. Medians of the regression parameters for SMCI and PMCI groups are shown in Table 5. The slopes and the intercepts of both groups were higher than zero ($p < 0.0005$). There were also clear differences between the two groups: PMCIs had five times higher slopes and almost three times higher intercepts than SMCIs ($p < 0.0005$).

The distributions of the slopes of both groups are presented in Fig. 2. On the basis of the visual inspection, the SMCI curve deviated from a Gaussian distribution containing also cases with higher slopes. Therefore, a hypothesis was put forth that the SMCI group actually contained two subgroups: one with truly stable DSI values and one with non-stable DSI values having signs of disease progression. A mixture distribution of two normal curves was fitted to the slopes of the SMCIs. The fits of unimodal and bimodal distributions were compared, and the results and estimated parameters are shown in the Supplementary Material. The results showed that the bimodal distribution fitted better to the slopes of the SMCIs than the unimodal distribution supporting the idea that two subgroups do exist within the SMCI group.

Table 5
Regression parameters of longitudinal Disease State Index values for SMCI and PMCI groups

	SMCI	PMCI
Slope*	0.002 (0.000, 0.006)$^+$	0.010 (0.005, 0.015)$^+$
Intercept*	0.295 (0.139, 0.621)$^+$	0.754 (0.626, 0.860)$^+$
n	7 (7; 7)	5 (3; 5)

Values are median (25th percentile, 75th percentile). SMCI, stable mild cognitive impairment; PMCI, progressive mild cognitive impairment, n, number of points in the regression, *statistically significant difference between the groups (Mann-Whitney U test, $p < 0.0005$), $^+$significantly different from zero (one-sample Wilcoxon Signed Rank test, $p < 0.0005$). Disease State Index values were derived using all variables together.

Visualizing progression of AD

In Fig. 1, the progression of AD is visualized using the DSF and the regression line of the DSI values. Most of the nodes in the DSF of a clear SMCI case are blue indicating that the patient data remained constantly unlike the data of those with AD. Also, the slope and the intercept of the regression line have low values (Fig. 1, topmost panel). On the contrary, almost all nodes of a clear PMCI case are red, indicating strong resemblance to previously diagnosed AD cases, and the slope and the intercept are higher as well (Fig. 1, lowest panel). A SMCI case with clearly increasing DSI values and the DSF changing from blue to red is also shown (Fig. 3, mid-panel). This case belongs to the subgroup of SMCI cases with non-stable DSI values in Fig. 2.

Differentiation using the trend parameters

MCI cases were classified as SMCI or PMCI using the regression parameters of the longitudinal DSI values, and the classification performance results are

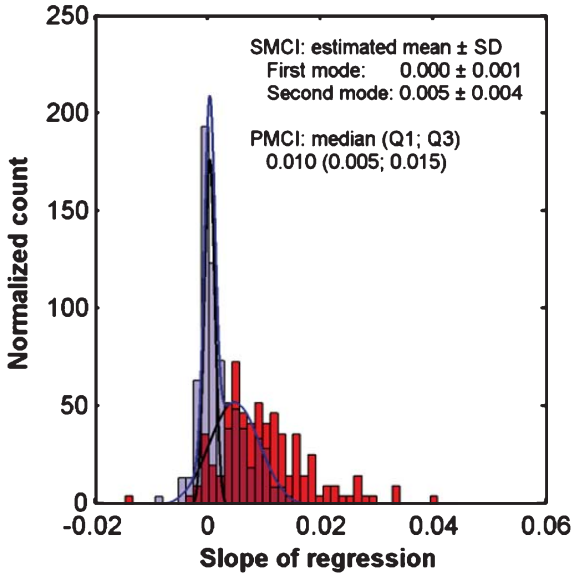

Fig. 2. Histograms of the slopes for stable (SMCI, blue) and progressive (PMCI, red) mild cognitive impairment cases. There appears to be two separate subgroups in the SMCI group. A mixture distribution of two normal curves fitted to the slopes of SMCIs is also shown. The areas of the histograms are scaled to one. (SD = standard deviation, Q1 = 25th quartile, Q3 = 75th quartile).

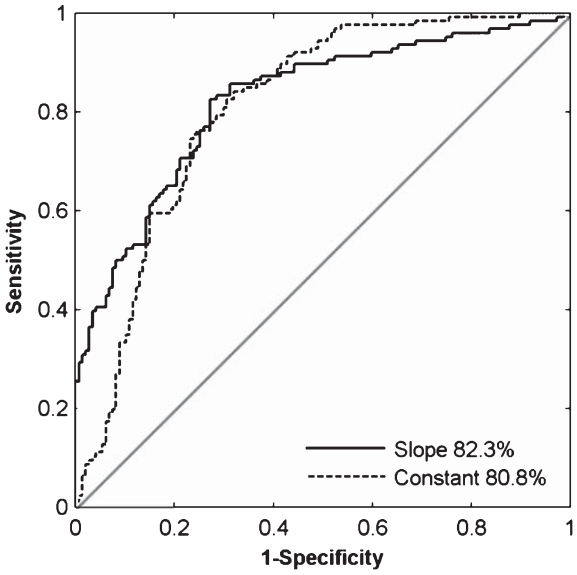

Fig. 3. Receiver operating characteristic curves of the slope (solid line) and the intercept (dashed line). Regression parameters were defined using total Disease State Index values over time.

presented in Table 6. AUCs were the highest when all available variables were used in the analysis (total). Classification accuracies were normally distributed, except for the slopes derived using NeuroBat. The

Table 6
Classification performance of the regression parameters of the longitudinal Disease State Index values derived using different datasets

	AUC (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Slope				
Total	82.3	76.9 ± 8.8	82.2 ± 13.7	73.0 ± 15.0
MMSE	77.1	71.8 ± 7.6	55.5 ± 15.5	86.5 ± 5.5
ADAS	76.8	68.7 ± 10.2	51.1 ± 19.2	83.6 ± 10.2
NeuroBat	76.6	69.2 ± 5.8	60.2 ± 13.2	76.9 ± 15.3
MRI	71.0	66.8 ± 8.1	49.5 ± 14.4	80.6 ± 14.7
Intercept				
Total	80.8	74.6 ± 8.7	75.1 ± 17.4	74.4 ± 12.2
MMSE	79.0	72.0 ± 5.0	84.2 ± 11.6	61.5 ± 11.6
ADAS	80.3	74.9 ± 8.8	74.4 ± 15.6	75.7 ± 10.5
NeuroBat	79.3	66.9 ± 6.1	74.4 ± 21.7	61.0 ± 14.0
MRI	69.6	60.4 ± 8.9	55.6 ± 16.2	63.9 ± 16.2

Results are mean ± standard deviation from the stratified 10-fold cross-validation, except for the AUC. Total, all available variables included when calculating Disease State Index values; MMSE, Mini-Mental State Examination; ADAS, Alzheimer's Disease Assessment Scale-cognitive subscale; NeuroBat, Neuropsychological Battery; MRI, brain volumes derived from magnetic resonance imaging; AUC, area under the receiver operating characteristic curve.

classification accuracy of the slopes (total) was significantly higher than the classification accuracies of the slopes derived using ADAS or MRI ($p = 0.001$ for total-ADAS and $p = 0.005$ for total-MRI comparisons). The classification accuracy of the intercepts (total) was significantly higher than classification accuracy of the MRI-derived intercepts ($p = 0.004$). Other pairwise comparisons of the slopes and the intercepts were not statistically significant (all $p > 0.01$, Bonferroni-corrected significance level was 0.0056). The classification accuracies of the slopes (total) and the intercepts (total) were very similar (76.9% and 74.6%, respectively, $p = 0.309$). ROC curves of the slopes (total) and the intercepts (total) are presented in Fig. 3.

DISCUSSION

Quantification of disease progression from MCI to AD was studied by applying the DSI method to heterogeneous longitudinal patient data and analyzing the behavior of the DSI values over time in subjects with MCI. Trend parameters of the longitudinal DSI values were obtained from regression and ability of them to differentiate between the groups of stable and progressive MCI was also studied.

In this study, it was assumed that the behavior of the longitudinal DSI values can be modeled linearly. The linear association was the strongest when the DSI values were based only on MRI features. Behavior of the total DSI values was not as linear because

neuropsychological tests were included and their temporal behavior was the least linear. The linear model may not necessarily be the best model for progression of AD but it was selected because of simplicity and due to paucity of data. Some subjects with PMCI had only a few DSI values available for the regression due to synchronization of the time stamps.

Jack and his colleagues [13] proposed that changes in biomarkers over time would be sigmoidal and biomarkers would become abnormal in a certain temporal order. These assumptions gained support in several studies and they still are core components of the recently revised model [14]. Caroli et al. [33] provided the first evidence supporting the first version of the model. They compared the fit of linear and sigmoidal model and concluded that the sigmoidal model fitted better for hippocampal volume, and amyloid-β and total-tau in CSF. The linear model fitted better for FDG-PET data. Instead of real longitudinal data, Caroli et al. [33] used data from healthy controls, PMCIs, and early and late ADs at the baseline to reflect the progression of AD. Mouiha and Duchesne [34] used the same kind of cross-sectional setting to study the relationship between biomarkers and disease severity. They fitted six different models (linear, quadratic, robust quadratic, local quadratic regression, penalized B-spline, and sigmoid) to baseline data from healthy controls, PMCI, and AD cases [34]. According to them, amyloid-β had a piece-wise quadratic relationship, hippocampal volume and CSF measures of phosphorylated tau and total tau were best modeled with penalized B-splines, and linear model was the best fit for FDG-PET [34].

The results in this study show that the change of DSI values over time as reflected by the slope of the linear regression equation is clearly different in the SMCI and PMCI groups. The slope of PMCI cases was five times higher than the slope of SMCI cases. When the slopes of SMCI cases were studied more thoroughly, it was noticed that there were two different subgroups in the SMCI group: a group with lower slopes and another group with higher slopes that overlap with the slopes of the PMCI cases. It is expected that the peak with higher slopes represents MCIs that would convert to AD or other dementia later if the follow-up was continued. Davatzikos et al. [20] and Cui et al. [19] also found in their studies that subjects in the SMCI group did not have uniform results. Some SMCI cases had markers similar to AD, suggesting that they may convert to AD in the future [19, 20].

Samtani et al. [35] modeled a subject's rate of disease progression using a logistic model with several covariates. Severity of the disease was measured using ADAS and the analysis was restricted to an AD population [35]. Another approach for modeling disease progression was presented by Escudero et al. [36]. They found profiles of disease and normality using an unsupervised learning method (k-means clustering). Escudero et al. [36] calculated a so-called Bioindex that describes a subject's degree of membership to the profile of disease on the basis of measured data. To study evolution of Bioindeces over time, a sigmoid function was fitted to the Bioindex values at different time points. They used the same approach as here and fitted an individual function to the Bioindeces of each subject and studied evolution of Bioindeces in the groups of SMCI and PMCI. As in this study, they found that converters had steeper progression towards AD than non-converters. However, Escudero et al. [36] did not take into account that MCI patients arrived in the study at different phases of the disease, and they did not synchronize the time stamps as we did.

Patient visits in this study were synchronized according to the time of receiving AD diagnosis. Using this method, the accuracy of the synchronization depends on the accuracy of the actual AD diagnoses. Also, data points of the SMCI cases are not synchronized because they do not have an AD diagnosis. Jedynak et al. [37] and Yang et al. [38] proposed more sophisticated methods for synchronization. Jedynak et al. [37] used multiple biomarkers to create a disease progression score, which set the subjects on the same timeline [37]. Biomarkers were assumed to follow a sigmoidal function when constructing the disease progression score [37]. Yang et al. [38] modeled evolution of ADAS 13 score over time with an exponential model and then defined the start of the cognitive decline using the model. Other biomarkers were then synchronized using the estimated period of cognitive decline. After the synchronization, evolution of biomarkers over time and relations between them were clearer and they supported the model presented by Jack et al. [13, 14, 38]. In the approach presented in [38], one needs to define an accurate model for the progression of ADAS 13 score over time, and the accuracy of the synchronization depends on the suitability of the model.

The dynamic range for the DSI depends on training sets used. In this study, the DSI values were calculated on the basis of data from SMCI cases at baseline and PMCI cases at the point of conversion to AD. Thus, the dynamic range lies between MCI and early AD. Using the same model of disease progression to study healthy controls and late AD groups would saturate DSI values close to zero and one, respectively. On the

other hand, if the training set consisted of PMCI and AD groups, the DSI would characterize changes at the later phase of the disease. Thus, if different training sets are used, the longitudinal behavior of the DSI values can be somewhat different. As another example, if training set included healthy and AD cases, slopes of the SMCI and PMCI groups should be closer to each other than they are in this study.

Training data for this study was selected from SMCI cases at the baseline and PMCI cases at the point of conversion because the initial purpose for the proposed method is in early diagnosis of AD. The main use case for the method is a situation where a subject with memory complaints arrives at a clinic. After some tests have been administered, computer-based decision support tools could help in objective assessment of patient data and possibly provide help for earlier diagnosis of AD. If the diagnosis cannot be made at the baseline, longitudinal quantification of progressing disease state provides additional information to base the diagnosis on. By selecting SMCI cases at the baseline and PMCI cases at the moment of receiving diagnosis as the training set, the system is optimized to detect early AD cases from an MCI population referred to a memory clinic. The DSI method is currently incorporated in a decision support tool that will be used in pilot studies and the training set used in the tool comprises SMCI and PMCI cases, similar to this study. When studies with other purposes (e.g., focus on conversion from normal cognition to MCI) are done in the future, then the practical issues of selecting the most appropriate training population will be addressed.

Recently, several studies have predicted the conversion from MCI to AD by combining multiple data modalities and identifying converters and non-converters on the basis of the data [19–23]. In these studies, multimodal data were combined using logistic regression [21, 22], the DSI method [22], support vector machine classifiers [19, 22, 23, 39], and a Naive Bayes classifier [22]. In [19, 20, 22, 40], it was found that combination of multimodal data resulted in better classification performance than the use of a single modality of data, e.g., using only neuropsychological tests. However, those studies did not report whether the differences were statistically significant. Ewers et al. [21] found that increasing number of variables in the model from one to four increased the classification accuracy, but the increase was not significant according to the 95% confidence intervals. Cui et al. [39] also combined different data modalities for predicting conversion from normal cognition to MCI. They reported that combination of neuropsychological test scores and MRI features resulted in significantly higher classification accuracy for the predictions than using either of the data modalities alone. Results from our study are in line with the previous research findings. Combination of all available data resulted in higher classification accuracies and AUCs than using only a single modality of data and increases in classification accuracies were not always statistically significant. To account for multiple comparisons, we used Bonferroni correction which is known to be a rather conservative method. However, in many comparisons, p-values were higher than 0.05.

It is worth noting that the calculation of the linear regression included DSI values from the point of conversion for PMCI cases. Thus, the classification performance measures presented here do not describe the ability of the trend parameters to predict conversion from MCI to AD. However, they demonstrate that the trend parameters of the DSI values are clearly different between the groups of SMCI and PMCI. Prediction of MCI to AD conversion with the DSI method using data from the ADNI database has already been studied in [22] and [25].

One interesting finding was that the MRI-derived longitudinal DSI values had the strongest linear association but the regression parameters of the MRI-based DSI values performed the worst in the classification. One explanation could be that changes related to normal aging in the brain may interfere with the results. For example, Koikkalainen et al. [41] removed effects of age and other confounding factors by dividing patients into subgroups and using linear regression. These procedures improved classification accuracies in their study. Another explanation could be that MRI may be a better indicator of the rate of disease progression than of the disease stage. Stronger linearity of the MRI-derived DSI over time might also be caused by the fact that MRI measures are not as prone to daily variations as neuropsychological tests may be.

Missing values were imputed with the values from the previous available visit. This approach resulted in slightly outdated data for some patient visits and biased the results towards non-progression. This approach was chosen so that all data used in the analyses really were available from a patient at the specific moments. This would not be the case, e.g., if missing values were replaced with the next available values or using other more complex imputation methods. Replacing missing values with next available values would have biased results toward progression to some extent and there would still have been missing values because some patients did not have any values available beyond the

last time point. If the missing values had not been imputed at all, the DSI values at different time points would have been calculated using different variables for each visit and this would have hindered the interpretation of the longitudinal results.

The study had some limitations. The final diagnoses for the subjects were determined on the basis of clinical evaluation and they were not verified with postmortem histological samples taken from the brain. Also, the study period of 48 months is relatively short. Thus, some subjects diagnosed currently as stable MCI may convert to AD later. This study utilized longitudinal data from a period of 2–4 years. In clinics, where the patients are diagnosed, there may not be data from such a long period available. Less longitudinal data will probably produce more variation in the slopes and the intercepts of the regression equation. On the other hand, this study suggests that quantifying longitudinal patient data using the DSI method provides valid information for decision support and is a valid methodology to follow-up a patient's condition in a quantitative manner.

In conclusion, this study demonstrates that combining sparse and heterogeneous data with the DSI method can be used for deriving a quantitative measure related to early AD progression. Significant trends were found in longitudinal DSI values: rate of change of DSI values was five times higher in the PMCI group than in the SMCI group. Classification of the subjects as converters and non-converters on the basis of the regression parameters (the slope and the intercept) also showed that SMCI and PMCI cases can be differentiated on the basis of the trend parameters.

ACKNOWLEDGMENTS

This work was partially funded under the 7th Framework Programme by the European Commission (http://cordis.europa.eu/ist; EU-Grant-224328-PredictAD; Name: From Patient Data to Personalized Healthcare in Alzheimer's Disease) and the SalWe Research Program for Mind and Body (Tekes – The Finnish Funding Agency for Technology and Innovation, grant 1104/10).

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1923).

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer's Association; Alzheimer's Drug Discovery Foundation; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; GE Healthcare; Innogenetics, N.V.; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (http://www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of California, Los Angeles. This research was also supported by NIH grants P30 AG010129 and K01 AG030514.

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://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

SUPPLEMENTARY MATERIAL

The supplementary material and tables are available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-130359.

REFERENCES

[1] Nestor PJ, Scheltens P, Hodges JR (2004) Advances in the early detection of Alzheimer's disease. *Nat Med* **10** Suppl, S34-S41.

[2] Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P, Winblad B, International Psychogeriatric Association Expert Conference

on mild cognitive impairment (2006) Mild cognitive impairment. *Lancet* **367**, 1262-1270.

[3] Petersen RC (2009) Early diagnosis of Alzheimer's disease: is MCI too late? *Curr Alzheimer Res* **6**, 324-330.

[4] Brooks LG, Loewenstein DA (2010) Assessing the progression of mild cognitive impairment to Alzheimer's disease: current trends and future directions. *Alzheimers Res Ther* **2**, 28.

[5] Sloane PD, Zimmerman S, Suchindran C, Reed P, Wang L, Boustani M, Sudha S (2002) The public health impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances. *Annu Rev Public Health* **23**, 213-231.

[6] Salloway S, Mintzer J, Weiner MF, Cummings JL (2008) Disease-modifying therapies in Alzheimer's disease. *Alzheimers Dement* **4**, 65-79.

[7] Galimberti D, Scarpini E (2011) Disease-modifying treatments for Alzheimer's disease. *Ther Adv Neurol Disord* **4**, 203-216.

[8] Duara R, Barker W, Loewenstein D, Bain L (2009) The basis for disease-modifying treatments for Alzheimer's disease: the Sixth Annual Mild Cognitive Impairment Symposium. *Alzheimers Dement* **5**, 66-74.

[9] Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E (2011) Alzheimer's disease. *Lancet* **377**, 1019-1031.

[10] Hampel H, Bürger K, Teipel SJ, Bokde AL, Zetterberg H, Blennow K (2008) Core candidate neurochemical and imaging biomarkers of Alzheimer's disease. *Alzheimers Dement* **4**, 38-48.

[11] Borroni B, Premi E, Di Luca M, Padovani A (2007) Combined biomarkers for early Alzheimer disease diagnosis. *Curr Med Chem* **14**, 1171-1178.

[12] Craig-Schapiro R, Fagan AM, Holtzman DM (2009) Biomarkers of Alzheimer's disease. *Neurobiol Dis* **35**, 128-140.

[13] Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* **9**, 119-128.

[14] Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* **12**, 207-216.

[15] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292.

[16] Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH (2011) The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 270-279.

[17] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.

[18] Jack CR Jr, Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH (2011) Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 257-262.

[19] Cui Y, Liu B, Luo S, Zhen X, Fan M, Liu T, Zhu W, Park M, Jiang T, Jin JS, the Alzheimer's Disease Neuroimaging Initiative (2011) Identification of conversion from mild cognitive impairment to Alzheimer's disease using multivariate predictors. *PLoS One* **6**, e21896.

[20] Davatzikos C, Bhatt P, Shaw LM, Batmanghelich KN, Trojanowski JQ (2011) Prediction of MCI to AD conversion, via MRI, CSF biomarkers, and pattern classification. *Neurobiol Aging* **32**, 2322.e19-2322.e27.

[21] Ewers M, Walsh C, Trojanowski JQ, Shaw LM, Petersen RC, Jack CR Jr, Feldman HH, Bokde AL, Alexander GE, Scheltens P, Vellas B, Dubois B, Weiner M, Hampel H, North American Alzheimer's Disease Neuroimaging Initiative (ADNI) (2012) Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. *Neurobiol Aging* **33**, 1203-1214.

[22] Mattila J, Koikkalainen J, Virkki A, Simonsen A, van Gils M, Waldemar G, Soininen H, Lötjönen J, the Alzheimer's Disease Neuroimaging Initiative (2011) A disease state fingerprint for evaluation of Alzheimer's disease. *J Alzheimers Dis* **27**, 163-176.

[23] Zhang D, Shen D, the Alzheimer's Disease Neuroimaging Initiative (2012) Predicting future clinical changes of MCI patients using longitudinal and multimodal biomarkers. *PLoS One* **7**, e33182.

[24] Gray KR, Aljabar P, Heckemann RA, Hammers A, Rueckert D, the Alzheimer's Disease Neuroimaging Initiative (2012) Random forest-based similarity measures for multi-modal classification of Alzheimer's disease. *Neuroimage* **65**, 167-175.

[25] Mattila J, Soininen H, Koikkalainen J, Rueckert D, Wolz R, Waldemar G, Lötjönen J, the Alzheimer's Disease Neuroimaging Initiative (2012) Optimizing the diagnosis of early Alzheimer's disease in mild cognitive impairment subjects. *J Alzheimers Dis* **32**, 969-979.

[26] Alzheimer's Disease Neuroimaging Initiative, http://adni.loni.ucla.edu, Accessed on May 4, 2013.

[27] Weiner MW, Aisen PS, Jack CR Jr, Jagust WJ, Trojanowski JQ, Shaw L, Saykin AJ, Morris JC, Cairns N, Beckett LA, Toga A, Green R, Walter S, Soares H, Snyder P, Siemers E, Potter W, Cole PE, Schmidt M, the Alzheimer's Disease Neuroimaging Initiative (2010) The Alzheimer's Disease Neuroimaging Initiative: progress report and future plans. *Alzheimers Dement* **6**, 202-211.

[28] ADNI1 Procedures Manual (2011), http://www.adni-info.org/Scientists/Pdfs/ADNI1_Procedures_Manual_Revised_12052011.pdf, Posted on May 12, 2011, Accessed on January 23, 2012.

[29] Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002) whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* **33**, 341-355.

[30] Dubois B, Feldman HH, Jacova C, DeKosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P (2007) Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* **6**, 734-746.

[31] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[32] Llano DA, Laforet G, Devanarayan V, the Alzheimer's Disease Neuroimaging Initiative (2011) Derivation of a new ADAS-cog composite using tree-based multivariate analysis: prediction of conversion from mild cognitive impairment to Alzheimer disease. *Alzheimer Dis Assoc Disord* **25**, 73-84.

[33] Caroli A, Frisoni GB, the Alzheimer's Disease Neuroimaging Initiative (2010) The dynamics of Alzheimer's disease biomarkers in the Alzheimer's Disease Neuroimaging Initiative cohort. *Neurobiol Aging* **31**, 1263-1274.

[34] Mouiha A, Duchesne S, the Alzheimer's Disease Neuroimaging Initiative (2012) Toward a dynamic biomarker model in Alzheimer's disease. *J Alzheimers Dis* **30**, 91-100.

[35] Samtani MN, Farnum M, Lobanov V, Yang E, Raghavan N, DiBernardo A, Narayan V, the Alzheimer's Disease Neuroimaging Initiative (2012) An improved model for disease progression in patients from the Alzheimer's Disease Neuroimaging Initiative. *J Clin Pharmacol* **52**, 629-644.

[36] Escudero J, Ifeachor E, Zajicek JP, the Alzheimer's Disease Neuroimaging Initiative (2012) Bioprofile analysis: a new approach for the analysis of biomedical data in Alzheimer's disease. *J Alzheimers Dis* **32**, 997-1010.

[37] Jedynak BM, Lang A, Liu B, Katz E, Zhang Y, Wyman BT, Raunig D, Jedynak CP, Caffo B, Prince JL, the Alzheimer's Disease Neuroimaging Initiative (2012) A computational neurodegenerative disease progression score: method and results with the Alzheimer's Disease Neuroimaging Initiative cohort. *Neuroimage* **63**, 1478-1486.

[38] Yang E, Farnum M, Lobanov V, Schultz T, Verbeeck R, Raghavan N, Samtani MN, Novak G, Narayan V, DiBernardo A, the Alzheimer's Disease Neuroimaging Initiative (2011) Quantifying the pathophysiological timeline of Alzheimer's disease. *J Alzheimers Dis* **26**, 745-753.

[39] Cui Y, Sachdev PS, Lipnicki DM, Jin JS, Luo S, Zhu W, Kochan NA, Reppermund S, Liu T, Trollor JN, Brodaty H, Wen W (2012) Predicting the development of mild cognitive impairment: a new use of pattern recognition. *Neuroimage* **60**, 894-901.

[40] Zhang D, Wang Y, Zhou L, Yuan H, Shen D, the Alzheimer's Disease Neuroimaging Initiative (2011) Multimodal classification of Alzheimer's disease and mild cognitive impairment. *Neuroimage* **55**, 856-867.

[41] Koikkalainen J, Pölönen H, Mattila J, van Gils M, Soininen H, Lötjönen J, the Alzheimer's Disease Neuroimaging Initiative (2012) Improved classification of Alzheimer's disease data via removal of nuisance variability. *PLoS One* **7**, e31112.