Quantitative longitudinal predictions of Alzheimer's disease by multi-modal predictive learning

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[**] Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.

Abstract

Background: Quantitatively predicting the progression of Alzheimer's disease (AD) in an individual on a continuous scale, such as AD assessment scale-cognitive (ADAS-cog) scores, is informative for a personalized approach as opposed to qualitatively classifying the individual into a broad disease category. We hypothesize that multi-modal data and predictive learning models can be employed for longitudinally predicting ADAS-cog scores.

Methods: Multivariate regression techniques were employed to model baseline multi-modal data (demographics, neuroimaging, and cerebrospinal fluid based markers, and genetic factors) and future ADAS-cog scores. Prediction models were subjected to repeated cross-validation and the resulting mean absolute error and cross-validated correlation of the model assessed.

Results: Prediction models on multi-modal data outperformed single modal data up to 36 months. Incorporating baseline ADAS-cog scores to prediction models marginally improved predictive performance.

Conclusions: Future ADAS-cog scores were successfully estimated via predictive learning aiding clinicians in identifying those at greater risk of decline and apply interventions at an earlier disease stage and inform likely future disease progression in individuals enrolled in AD clinical trials.

Keywords: Alzheimer's disease, Magnetic resonance imaging, Machine Learning, Neuropsychology, Multivariate, PLS, ADAS-cog

1 Background

Alzheimer's disease (AD) is an irreversible and multi-factorial neurodegenerative disease with a progressive decline in cognitive abilities [1]. AD affects several tens of millions of people globally. Yet, the pathogenesis of AD remains unclear [2]. Cognitive tests, brain volumetry from magnetic resonance imaging (MRI), amyloid load and glucose consumption levels from positron emission tomography (PET), and protein analysis of cerebrospinal fluid (CSF) provide valuable and complementary disease markers to chart the disease progression [3]. Qualitative manual analysis of these markers to diagnose patients could be potentially aided by automated algorithms.

The classification based on clinical diagnosis places an individual into normal, mild cognitive impairment (MCI), or AD groups [4]. Memory loss (either self-reported or by an associate) is observed during the initial stages of AD [5]. Declining cognitive skills is also common and can potentially lead to dementia [6]. Hence, it is imperative that the disease progression is carefully monitored at the earliest stages [7]. AD risk factors include sociodemographic factors (e.g., increasing age and fewer years of education), genetic (APOE expression) and patient medical and family history [8]. A clinical diagnosis of AD is currently a challenge due to lack of clear diagnostic markers of AD, and overlapping clinical features with other dementia types. However at post-mortem, AD is characterized by the presence of amyloid β-peptide plaques and accumulations of **τ** proteins in the brain histology samples [9].

The progressive nature of AD makes diagnosing an individual into any of the discrete groups a challenging proposition [10,11]. Conventional progression tracking analyzes clinical changes in MRI, CSF and cognitive biomarkers [12,13], but this could be inefficient as the changes can be slow and difficult to detect [14,15]. The change in these biomarkers is nonlinear with AD's progression, further complicating longitudinal tracking. Therefore, quantifying and tracking the

condition of the patient by continuous measures such as ADAS-cog scores has been advocated [16,17]. ADAS-cog is widely used clinically (to measure language, memory, praxis, and other cognitive abilities) and provides an accurate description of the cognitive state on a continuous scale, making it an ideal choice in our study [18,19]. The availability of standardized multi-modal data and corresponding longitudinal ADAS-cog scores from research organizations, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) project, has enabled the development of novel techniques for tracking AD progression by employing machine learning [20]. However, predicting ADAS-cog scores has been reported as very difficult [21]. In the recent Alzheimer's Disease Prediction of Longitudinal Evolution (TADPOLE) Challenge (https://tadpole.grand-challenge.org/), forecasts of clinical diagnosis and ventricle volume were very good, whereas, for ADAS-cog, no team participating in the challenge was able to generate forecasts that were significantly better than chance.

Multivariate regression techniques, such as partial least squares regression (PLSR), support-vector regression (SVR) and random forest regression, enable modeling complex relationships between baseline multi-modal ADNI data (predictors) with future ADAS-cog 13 scores [22,23]. The multivariate nature of the modeling is desirable for the ADAS-cog score trajectory analysis due to the complementary nature of the AD measures. The resulting trajectory predictions could alert clinicians to prescribe appropriately (once disease modifying interventions are available). Moreover, knowing the likely future trajectory of the disease will provide a benchmark with which to test clinical evolution in patients enrolled in clinical trials.

We hypothesized that the multivariate regression techniques are well suited for multi-factorial diseases and that the progression of AD, as indicated by ADAS-cog scores in subsequent timelines,

can be accurately predicted. Furthermore, the inclusion of baseline ADAS-cog scores could improve the predictions of the model in subsequent follow-ups.

2 Methods

2.1 ADNI Dataset

Data in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). In addition to the various summary tables directly provided by ADNI, we used summary tables prepared for the TADPOLE grand challenge based on ADNI data at https://tadpole.grand-challenge) [21,24]. The data are from the TADPOLE tables if not otherwise stated. Specific variable names are provided as supplementary Table S.1. The ADNI project started in 2003 as a public-private partnership, led by PI Michael W. Weiner, MD. The main objective of ADNI is to evaluate the application of serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment in a multi-modal approach to determine the longitudinal progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). We utilized pre-processed ADNI data because of the standardized processing pipeline that ensured the quality of the data. This multimodal data is readily available for other researchers enabling a direct comparison of the study results. Readers are directed to www.adni-info.org for detailed information on the ADNI project and the TADPOLE challenge https://tadpole.grand-challenge.org constructed by the EuroPOND consortium (http://europond.eu).

2.1.1 Subjects

The characteristics of subjects recruited in the ADNI dataset are described in detail here http://adni.loni.usc.edu/. The trends of the ADAS-cog 13 scores utilized in this study are provided in Figure S.1 and the details of subject characteristics are provided in Table S.2 of the

supplementary section. There are fewer subjects in follow-up visits than in the baseline visit due to subject attrition and missing data. Note that some subjects change diagnostic status over the follow-up period. The roster identification (RID) numbers of the included subjects are provided as comma-separated values in the supplementary section.

2.1.2 MRI

As MRI features, we used 9 features: intracranial volume (ICV), and volumes of the hippocampus, entorhinal cortex, and lateral ventricles as well as the latter four divided by the ICV. These features were selected based on previous studies [25]. We included volumes divided by the ICV as it is unclear whether raw or ICV-corrected volumes are better predictors of dementia [25,26]. MR imaging protocol details are provided by ADNI at http://adni.loni.usc.edu/methods/mri-tool/mri-analysis/. Cortical reconstruction and volumetric segmentation had been performed with the FreeSurfer 5.1 image analysis suite. A brief description of the processing is provided in the supplementary material (Section B) [27].

2.1.3 AV-45 PET

As AV-45 PET features, we used standardized uptake values (SUVs) in four regions: frontal cortex, cingulate, lateral parietal cortex, and lateral temporal cortex. The AV-45 PET measures amyloid-beta load in the brain. AV-45 PET imaging and preprocessing details are available at http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/ [28]. We used regional SUV ratios processed according to the UC Berkeley protocol [28–30]. Each AV-45 PET scan was co-registered to the corresponding MRI and the mean AV-45 uptake within the regions of interest and reference regions was calculated. Regions of interest were composites of frontal regions, anterior/posterior cingulate regions, lateral parietal regions, and lateral temporal regions [31]. The

final PET measurements were the average amyloid-beta uptakes in the four ROIs normalized by the whole cerebellum reference region.

2.1.4 FDG PET

As FDG-PET features, we used average SUVs in five brain regions: bilateral angular gyri, bilateral posterior cingulate gyri, and bilateral inferior temporal gyri. The FDG PET data measures glucose consumption and is shown to be strongly related to dementia and cognitive impairment when compared to normal control subjects [30,32,33]. Motion correction and co-registration with MRI was performed on the acquired PET data. The highest 50% of voxel values within a hand-drawn pons/cerebellar vermis region were selected and their mean was used to normalize each ROI measurement resulting in the final FDG PET measurements. Regions of interests were bilateral angular gyri, bilateral posterior cingulate gyri, and bilateral inferior temporal gyri.

2.1.5 CSF proteins

The baseline CSF $A\beta_{42}$, t-tau, and p-tau were used as CSF features [34]. CSF was collected in the morning after an overnight fast using a 20- or 24-gauge spinal needle, frozen within 1 hour of collection, and transported on dry ice to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center. The levels of $A\beta_{42}$, t-tau, and p-tau in CSF were used.

2.1.6 Neuropsychology and behavioral (NePB) assessments

The NePB assessments reflect the cognitive abilities of the subjects. Subjects underwent a battery of NePB tests [35]. We selected to include 5 NePB scores as NePB features: the summary score from Mini-Mental State Examination (MMSE) [36], three summary scores of Rey's auditory verbal learning test (RAVLT; learning, immediate, and percent forgetting) [37], and a summary score from the functional activities Questionnaire (FAQ) [38].

174

175 **2.1.7 Risk factors: age, education, and APOE**

176 Past studies have found several risk factors contributing to AD [8]. We considered age, the number
177 of APOE e4 alleles, and the years of education. With aging, normal cognitive decline is an accepted
178 phenomenon, but lower education and lower cerebral metabolic activity could accelerate the normal
179 decline [39]. The APOE e4 allele, present in approximately 10-15% of people, increases the risk for
180 late-onset AD and lowers the age of onset. One copy of e4 (e3/e4) can increase risk by 2-3 times
181 while homozygotes (e4/e4) can be at 12 times increased risk [40]. We coded APOE e4 status of
182 absence, single copy or homozygous coded as 0, 1 and 2 respectively.

183

184 **2.1.8 ADAS-cog scores**

185 The ADAS-cog 11 task scale was developed to assess the efficacy of anti-dementia treatments.
186 Further developments to the scale shifted its sensitivity towards pre-dementia syndromes as well,
187 primarily mild cognitive impairment (MCI). The ADAS-cog 13 task scale was one such
188 improvement on the original ADAS-cog 11, with additional memory and attention/executive
189 function tasks [41]. The final 13 tasks test verbal memory (3 tasks), clinician-rated perception (4
190 tasks), and general cognition (6 tasks). It was found to perform better than the ADAS-cog 11 at
191 discriminating between MCI and mild AD patients, as well as have better sensitivity to treatment
192 effects in MCI [42]. As the ADAS-cog 13 fully encompasses the ADAS-cog 11 tasks, it is also
193 backward compatible. As such, we used the ADAS-cog 13 scale for our study as a continuous
194 quantitative measure of a subject's disease status. The scores at baseline, 12-month, 24-month and
195 36-month timelines were obtained from the ADNI dataset (Table S.2). The value (0 to 85) of these
196 scores is lowest for the normal control group and increases with disease progression and the scores
197 are highest for AD subjects.

198

199 **2.2 Multivariate regression analysis**

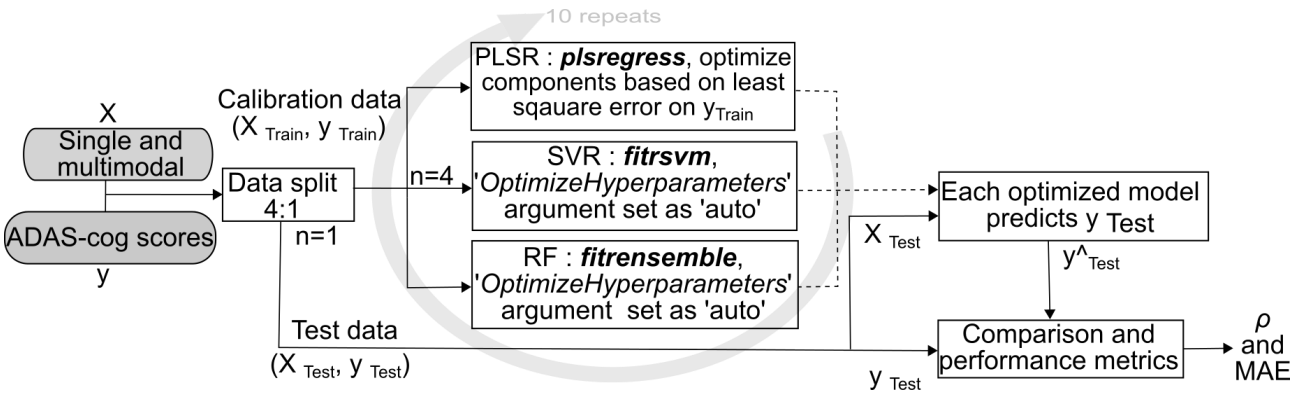
200 We employed multivariate regression to predict ADAS-cog scores based on predictor variables
201 detailed in section 2.1. We considered four different prediction tasks: predicting ADAS-cog score at
202 baseline and at 12, 24, or 36 months after the baseline. In all of these tasks, the predictor variables
203 are from the baseline visit. The group of features (predictors) used for regression are denoted by the
204 column vectors X_i, (i = 0, 1, . . ., L), where L is the number of features (Figure S.2). The ADAS-
205 cog scores (dependent variable or response variable) are denoted by the column vector Y.

206

207 We employed widely used machine learning techniques including partial least squares regression
208 (PLSR) [43], support vector regression (SVR) [44], and random forest regression (RF) and created
209 prediction models [45]. Additionally, a genetic algorithm (GA) was utilized to rank the variables in
210 the order of importance in the multi-modal case [46]. The details on these methods are provided in
211 the supplementary section.

212

213 **2.3 Regression modeling and performance metrics**



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215 **Figure 1:** Schematic of regression modeling. X is single or multi-modal predictors and Y is the
216 target value to be predicted. We utilized 5-fold cross-validation repeated 10 times to account for the
217 random assignment of subjects to different folds. Partial least squares regression (PLSR), support-
218 vector regression (SVR) and random forest regression (RF) models were trained and tuned based on
219 training folds and evaluated on test folds. The utilized Matlab function and hyperparameter tuning

are shown in italics. Cross-validated correlation ($\boldsymbol{\rho}$) and mean absolute error (MAE) metrics were employed and average performance for 10 runs computed.

The prediction of the ADAS scores (at baseline, 12-months, 24-months, and 36 months) was performed by employing PLSR, SVR, and RF. Both single modal (each modality of Section 2.1 alone) and multi-modal predictors (all modalities of Section 2.1 combined,) were considered. All the predictors were from the baseline visit. We evaluated the prediction models using 5-fold repeated cross-validation with 10 repeats, see **Figure 1** and Figure S.2. Under single modalities Age, years of education (Edu), number of APOE e4 alleles (APOE) were exactly 1 variable each, CSF had 3 variables, AVF45-PET had 4 variables, NePB and FDG had 5 variables each, MRI had 9 variables and hence the multimodal model had a total of 29 variables (Figure S.2). All variables were assumed to be continuous and we standardized the variables to be zero-mean and unit standard deviation. The model was evaluated in terms of correlation coefficient ($\boldsymbol{\rho}$) and the mean absolute error (MAE) between the actual ADAS-cog 13 scores and its model-predicted values. From the 5-fold cross-validation, we averaged the resulting 5 distinct values and computed 95% confidence intervals (CIs) using the bootstrapping method. Similarly, MAE and its CIs were computed. The process was repeated 10 times and its distribution analyzed. For mathematical details of these performance metrics as well as the CI computation in the case of repeated cross-validation that takes into account inter-dependency of distinct repeats, readers may consult Lewis et.al. [47].

The analyses were performed on MATLAB 2018b (The Mathworks Inc, Natick, MA) using native machine learning functions. The PLSR was executed with *plsregress* function and the optimal number of PLS components was manually selected based on the least root mean square error for training data [48]. SVR was executed with *fitrsvm* and RF with *fitrensemble* and in both methods the models were tuned by setting *OptimizeHyperparameters* argument as *auto* [49,50].

Additionally, Additionally, GA-PLS was utilized to analyze the importance of each modality in the multimodal PLSR regression models [51].

(The main codes and resulting *.mat* file are available on GitHub: https://github.com/mithp/ADAS_multimodal.git)

3 Results

As depicted in **Figure 1**, we created single modality and multi-modal regression models and compared their performance. The comparison (**Figure 3**) shows that multi-modal based prediction models outperform single modality consistently in all the timelines (baseline and subsequent 12, 24 and 36-month follow-up) in all subjects tested (i.e., collapsing over diagnostic categories). The correlation between the predicted ADAS-Cog 13 based on multi-modal data and that observed at 12, 24 and 36 months, reached 0.86, 0.82, and 0.75, respectively. The performance comparison (Figure S.3) shows that the differences among PLSR, SVR, and RF were not significant (i.e., $p > 0.05$), except for some instances where PLSR underperformed compared to RF (baseline and 12 months: MRI, CSF, and FDG; 24 and 36 months: APOE and multi-modal). However, PLSR models were computationally faster and performed consistently.

By analyzing the importance of measures (**Figure 2**) contributing to PLSR's correlation we observe that the neuropsychological and behavioral parameters (NePB) were most important and consistent across time periods for predicting ADAS score, followed by CSF and MRI biomarkers. Despite the association of age at baseline, years of education (Edu.) and APOE e4 status with AD risk, thers parameters were found to be least important, perhaps because these factors are somehow reflected in other parameters. By contrast, the importance of amyloid and τ increased when predictions were made 36 months in advance (**Figure 2**). Additionally, metabolic activity in temporal right and left sides were on the opposite ends of the importance in the ADAS-cog score predictions.

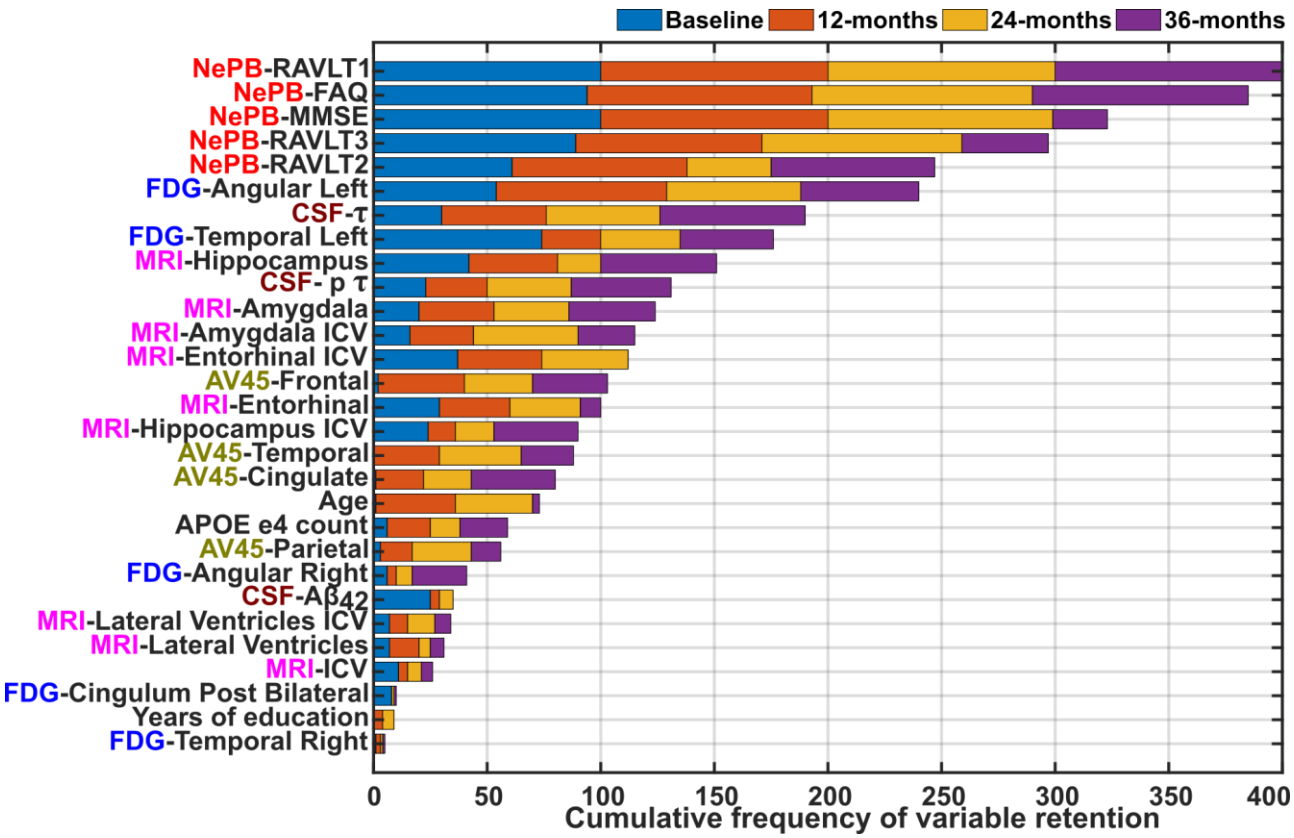

Figure 2: Genetic algorithm-based importance of parameters in correlations as observed for 100 runs for every time period. The frequency indicates the proportional contribution in ADAS-cog 13 score prediction. The modality group is prefixed to the variable names.

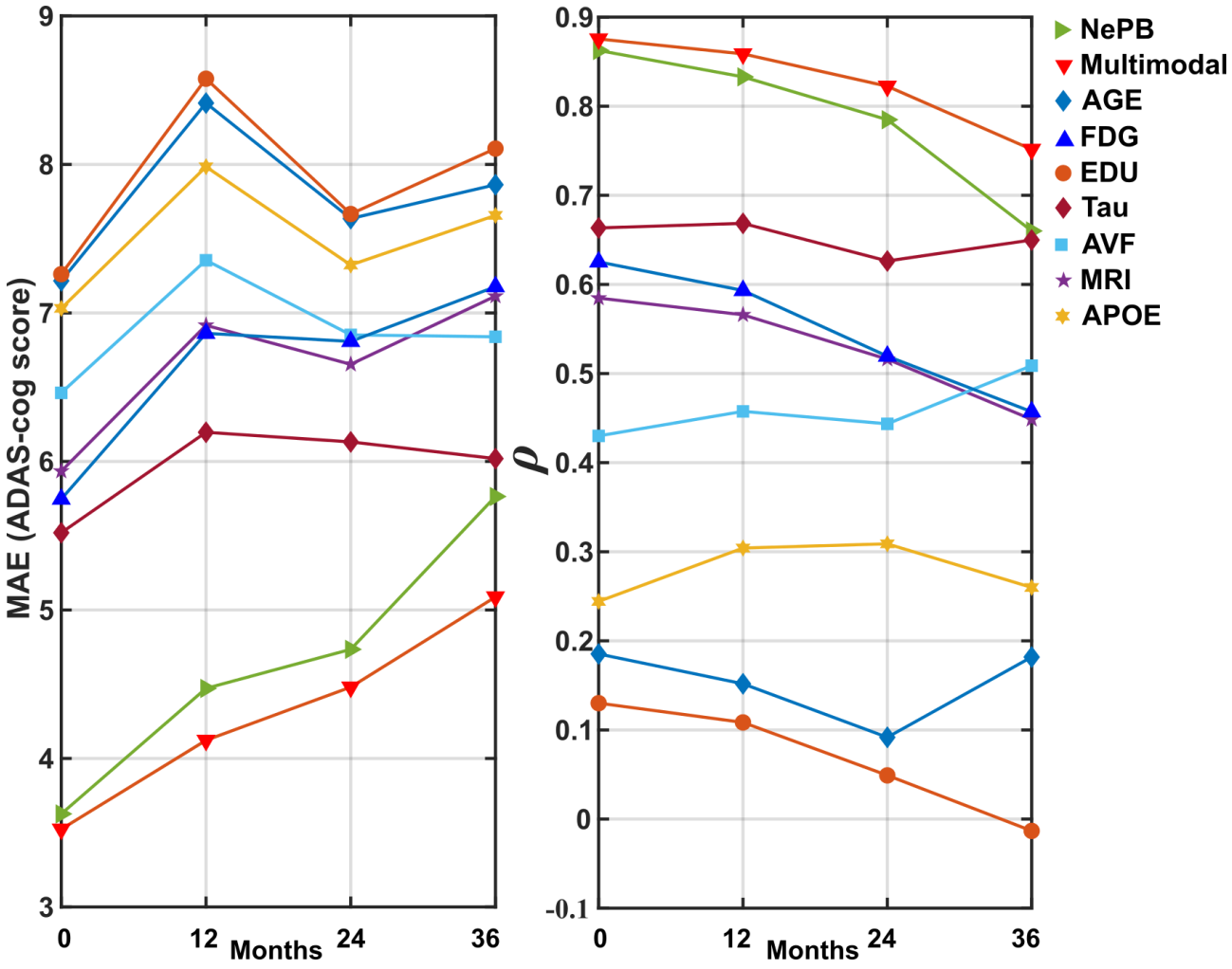

Figure 3: Comparison of single and multi-modal dataset performance – collapsing across diagnostic status – with partial least squares regression. The performance measures cross-validation correlation (***ρ***) and mean absolute error (MAE) for ADAS-cog scores are plotted for predictions at 0, 12, 24 and 36 months in advance.

Grouping data based on diagnosis at baseline (**Figure 4**) and analyzing the performance further magnified the poor correlation when a single modality approach was employed to predict this multi-factorial disease. We observe that NePB, single modal, data shows the best predictive performance, in keeping with the fact that the to-be-predicted variable (ADAS-Cog 13) also contains NeBP outcomes. However, the multimodal approach performs better than MCI and AD groups especially

during 24- and 36-month time periods. Due to the high variation in ADAS scores in AD groups the correlation (ρ) and MAE were not inversely proportional to each other.

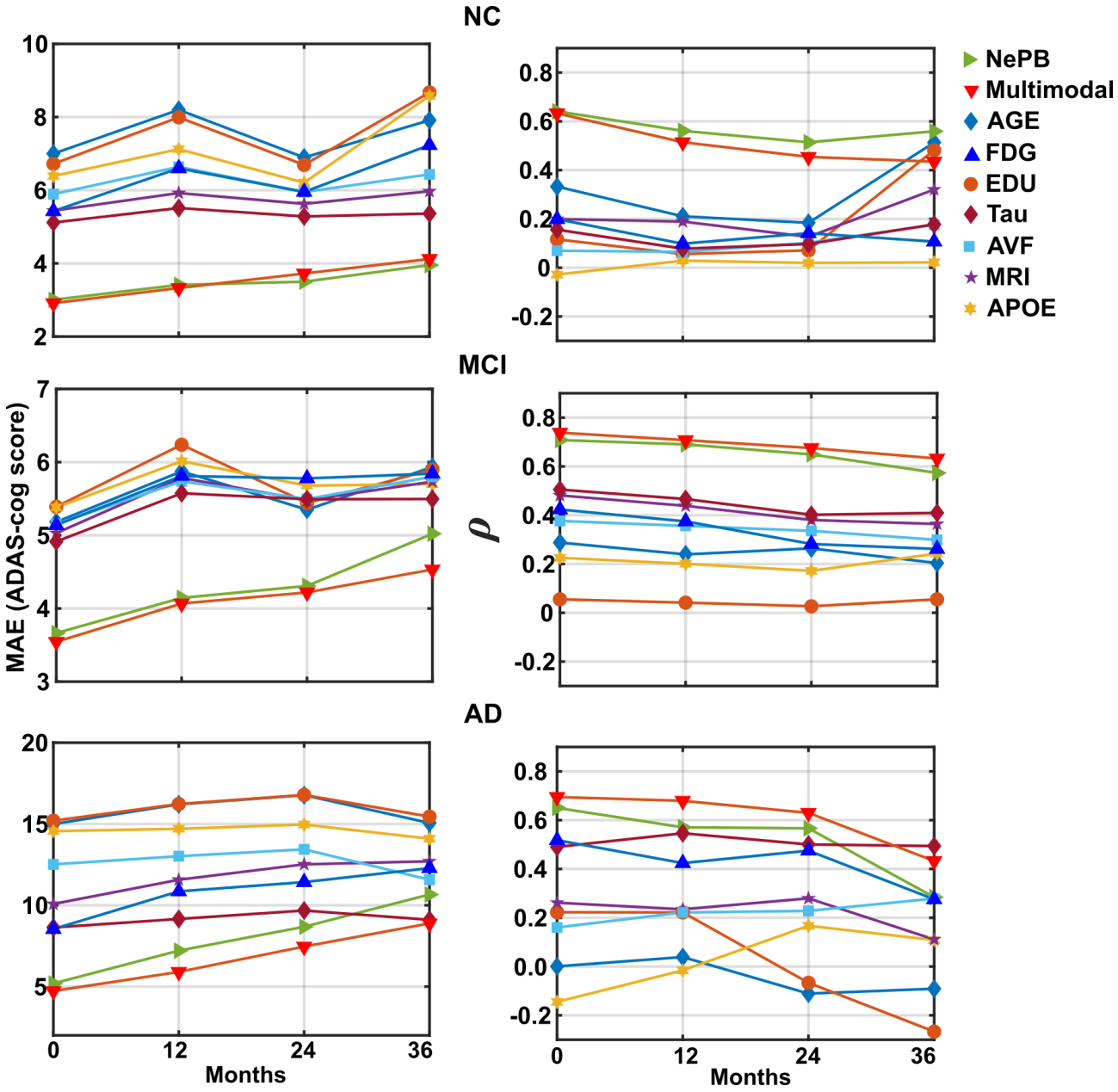

Figure 4: Performance of PLSR on single- and multi-modal data stratified according to baseline clinical diagnosis [normal cognition (**NC**), mild cognitive impairment (**MCI**) and Alzheimer's disease (**AD**)]. The performance measures cross-validation correlation (ρ) and mean absolute error (MAE) for ADAS-cog scores are plotted for predictions at 0, 12, 24 and 36 months in advance.

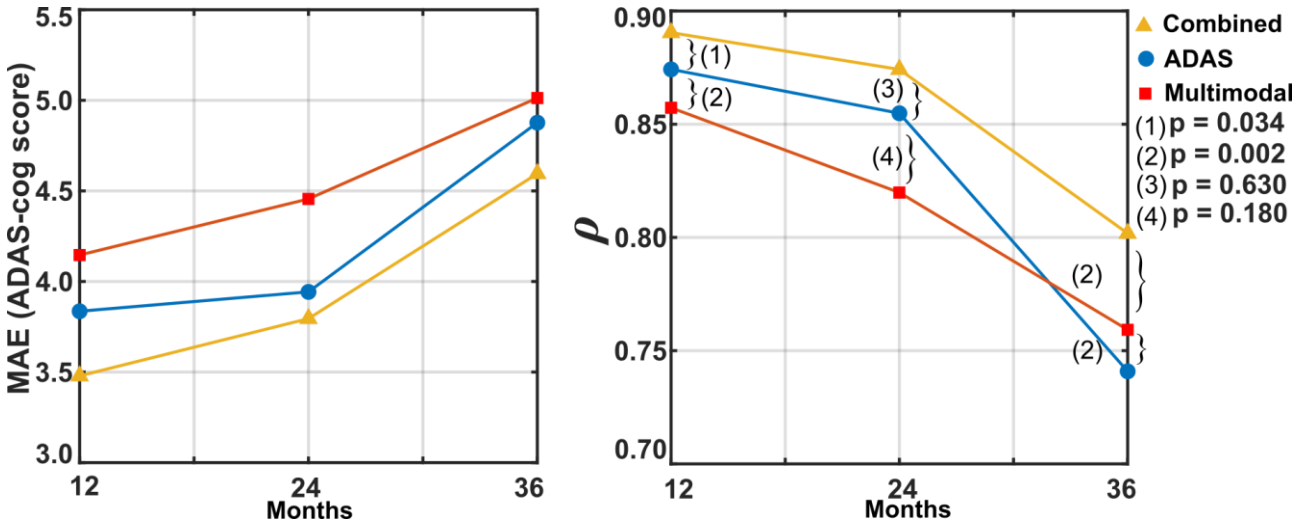

Figure 5: Performance comparison of prediction models utilizing only ADAS scores *vs.* multimodal data with and without the combination with baseline ADAS scores. The p-values correspond to pair-wise differences between the three prediction models at different time periods.

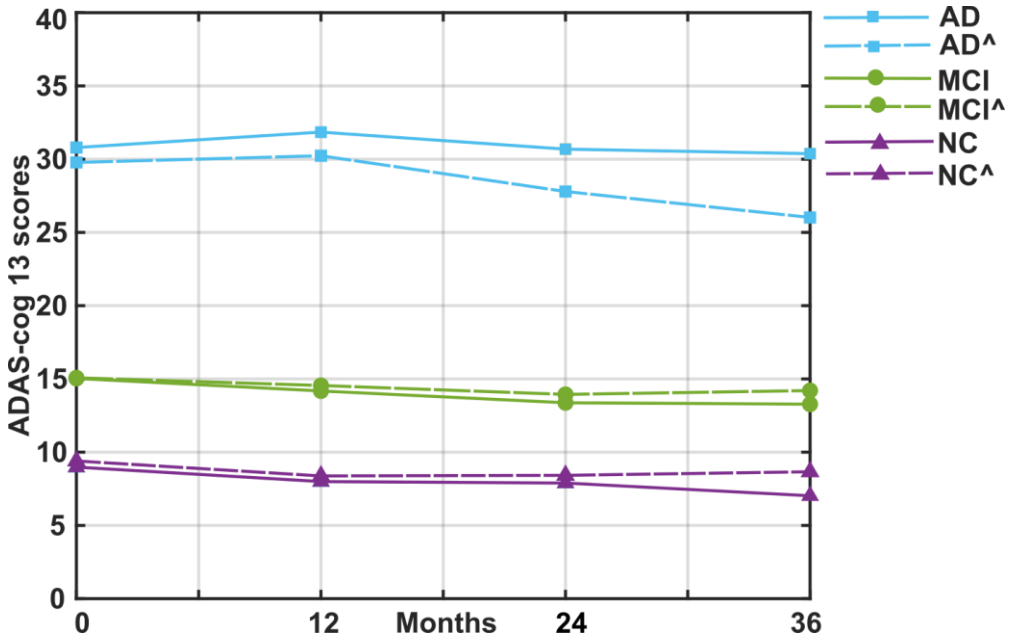

Figure 6: The mean of actual ADAS-cog 13 scores of subjects over 36 months is plotted (solid line) for the 3 diagnostic groups (normal cognition (NC), mild cognitive impairment (MCI) and Alzheimer's disease (AD)). The learning model predicted scores for these time periods are also plotted (dashed lines) for each diagnostic group (model predictions indicated with a caret (^) symbol).

Our multimodal approach (multivariate) based prediction models with the inclusion of baseline ADAS-cog scores were better ($\boldsymbol{\rho}$ = 0.80 to 0.90, **Figure 5**) than prediction models based only on baseline ADAS-cog scores (univariate, $\boldsymbol{\rho}$ = 0.75 to 0.87). The inclusion of the ADAS-cog score with other baseline multi-modal predictors was observed with improvements (p = 0.002 to 0.18) in the correlations. Overall, the prediction models predict well across the time periods and this can be observed when we compare the mean predicted values versus the actual mean values (**Figure 6**).

4 Discussion

We present a multi-modal regression approach to quantitatively track the progression of Alzheimer's disease and show that it outperforms the conventional single modal approach. Quantification of AD aids clinicians in decisions with treatment and a multi-modal approach ensures that the prediction models consider all biomarkers contributing to the disease condition. Furthermore, conventional classification of patients into normal, MCI or AD could be avoided as a clear distinction amongst the group is a challenging task [52].

The classification of subjects based on a few modalities has been the focus of most recent studies. Although high classification accuracy (>80%) has been reported [11], we speculate that the impact of mislabeling a subject in the wrong category (and hence, wrong therapy prescribed) is higher than the error in predicting ADAS-cog scores (<5 units). Additionally, ADAS-cog scores are easy to interpret and follow the longitudinal tracking of AD progression. In agreement with the classification-based studies [4], the multi-modal approach outperforms the single modality, however, in this study multi-modal data were used for predicting the ADAS-cog scores. Furthermore, our multi-modal approach shows that ADAS-cog scores are conducive to longitudinal predictions contrary to Marinescu et al [21], where ADAS-cog scores were concluded not

predictable. We, however, acknowledge that studies were not set up equally as there were time constraints, differences in subjects and underutilization of longitudinal data.

Clinically, NePB tests and ADAS-cog scores measure the subject's cognitive abilities and this similarity was showcased with the observance of higher correlations (**Figure 3**). CSF biomarkers showed high correlations several studies support this strong relationship between CSF biomarkers and AD state [34]. As the precise pathophysiology and relative contribution of different pathogenic factors to AD at different phases of disease progression are currently still under investigation, the results advocate that instead of manually estimating the best markers, a multi-modal approach is beneficial. However, we acknowledge that the variable selection methods can be utilized to select the best AD measures (or create sparse models) utilized in multimodal modeling further improving the robustness of the prediction model.

The multivariate techniques (i.e., PLSR, SVR, and RF) were observed to perform very similarly in their predictions but the computation times were different, and this prompted us to favor PLSR. Other nonlinear model selection techniques could improve current results [53]. The subject attrition during follow-ups may have diminished the predictive performance of the model.

5 Conclusion

ADAS-cog 13 scores reflect the current cognitive state of individuals, and through multivariate regression and a multi-modal dataset, our results show that quantitative longitudinal prediction of AD progression is possible. Thus, the automated multi-modal approach may help clinicians make timely decisions for interventions at all stages of AD and inform likely disease progression at the start of clinical trials.

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7 Figure legends

Figure 1: Schematic of regression modeling. X is single or multi-modal predictors and Y is the target value to be predicted. We utilized 5-fold cross-validation repeated 10 times to account for the random assignment of subjects to different folds. Partial least squares regression (PLSR), support-vector regression (SVR) and random forest regression (RF) models were trained and tuned based on training folds and evaluated on test folds. The utilized Matlab function and hyperparameter tuning are shown in italics. Cross-validated correlation (***ρ***) and mean absolute error (MAE) metrics were employed and average performance for 10 runs computed.

Figure 2: Genetic algorithm-based importance of parameters in correlations as observed for 100 runs for every time period. The frequency indicates the proportional contribution in ADAS-cog 13 score prediction. The modality group is prefixed to the variable names.

Figure 3: Comparison of single and multi-modal dataset performance – collapsing across diagnostic status – with partial least squares regression. The performance measures cross-validation correlation (***ρ***) and mean absolute error (MAE) for ADAS-cog scores are plotted for predictions at 0, 12, 24 and 36 months in advance.

Figure 4: Performance of PLSR on single- and multi-modal data stratified according to baseline clinical diagnosis [normal cognition (**NC**), mild cognitive impairment (**MCI**) and Alzheimer's disease (**AD**)]. The performance measures cross-validation correlation (***ρ***) and mean absolute error (MAE) for ADAS-cog scores are plotted for predictions at 0, 12, 24 and 36 months in advance.

Figure 5: Performance comparison of prediction models utilizing only ADAS scores *vs.* multimodal data with and without the combination with baseline ADAS scores. The p-values correspond to pair-wise differences between the three prediction models at different time periods.

Figure 6: The mean of actual ADAS-cog 13 scores of subjects over 36 months is plotted (solid line) for the 3 diagnostic groups (normal cognition (NC), mild cognitive impairment (MCI) and Alzheimer's disease (AD)). The learning model predicted scores for these time periods are also plotted (dashed lines) for each diagnostic group (model predictions indicated with a caret (^) symbol).

Figures in supplementary section

Figure S.1: The mean ADAS-cog 13 scores of subjects for different time periods and conversion of subjects in different categories. The subjects are grouped by the diagnosis as normal cognition (NC), mild cognitive impairment (MCI) and Alzheimer's disease (AD).

Figure S.2: Regression modeling structure**.** Single modality uses one predictor at a time while multi-modal uses all the predictors as indicated above. The sample size for baseline (N = 757), 12-months (N = 629), 24-months (N = 563) and 36-months (N = 314) were different due to missing

values (cohort attrition). The predictors consist of age at baseline, years of formal education (Edu.), APOE e4 status (absence, single copy or homozygous coded as 0, 1 and 2 respectively), MRI-derived parameters, neuropsychiatric and behavioral assessment (NePB), AV45-PET measurements, CSF biomarkers (amyloid-β, τ, pτ) and FDG-PET measures. The number of features is indicated above each modality abbreviations. All the variables were considered as continuous and standardized to be zero-mean and unit standard deviation.

Figure S.3: Comparison of single and multi-modal dataset performance – collapsing across diagnostic status – with partial least squares regression (PLSR), support-vector regression (SVR) and random forest regression (RF). The performances are shown for cross-validation correlation ($\boldsymbol{\rho}$) and mean absolute error (MAE).

Figure S.4: Genetic algorithm-based importance of parameters in contributing to increasing correlation as observed for 100 runs for the 36-month time period. The frequency indicates the proportional contribution in ADAS-cog 13 score prediction.

8 Table legends

Table S.1: Specific variable names from the TADPOLE D1_D2 dataset (1 to 5, details as in TADPOLE_D1_D2_Dict.csv) and FDG-PET from UCBERKELEYFDG_07_30_15 table.

Table S.2: Summary of the subject demographics and ADAS-cog 13 scores.

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9 Highlights

- A quantitative approach to track Alzheimer's disease.
- The multi-modal approach enabled predicting ADAS-cog scores from 12 to 36 months.
- The combination of multimodal data and baseline ADAS scores enhanced the predictions of future timelines.

10 Authors contributions

Prakash, M.: Algorithm design and Data analysis.

Abdelaziz, M.: Data analysis.

Zhang, L. and **Strange, B.:** Clinical validation and supervision.

Tohka, J.: Study design and conception.

All authors contributed to the preparation and approval of the final submitted manuscript.

11 Conflict of Interest

The authors have no conflicts of interest related to the execution of this study and the preparation of the manuscript.