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Article

Towards multimodal longitudinal analysis for predicting cognitive decline

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SUMMARY

Understanding and predicting cognitive decline in Alzheimer's disease (AD) is crucial for timely intervention and management of disease symptoms and progression. While neuroimaging biomarkers and clinical assessments are valuable individually, their combined predictive power and interaction with demographic and cognitive variables remain underexplored. Our study lays the groundwork for comprehensive longitudinal analyses by integrating neuroimaging markers and clinical data to predict cognitive changes over time. Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we applied feature-driven supervised machine learning techniques for assessing cognitive decline predictability. We hypothesized that combining neuroimaging biomarkers with demographic and clinical assessment variables significantly improves the prediction of cognitive decline in AD. Our results show that while imaging biomarkers alone offer moderate predictive capabilities, utilizing key clinical assessment and demographic variables in conjunction with imaging biomarkers significantly improves the model performance. Furthermore, our results indicate that non-imaging variables alone can serve as effective and cost-efficient predictors of cognitive decline. We also introduce the Neuroscience-Longitudinal-and-Multimodal-Analysis-System (NeuroLAMA), an open and extensive data engineering and machine-learning system, to support continued investigation into prediction of cognitive decline using non-imaging variables by the community. Our study underscores the need for integrating multi-dimensional data in future longitudinal research to capture time-dependent patterns in cognitive decline and guide the development of targeted intervention strategies.

INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders, and is characterized by progressive cognitive decline and structural brain changes (1). Early detection and accurate monitoring of cognitive impairment are vital for managing disease progression and evaluating the efficacy of therapeutic interventions. Biomarkers refer to measurable indicators such as changes in brain volume, activity patterns, or structural and functional connectivity, identified through imaging techniques like magnetic resonance imaging (MRI) and positron emission tomography (PET) (2). These imaging-based biomarkers provide quantitative measures that reflect underlying neurodegenerative changes, making them invaluable tools for research and clinical practice. Cognitive and functional performance is often assessed using standardized neuropsychological tests, which, when combined with imaging-based biomarkers, offer a comprehensive approach to understanding disease progression and treatment efficacy. The change in cognitive and functional performance over time serves as a measure of disease progression, offering insights into how patients' cognitive and functional abilities evolve (3). Despite the known value of neuroimaging biomarkers and clinical assessments individually, their predictive relationship and how they interact with other factors, such as demographic and cognitive variables, remain areas ripe for exploration.

Recent studies underscore the importance of integrating neuroimaging biomarkers with clinical assessments and demographic factors to enhance the prediction of cognitive decline. For instance, previous studies demonstrated that combining plasma biomarkers with traditional imaging techniques improves the prediction of cognitive decline in non-demented individuals, highlighting the value of a multifaceted approach (4, 5). These findings suggest that while neuroimaging and clinical assessments provide valuable insights on their own, combining them with demographic and cognitive variables may offer complementary information that can enhance predictive performance in certain contexts.

The data we used in our study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal, multi-center study launched in 2004 with the aim of developing clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of AD (6). The ADNI study has, through the years, collected data from a wide range of participants, including cognitively normal older adults, individuals with mild cognitive impairment (MCI), and patients with AD, enabling researchers to investigate patterns of cognitive decline and identify potential early indicators of the disease. The comprehensive data provided by ADNI included neuroimaging scans (such as MRI and PET), cognitive assessments, genetic information, and clinical evaluations.

Our study investigated the predictive power of different combinations of clinical assessment and demographic variables for changes in cognitive performance. These variables are derived from factors such as the subject's age, length of formal education, quantitative memory assessment scores, and physical activity levels. Our analysis examined the effectiveness of such non-imaging derived variables for predicting cognitive decline, when used in conjunction with neuroimaging biomarkers. Additionally, we assessed the predictive power of using only clinical assessment and demographic variables for cognitive decline prediction.

Our primary hypothesis in this study was that non-imaging factors including demographic and clinical assessment

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AGE (years)	GENDER	CDRSB	CDRSBDIFF
MIN: 53 MAX: 109 AVG: 85	M: 359 F: 302	MIN: 0.0 MAX: 18.0 AVG: 1.88 STD: 2.75	MIN: 0 MAX: 17.5 AVG: 3.29 STD: 3.93

Table 1: Demographic and cognitive characteristics of the study cohort used for predictive modeling of cognitive decline. Variables presented include participant age at baseline (in years), gender (M = male, F = female; values represent number of individuals), and baseline cognitive scores. Cognitive impairment was quantified using the Clinical Dementia Rating Sum of Boxes (CDRSB), where higher scores indicated greater impairment. CDRSBDIFF represents the change in CDRSB score across consecutive assessments and was used in our study as a measure of cognitive decline over time. All numerical values represent either means (AVG) with standard deviations (STD), the minimum (MIN) or maximum (MAX) values, or absolute counts.

data, can serve as effective predictors of cognitive decline in AD including when used alone. The key takeaway is that while imaging biomarkers alone offer moderate predictive capabilities, adding key clinical assessment and demographic factors significantly enhances model performance and strongly suggests that non-imaging-derived factors can accurately predict cognitive decline. This highlights the need for further investigation into a wider space of such non-imaging variables to better understand their predictive capabilities.

RESULTS

We analyzed data from individuals from ADNI, with relevant demographic, clinical, and neuroimaging data available (6). The age and gender distribution of the cohort and the statistical distributions of CDRSB and CDRSBDIFF, are reported (**Table 1**).

Biomarker and Dementia Association

We first analyzed the association between the Spatial Pattern of Abnormality for Recognition of Early Alzheimer's Disease (SPARE_AD), a reliable biomarker of brain atrophy, and the change in the Clinical Dementia Rating Sum of Boxes (CDRSB), a quantitative measure of functional impairment (2). CDRSB is a standardized cognitive and functional assessment tool used to quantify dementia severity across six domains, including memory, orientation, and problem-solving abilities (2). The change in CDRSB (across consecutive visits) is denoted by CDRSBDIFF. SPARE_AD is computed from structural MRI scans that quantify Alzheimer's-related brain atrophy. It is computed for both healthy individuals and those with AD, with higher SPARE_AD values indicating greater atrophy, particularly in regions such as the medial temporal lobe, and a stronger association with cognitive decline (2).

We employed simple linear regression, predicting CDRSBDIFF using SPARE_AD as well as the reverse correlation i.e., predicting SPARE_AD from CDRSBDIFF (**Figure 1**). The predictive accuracy in both cases is low-to-moderate (simple linear regression, $R^2 = 0.19$ and $R^2 = 0.21$), which indicate a weak-to-moderate association, despite the modest explanatory power of SPARE_AD alone.

Employing Non-imaging Variables in Conjunction with Imaging Variables

We then evaluated whether additional non-imaging variables, used together with SPARE_AD, improved prediction of cognitive decline. The non-imaging variables considered were AGE_2024 (subject age in 2024), MMSCORE (mini-mental state examination score, a quantitative measure across multiple cognitive domains such as orientation

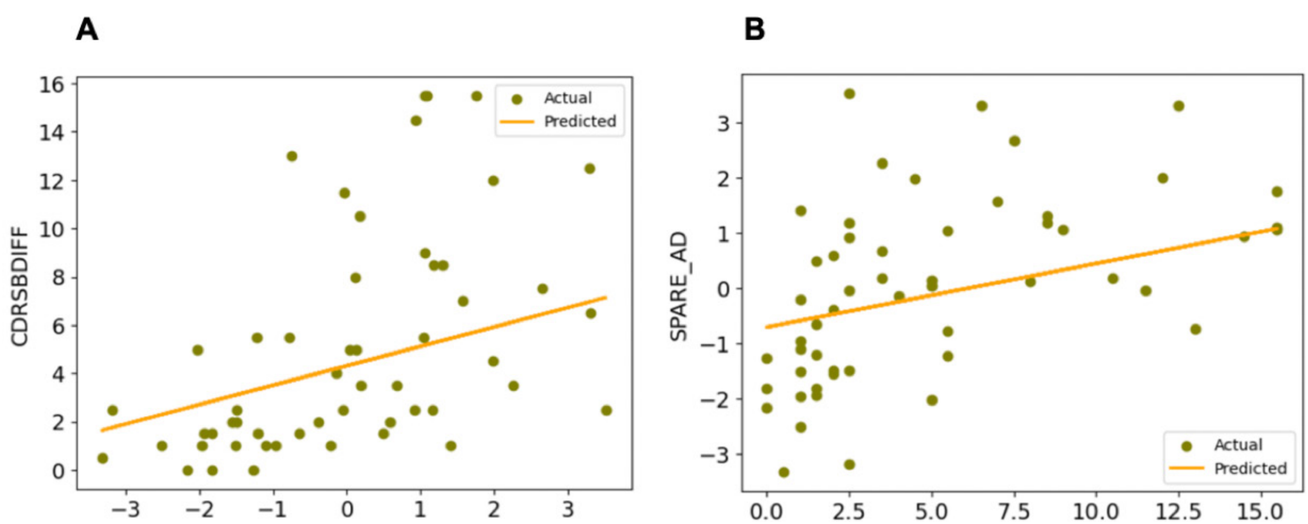

Figure 1: Association between SPARE_AD, a structural MRI biomarker, and CDRSBDIFF, a measure of cognitive decline. This figure shows results from linear regression analyses examining the relationship between SPARE_AD, a continuous imaging-derived biomarker reflecting AD-like brain atrophy, and CDRSBDIFF, defined as the change in Clinical Dementia Rating Sum of Boxes score across visits. (A) Regression model with CDRSBDIFF as the dependent variable and SPARE_AD as the independent variable. The model had a mean square error (MSE) of 16.46 and coefficient of determination (R^2) of 0.19. (B) Regression model with SPARE_AD predicted from CDRSBDIF. The model had a mean square error (MSE) of 2.1 and coefficient of determination (R^2) of 0.21. Analyses are based on cross-sectional data; no biological or technical replicates are applicable.

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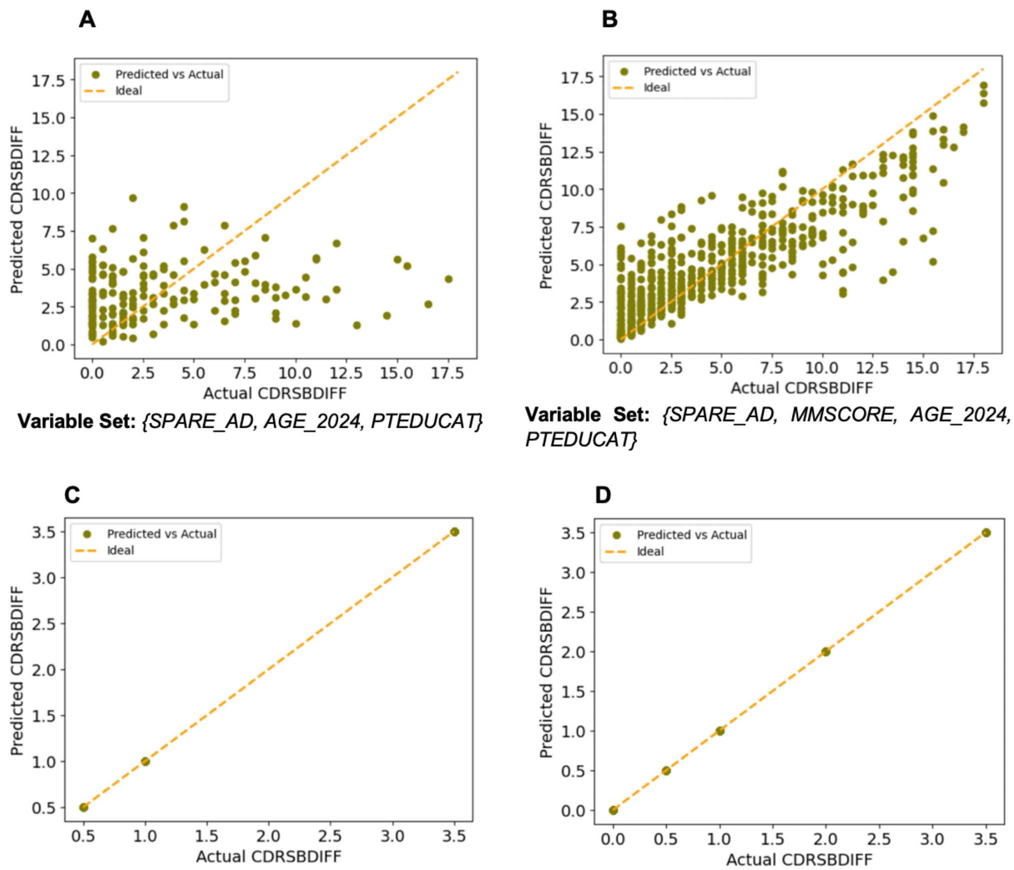

Variable Set: *{SPARE_AD, AGE_2024, PTEDUCAT}*

Variable Set: *{SPARE_AD, MMSCORE, AGE_2024, PTEDUCAT}*

Variable Set: *{SPARE_AD, AMASAVG, MMSCORE, AGE_2024, PTEDUCAT}*

Variable Set: *{SPARE_AD, PEDAVG, MMSCORE, AGE_2024, PTEDUCAT}*

Figure 2: Predicting cognitive decline using SPARE_AD and non-imaging variables. This set of figures shows results from linear regression based predictive modeling of cognitive decline (CDRSBDIFF) using the AD-like atrophy–indicating imaging biomarker SPARE_AD in combination with different subsets of non-imaging features. The complete set of non-imaging features that the subsets are drawn from includes the subject age in 2024 (AGE_2024), the mini-mental state examination score (MMSCORE), a memory recall indicator (AMASAVG), a measure of physical activity levels (PEDAVG), and the years of formal education (PTEDUCAT). Each figure illustrates the predicted CDRSBDIFF versus the actual CDRSBDIFF. (A) Regression model using SPARE_AD, AGE_2024, and PTEDUCAT to predict CDRSBDIFF. The target variable has 37 distinct values, with 857 observations. The model had a mean squared error (MSE) of 15.81 and a coefficient of determination (R^2) of –0.03. The most predictive variable is SPARE_AD with a feature importance score of 0.59, followed by AGE_2024 and PTEDUCAT with importance scores of 0.25 and 0.16 respectively. (B) Regression model using SPARE_AD, AGE_2024, PTEDUCAT, and MMSCORE. The target variable has 37 distinct values, with 3,077 observations. The model had a mean squared error (MSE) of 5.19 and a coefficient of determination (R^2) of 0.72. (C) Regression model using AMASAVG, SPARE_AD, PTEDUCAT, AGE_2024, and MMSCORE. The target variable has 3 distinct values, with 127 observations. The model had a mean squared error (MSE) of 0.00 and a coefficient of determination (R^2) of 1.00. (D) Regression model using PTEDUCAT, AGE_2024, SPARE_AD, PEDAVG, and MMSCORE. The target variable has 5 distinct values, with 251 observations. The model had a mean squared error (MSE) of 0.00 and a coefficient of determination (R^2) of 1.00.

and memory), AMASAVG (Abbreviated Multidimensional Acculturation Scale average, a self-reported psychological assessment of cultural adaptation), PTEDUCAT (years of formal education), and PEDAVG (a self-reported measure of physical activity level). Random-forest regression was used because it provided better performance than simple linear regression and decision trees. These results include the quality of prediction, as well as the feature importance of individual variables (**Figure 2**).

Beyond the effect of individual non-imaging variables, a more informative picture emerges when different combinations of variables are considered. Prediction accuracy is reported using the coefficient of determination and the mean squared error (random-forest regression, R^2 and MSE). Model 1, which includes only SPARE_AD, AGE_2024, and PTEDUCAT, shows virtually no predictive ability (random-forest regression, $R^2 = -0.03$; MSE = 15.81; **Figure 2A**). When MMSCORE is added in Model 2, prediction accuracy improves substantially, indicating that baseline cognitive status contributes strongly to explaining future decline (random-forest regression, $R^2 = 0.72$; MSE = 5.19; **Figure 2B**). In Model 3, the previous variables are combined with AMASAVG, a speech-derived memory measure, and this model achieves perfect in-sample prediction (random-forest regression, $R^2 = 1.00$; MSE = 0.00; **Figure 2C**). A similar pattern is observed in Model 4, which replaces AMASAVG with PEDAVG and also attains perfect in-sample prediction (random-forest regression, $R^2 = 1.00$; MSE = 0.00; **Figure 2D**).

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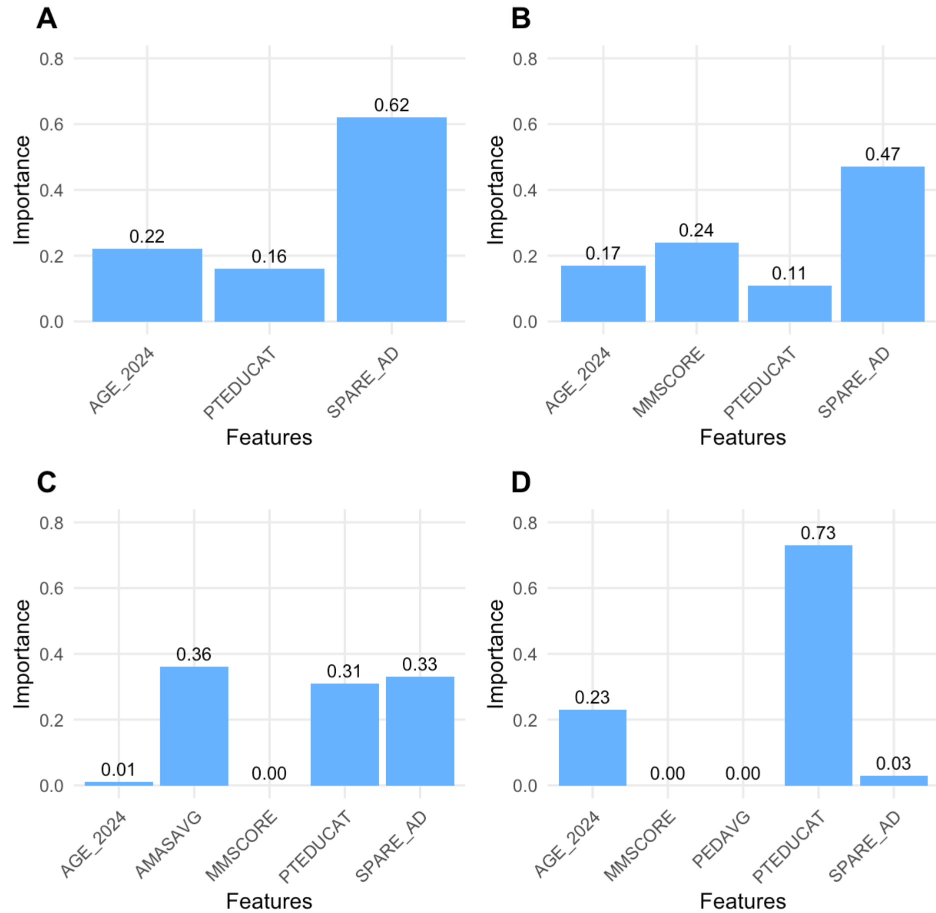

Figure 3: Predictive power of individual variables, within a model. This set of figures shows results from the extraction of feature importance scores for the 4 different models employing the 4 different sets of predictor variables that we evaluated. (A) No predictive value was observed, given a negative coefficient of determination ($R^2 < 0$), and therefore feature importance results were not interpreted. (B) The most predictive variable is SPARE_AD with a feature importance score of 0.44, followed by MMSCORE, AGE_2024, and PTEDUCAT with importance scores of 0,21, 0.21, and 0.13 respectively. (C) The most predictive variable is AMASAVG with a feature importance score of 0.36, followed by SPARE_AD, PTEDUCAT, AGE_2024, and MMSCORE with importance scores, 0.33, 0.31, 0.01 and 0.00 respectively. (D) The most predictive variable is PTEDUCAT with a feature importance score of 0.73, followed by AGE_2024, SPARE_AD, PEDAVG, and MMSCORE with importance scores of 0.23, 0.03, 0.00, and 0.00 respectively.

We then evaluated employing additional, non-imaging derived variables in conjunction with SPARE_AD, for predictive cognitive decline, with different sets of variables employed as a group of predictors. These non-imaging variables are the following: AGE_2024, the subject age in 2024, the mini-mental state examination score (MMSCORE), a quantitative measure involving multiple cognitive domains such as orientation and memory, the Abbreviated Multidimensional Acculturation Scale average (AMASAVG), a self-reported psychological assessment that evaluates cultural adaptation, PTEDUCAT, the number of years of formal education, and PEDAVG, a measure of physical activity levels, derived from self-reported questionnaires. Here we provide results for random-forest regression, which emerged as the best performing model (over linear regression and decision tree). These results include the quality of prediction, as well as the feature importance of individual variables (**Figure 2**).

For Model 1, the imaging biomarker (SPARE_AD) plays the dominant role with the feature importance score of 0.62 (**Figure 3A**). It is important, however, to note that Model 1 achieved no predictivity (random-forest-regression, $R^2 < 0$). For Model 2, SPARE_AD is again the dominant predictor variable, with a leading feature importance score of 0.47 (**Figure 3B**). For Model 3, the auditory memory variable (AMASAVG) is the most influential, with an importance score of 0.36 (**Figure 3C**). For Model 4, the top predictor is the education level (PTEDUCAT) with an importance score of 0.73 (**Figure 3D**). It is noteworthy that in Models 3 and 4, the non-imaging variables AMASAVG and PTEDUCAT, respectively, emerge as the most predictive features, exceeding the contribution of the other variables by a substantial margin.

Employing Non–imaging Variables Exclusively

We then evaluated variable set 5, which comprises of exclusively non–imaging derived variables.

We find the predictive accuracy to be high (random-forest regression, $R^2 = 0.73$ and MSE = 0.74; **Figure 4**). This is taking into account the target class cardinality of 14 and a robust sample size of 697 observations. The feature importance scores indicate that AGE_2024 is the dominant predictive

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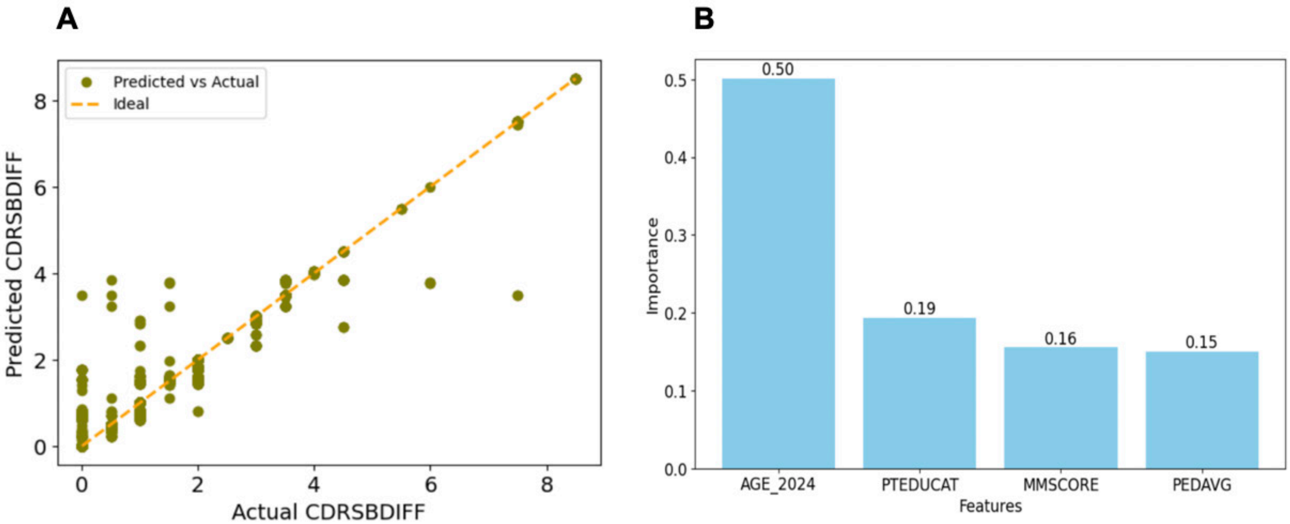

Figure 4: Predicting CDRSBDIFF using non-imaging variables alone. This figure shows the performance of models trained to predict cognitive decline (CDRSBDIFF) using only non-imaging-derived variables, i.e., with the AD-like atrophy indicating imaging biomarker SPARE_AD excluded. The non-imaging-derived variables include includes the subject age in 2024: AGE_2024, the mini-mental-state-examination score: MMSCORE, a measure of physical activity levels: PEDAVG, and the years of formal education: PTEDUCAT. (A) Prediction accuracy, where the target class (CDRSBDIFF) had 14 distinct instances and the number of observations was 697. The model had a coefficient of determination (R^2) of 0.73 and mean square error (MSE) of 0.74. (B) Feature importance rankings from the fitted models. Results are based on cross-validation; no biological or technical replicates apply.

variable, although the predictive contributions of PTEDUCAT, MMSCORE, and PEDAVG are also non-trivial (**Figure 4**).

An XGBoost classifier was applied to predict an individual's diagnostic group (Alzheimer's disease (AD), mild cognitive impairment (MCI), or cognitively normal (CN)), based solely on non-imaging variables. The diagnostic labels were defined from the CDRSB scores: individuals with CDRSB ≤ 0.5 were categorized as CN, those with scores between 0.5 and 4.0 as MCI, and those with scores greater than 4.0 as AD. In this task, XGBoost demonstrated higher performance metrics compared with random forest. The classifier achieved a precision of 0.90, recall of 0.92, and F1-score of 0.91 for AD instances; 0.98 precision, 0.92 recall, and 0.95 F1-score for CN instances; and 0.92 precision, 0.97 recall, and 0.95 F1-score for MCI instances.

DISCUSSION

Our primary hypothesis was that non-imaging factors, such as demographic variables and clinical assessment scores, can effectively predict cognitive decline in Alzheimer's disease, including when used independently of neuroimaging biomarkers. Our findings support this hypothesis. While SPARE_AD, an imaging biomarker reflecting Alzheimer's-related brain atrophy, shows limited predictive power when used alone, incorporating non-imaging variables significantly improves prediction of cognitive decline, as measured by CDRSBDIFF. This underscores the value of a multidimensional approach that combines structural brain changes with cognitive reserve and demographic context. Our analysis suggests that predictive models relying solely on imaging provide an incomplete picture, and that integrating cognitive and demographic information is essential for more accurate and holistic prediction of disease progression.

The results with non-imaging variables demonstrate that accurate prediction of cognitive status across AD, MCI, and CN groups is achievable using age, education, cognitive scores, and physical activity data. The results with employing the non-imaging variable AMASAVG (an indicator of memory recall) and PEDAVG (a physical activity level indicator) must be interpreted cautiously. The result employing AMASAVG is based on only 127 participants, and the outcome variable (CDRSBDIFF, a measure of cognitive decline) spans just 3 unique values in this subset. Similarly, the result using PEDAVG is based on 251 participants and the outcome variable spans just 5 unique values. The generalizability of these results is hence limited.

The choice of the machine-learning algorithm is important as well, given that random forest regression performed better than XGBoost in our study. This is likely because the random forest approach is more stable and less sensitive to small variations in the data, as it aggregates multiple independent views of the data to produce more balanced and reliable predictions - particularly useful in settings like ours with moderate sample sizes and diverse variables. XGBoost, on the other hand, builds predictions in a step-by-step manner, which can lead to instability. The dependency of the feature importance of particular variables on accompany variables is also interesting. The shifts in feature importance highlight that different types of information drive predictive power depending on context, and that speech and cognitive test variables may sometimes outperform imaging markers. Nonetheless, feature importance values should be interpreted with caution, as they are influenced by model assumptions, dataset structure, and interactions among variables.

Finally, the results for cognitive decline category prediction demonstrate remarkable accuracy, even though only non-imaging variables were used. While this is a preliminary finding based on a limited set of clinical and demographic variables,

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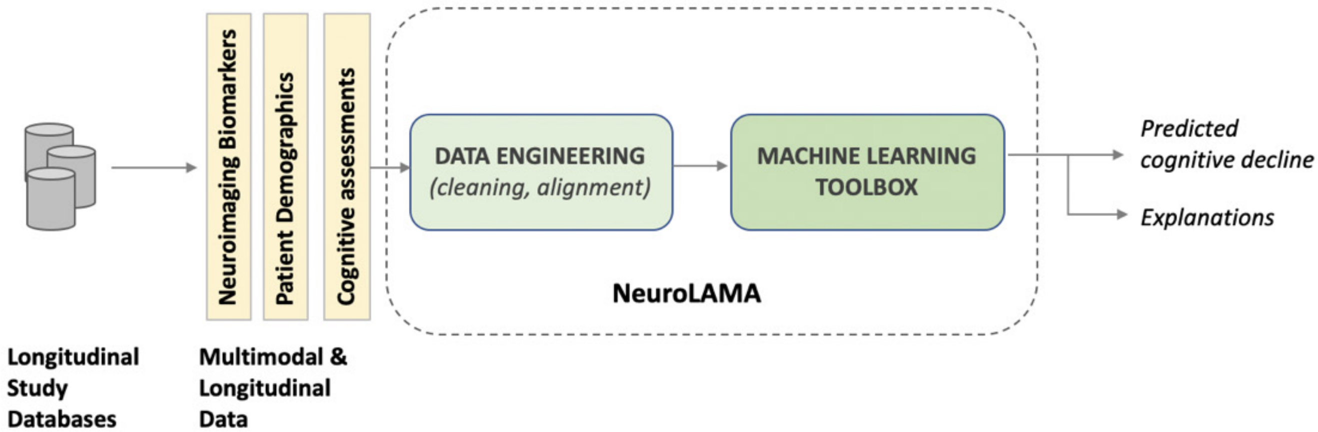

Figure 5: Schematic for NeuroLAMA: Neuroscience Longitudinal and Multimodal Analysis System. NeuroLAMA integrates imaging, cognitive, and non-imaging data for predictive modeling and longitudinal analysis. The system incorporates preprocessing, model training, and explainability modules.

it suggests that accurate prediction of cognitive decline is possible using such readily accessible factors. These findings support the need for further investigation into a broader range of such accessible variables. If validated, it could significantly impact the development of scalable and resource-efficient screening tools for clinical and community settings.

Despite the promising results, some limitations should be noted. While the models perform well on the provided data, external validation with other cohorts is necessary to confirm the generalizability of the findings. Future studies should incorporate larger and more balanced datasets to mitigate the potential impact of small target class cardinality and limited sample sizes in certain predictor sets, ensuring more robust and reliable predictive performance.

From the longitudinal data analysis perspective, we have employed the subject age in year 2024 (versus age at time of each visit). Since all study data comes from ADNI, using age in 2024 provides a uniform reference point across participants, ensuring consistency in comparisons. The potential for deeper longitudinal analysis is much greater with such a dataset. Future work should emphasize building predictive models that leverage the temporal dimension to enhance understanding of disease progression over time. Longitudinal analysis would require models that are capable of predicting cognitive decline in future time states (years), given the prior trajectory of cognitive decline and the associated demographic variables. We could employ advanced machine learning approaches, such as recurrent-neural-networks (RNNs) and transformer models, to model the sequential aspects of cognitive decline and brain changes (9). These methods would be particularly effective in capturing time-dependent patterns that static models may overlook, offering a more dynamic prediction of future cognitive states. Further research can also investigate the integration of additional longitudinal variables that contribute to cognitive resilience and decline, such as physical activity patterns, social engagement, and comprehensive lifestyle measures. Including genetic information (e.g., APOE-ε4 genotype) and other biomarkers (e.g., tau and amyloid levels) could provide a more detailed picture of the interplay between genetic risk factors and observed brain and cognitive changes over time in AD. Moreover, we can use longitudinal data to analyze how changes in variables like SPARE_AD interact with shifts in cognitive reserve and other protective factors over multiple time points (10). Understanding these interactions will be essential for developing targeted interventions aimed at delaying the onset of cognitive decline and mitigating the impact of AD.

Our continued work will focus on developing both the machine-learning as well as the clinical analysis thrusts of the work. In machine learning, we are working on developing and providing more advanced analysis algorithms, specifically RNNs and transformers, in the Neuroscience-Longitudinal-and-Multimodal-Analysis (NeuroLAMA) system. Our long-term goal is that of uncovering specific predictors, including combinations thereof, towards cognitive decline and by leveraging heterogenous potential factors. Our aim with NeuroLAMA is to provide an open machine learning resource to the community, for analysis of prominent datasets of longitudinal neuroscience studies (such as ADNI). In clinical analysis, our focus will be on applying these longitudinal models to diverse populations to ensure findings are applicable across different racial, ethnic, and socio-economic groups. This would enhance the equity and generalizability of the predictive models and inform culturally tailored interventions that address the unique needs of various populations.

MATERIALS AND METHODS

Dataset

The data included was obtained from ADNI-4 (6).

Methodology

The methodology was structured around two key components: (i) data engineering, in which data from ADNI was prepared for machine learning analyses specific to this study, and (ii) machine learning implementation, through which classification-based predictive and explainability analyses were conducted.

The CDRSB score from ADNI was employed as a measure of cognitive and functional impairment. As a composite score, CDRSB is derived from structured clinical interviews assessing domains such as memory, orientation, problem-solving, and daily activities; higher scores are associated with greater impairment (6). To monitor cognitive decline over time, CDRSBDIFF was calculated, representing the change in CDRSB at each assessment relative to the individual's baseline score (i.e., their first recorded score in the study). An assessment is defined as a clinical cognitive evaluation during which CDRSB is recorded. For this analysis, subjects with between 6 and 10 assessments were included, resulting in a cohort of 661 individuals.

SPARE_AD was included as a neuroimaging biomarker reflecting patterns of atrophy in regions vulnerable to Alzheimer's disease, including the medial temporal lobe, posterior cingulate, and precuneus. This score is applicable to both healthy controls and individuals with AD, with higher values indicating greater resemblance to disease-associated atrophy. SPARE_AD has previously been shown to correlate with cognitive decline and disease progression.

Data Engineering

Data engineering involved extracting and integrating data from multiple ADNI tables that included clinical, demographic, neuroimaging, physical activity, and cognitive decline variables. These tables were merged into a single consolidated table with the "RID" (subject identifier) as the unique key to join records across tables. Finally, this integrated table was further filtered to only retain subjects who had at least six and at most ten recorded assessments. The data engineering functionality was implemented in Python 3.9 and using the Pandas data processing library (12, 13).

Machine Learning Implementation

NeuroLAMA is an open and extensible machine-learning system that we have designed and developed for such analyses (**Figure 5**) (14).

The Scikit-Learn framework was used for the implementation of the various classification based prediction algorithms that we evaluated, of which the best performing ones are reported in the results (15). The machine-learning code for the analysis reported in this study is available at: https://github.com/datasciencey/neurolama.

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