Towards Multimodal Longitudinal Analysis for Predicting Cognitive Decline

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ABSTRACT

Understanding and predicting cognitive decline in Alzheimer's disease (AD) is crucial for timely intervention and management. While neuroimaging biomarkers and clinical assessments are valuable individually, their combined predictive power and interaction with demographic and cognitive variables remain underexplored. This 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. Our results show that while imaging biomarkers alone offer moderate predictive capabilities, including key clinical assessment and demographic variables in conjunction with imaging biomarkers significantly improves the model performance. Further, we achieve high accuracy for predicting cognitive decline and diagnostic group even with excluding the imaging derived variables. The analysis highlights the importance of non-imaging derived factors in predicting cognitive decline. This 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. We also introduce NeuroLAMA - an open and extensible data engineering and machine-learning system, to support the continued investigation by the community.

INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders, 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

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

evaluating the efficacy of therapeutic interventions. Biomarkers derived from neuroimaging, such as the “Spatial Pattern of Abnormality for Recognition of Early Alzheimer's Disease” (**SPARE_AD,** from the ADNI dataset that we describe shortly), have been established as reliable indicators of brain atrophy associated with Alzheimer’s disease (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. 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, understanding their predictive relationship and how they interact with other factors such as demographic and cognitive variables remains an area 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, a 2024 study 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). Similarly, research published in 2023 found that multi-modal neuroimaging signatures, when combined with clinical data, effectively predict cognitive decline in individuals with multiple sclerosis, emphasizing the need to consider various factors in predictive modeling (5). These findings suggest that while neuroimaging and clinical assessments are valuable individually, their predictive power is significantly enhanced when analyzed in conjunction with demographic and cognitive variables.

This study investigates the predictive power of different combinations of clinical assessment and demographic variables, such as age, education length, Mini-Mental-State-Examination (MMSE) score etc. employed in conjunction with neuroimaging biomarkers, for changes in cognitive performance. Additionally, we also assessed the predictive power of using *only* clinical assessment and demographic variables for cognitive decline prediction.

Dataset and Analysis Cohort The source of our data ADNI - the Alzheimer's Disease Neuroimaging Initiative is 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 Alzheimer's disease (AD) (6). The study collects data from a wide range of participants, including cognitively normal older adults, individuals with 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 includes neuroimaging scans (such as MRI and PET), cognitive assessments, genetic information, and clinical evaluations.

We employ the ADNI Clinical Dementia Rating Sum of Boxes **CDRSB score** as the quantitative measure of cognitive and functional impairment in individuals. The CDSRB score is further used to calculate the derived variable **'CDRSBDIFF'** which is the change in CDSRB (at that assessment) over the *first assessment* in the study data (our baseline). For this analysis we selected individuals that had **at least 6 and at most 10** assessments over the years with recorded CDRSB scores, resulting in a cohort of 661 subjects. Table 1 provides the basic age and gender distribution of these subjects, as well as the statistical distribution of CDSRB and CDRSBDIFF in the data analyzed.

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

Table 1: Demographic and cognitive impairment distribution of study cohort

The primary hypothesis of this study is that combining neuroimaging biomarkers with demographic and clinical assessment factors enhances the prediction of changes in cognitive decline. This is validated by our results. We further demonstrate that non-imaging variables alone can provide cost-effective and meaningful predictions. The key takeaways include 1. While imaging biomarkers alone offer moderate predictive capabilities, including key clinical assessment and demographic factors significantly improves the model performance. 2. It is possible to predict cognitive decline with high accuracy, with exclusively non-imaging derived factors.

MATERIALS AND METHODS

Our methodology involved the two key components of (i) **Data Engineering:** which is preparing the data from ADNI for our specific machine learning analyses, and (ii) **Machine Learning Implementation:** for conducting the classification based predictive and explainability analyses reported.

Data Engineering This 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, and as mentioned earlier, we further filtered this integrated table to only retain subjects who had at least six and at most ten recorded assessments. The data engineering functionality was implemented in Python (12) and using the Pandas data processing library (13).

Machine Learning Implementation Figure 4 provides a schematic architecture of the first version of the NeuroLAMA system (Neuro Longitudinal and Multimodal Analysis), which is an open and extensible machine-learning system we have developed, for such analyses.

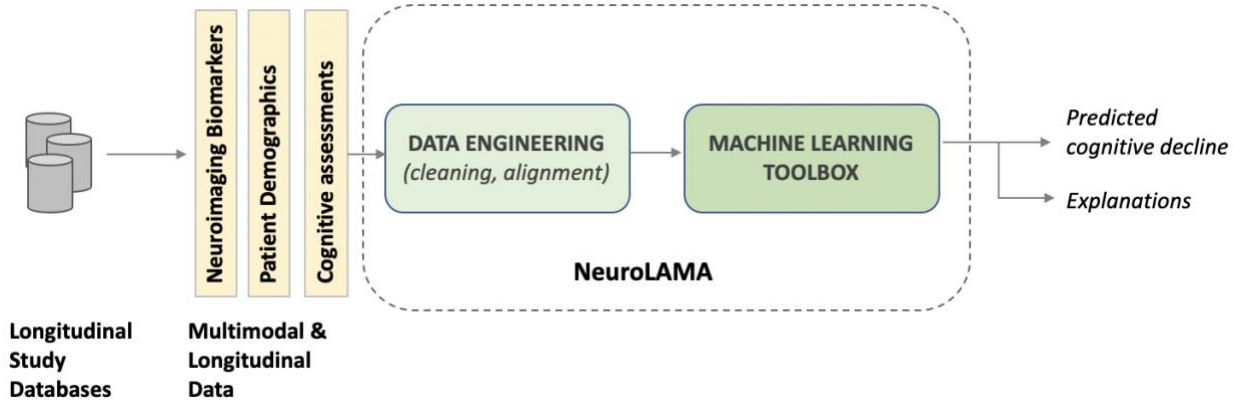


Figure 4: The NeuroLAMA System for Multimodal Longitudinal Predictive Analysis

We utilized the Scikit-Learn framework (14) for the implementation of the various classification based prediction algorithms that we evaluated, of which the best performing ones are reported in the results. 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 over prominent datasets of longitudinal Neuroscience studies (such as ADNI). It is available at www.neurolama.org.

RESULTS

We first analyzed the association between SPARE_AD and CDRSBDIFF by employing simple Linear Regression. Figure 1 provides the plots and metrics for Linear Regression based prediction of CDRSBDIFF with SPARE_AD (left) as well as the reverse correlation (predicting SPARE_AD with CDRSBDIFF). The predictive accuracy of CDRSBDIFF with SPARE_AD, and conversely (predicting SPARE_AD with CDRSBDIFF) is low (R^2 values of 0.19 and 0.21 respectively in

Figure 1). While it may not be entirely surprising, the low correlation remains significant to quantify given that SPARE_AD is a highly synthesized variable specifically designed to capture Alzheimer's-related brain atrophy (2). This finding underscores the motivation to explore other types of variables for improving prediction accuracy.

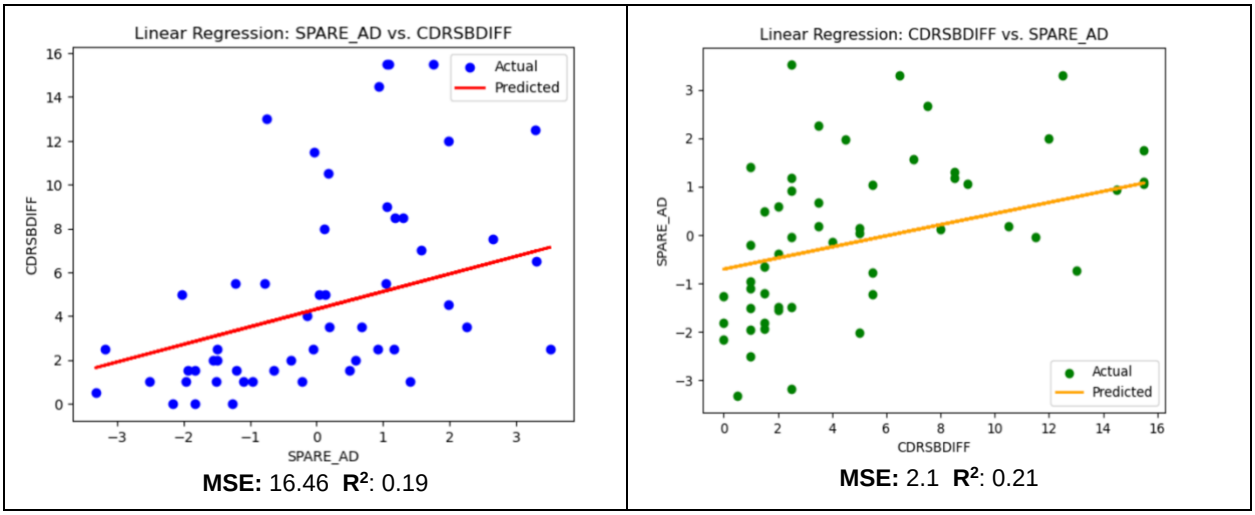


Figure 1: Association of SPARE_AD with CDRSBDIFF

The left column of Table 2 provides the 5 additional variables we considered, of which the **AMASAVG** is also a variable derived from imaging markers, but the others are demographic or clinical assessment related factors. The right column provides the 5 different combinations of variables that we employed, for predicting CDRSBDIFF. Figure 2 provides the results for sets 1-4, combinations that include SPARE_AD, and (in one case) AMASAVG as well. We provide the predictive accuracy as well as the feature importance. The results are provided for the Random-Forest Regression classifier, which emerged as the best performing model over Linear-Regression and Decision Tree, that were also evaluated.

Variables Sets	
AGE_2024: *Subject age in years in 2024* **MMSCORE:** *Mini-mental-state-examination score* **AMASAVG:** *Average of anterior medial temporal lobe atrophy scores* **PTEDUCAT:** *Number of years of formal education* **PEDAVG:** *Average physical activity (derived from self-reported questionnaires)*	1. {SPARE_AD, AGE_2024, PTEDUCAT} 2. {SPARE_AD, MMSCORE, AGE_2024, PTEDUCAT} 3. {AMASAVG, SPARE_AD, MMSCORE, AGE_2024, PTEDUCAT} 4. {PEDAVG, SPARE_AD, MMSCORE, AGE_2024, PTEDUCAT} 5. {PEDAVG, MMSCORE, AGE_2024, PTEDUCAT}

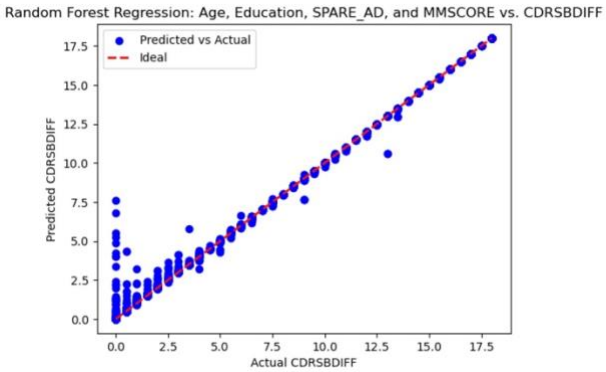
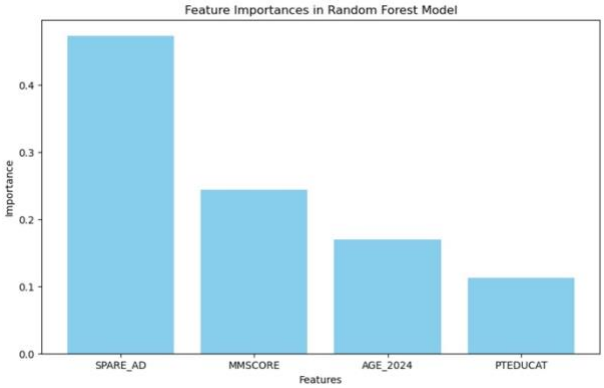
Table 2: Variables sets for predicting CDRSBDIFF

The results demonstrate a dramatic improvement in CDRSBDIFF prediction accuracy for all 4 variable sets, with perfect (or near perfect) R^2 scores of 0.99 or 1.0 (Figure 2). This is indicative of the merit of considering such clinical assessment related or demographic factors, in conjunction with imaging biomarkers for cognitive decline prediction. Further, there are several interesting observations from the associated feature importance results, namely:

(i) SPARE_AD, with a feature importance of 0.47 is the dominant feature in variable sets 1-2 above. Note that the other variables such as MMSCORE, AGE_2024, and PTEDUCAT also have substantial predictive contribution in sets 1-2.

(ii) AMASAVG (employed in variable set 3) with a feature importance of 0.36 emerges ahead of SPARE_AD, demonstrating the predictive power of another imaging biomarker. We also note the relative significant decline in the feature importance of AGE_2024 and MMSCORE in set 3.

(iii) In set 4, where we include PEDAVG (physical activity) we see PTEDUCAT emerge as the dominant variable, with a feature importance of 0.74 that is significantly more than that of SPARE_AD with 0.03. The emergence of PTEDUCAT as the most predictive feature in the presence of PEDAVG highlights the *context-dependent* nature of feature importance. This shift emphasizes how the inclusion of lifestyle factors, such as physical activity, can elevate the predictive contributions of non-imaging variables, suggesting that the interaction between variables can significantly reshape predictive hierarchies.

Predictive accuracy	**Feature Importance**
$y\ axis$: Predicted CDRSBDIFF $x\ axis$: Actual CDRSBDIFF	$y\ axis$: Feature Importance $x\ axis$: Features
 **MSE:** 0.19 **R^2**: 0.99	 **SPARE_AD:**0.47 **MMSCORE:**0.24 **AGE_2024**: 0.17 **PTEDUCAT:** 0.11

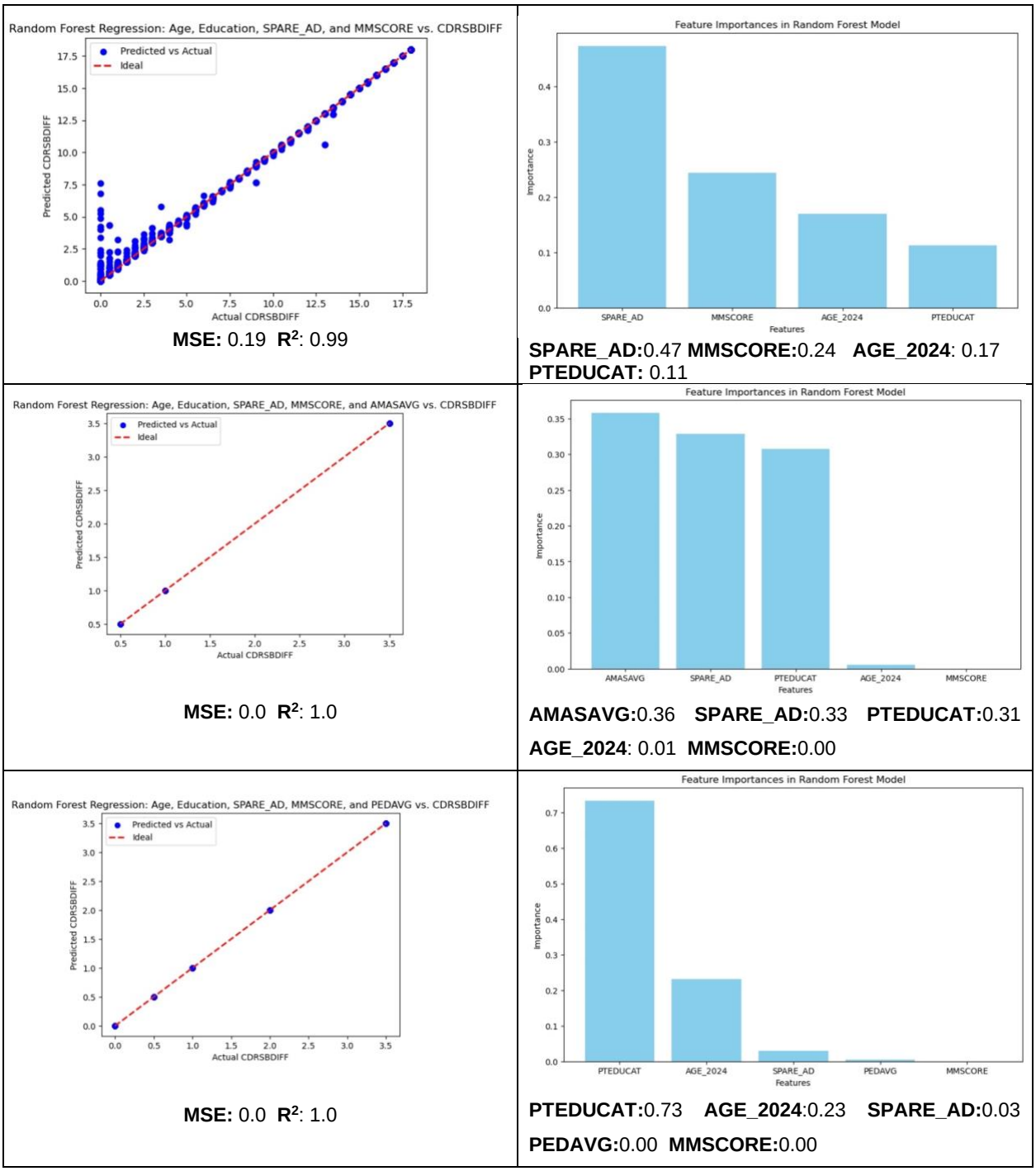


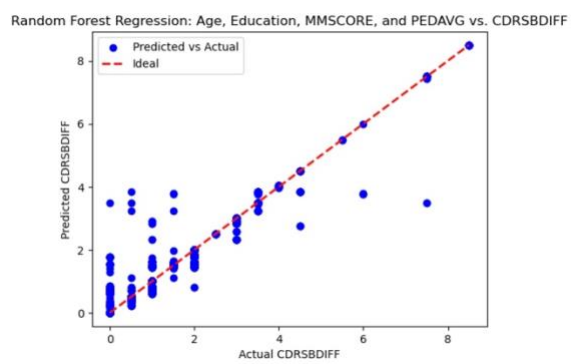
Figure 2: Investigating different variable combinations for predicting CDRSBDIFF

Our final analysis is on variable set 5 with only non-imaging derived variables. We evaluated both Random Forest Regression as well as XGBoost classifiers and provide the results in Figure 3 for Random Forest Regression (that proved superior). There are interesting observations from this result as well, namely:

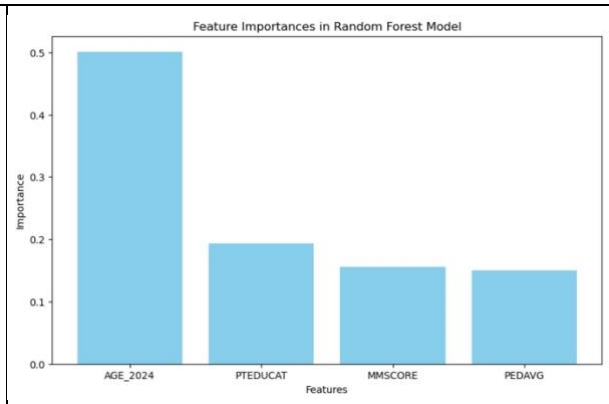
(i) We see a very high predictive accuracy with these non-imaging variables, with an overall R^2 score of 0.94 (Figure 3 left-column).

(ii) While age is expected to be a dominant factor, the importance of education, global cognitive function (with MMSCORE), and physical activity is significant as well (the feature importance of 0.19, 0.16 and 0.15 for PTEDUCAT, MMSCORE and PEDAVG respectively in Figure 3 right-column).

We further employed the classifier to predict the diagnostic group of the individual i.e., whether the individual is classified as AD/CN/MCI (Alzheimer's Disease/Cognitively Normal/Mild Cognitive Impairment) based upon the value of CDRSB (2). The results demonstrate a high accuracy for all three groups, with Precision as well as Recall values of 0.90 or above (Table 3).



MSE: 0.0 9 **R^2**: 0.94



AGE_2024:0.50 **PTEDUCAT:**0.19 **MMSCORE:**0.16 **PEDAVG:**0.15

Figure 3: Predicting CDRSBDIFF with non-imaging variables

Category	Precision	Recall	F1-score
AD	0.90	0.92	0.91
CN	0.98	0.92	0.95
MCI	0.92	0.97	0.95

AD=Alzheimer's Disease CN=Cognitively Normal MCI=Mild Cognitive Impairment

Table 3: Predicting diagnostic group with non-imaging variables

Overall, the results of this final analysis demonstrate impressive predictive accuracy despite not including neuroimaging data such as SPARE_AD or AMASAVG. Achieving high accuracy using only these demographic and cognitive assessment variables highlights the potential for more accessible and cost-effective prediction models.

DISCUSSION

The findings from this study highlight the importance of integrating neuroimaging biomarkers, cognitive scores, and demographic variables to predict changes in cognitive function, as measured by CDRSBDIFF. The analyses demonstrate that SPARE_AD, a robust imaging biomarker reflecting Alzheimer's-related brain atrophy, is limited as predictor of cognitive decline. However, the predictive power is enhanced when additional variables, such as age, education level, and MMSCORE, are included. This multi-dimensional approach aligns with the understanding that cognitive decline is influenced by an interplay of structural brain changes, cognitive reserve, and demographic factors.

The results with non-imaging variables illustrate that even without neuroimaging biomarkers, accurate prediction of cognitive status across AD, MCI, and CN groups is possible using age, education, cognitive scores, and physical activity data. This finding holds significance for developing scalable, resource-efficient screening tools in clinical and community settings.

Despite the promising results, some limitations should be noted. While the models performed well on the provided data, external validation with other cohorts is necessary to confirm the generalizability of the findings. Additionally, potential confounding factors not included in the current analysis, such as *lifestyle attributes* (7) as well as *genetic predispositions* (such as APOE-ε4 status) (8), may further elucidate the complex relationships affecting cognitive decline.

Given the longitudinal nature of the data used in this study, future work should emphasize building predictive models that leverage the temporal dimension to enhance understanding of disease progression over time. This essentially implies that the models must be capable of predicting cognitive decline in future time states (years), given the decline trajectory history thus far and the associated demographic variables. Advanced machine learning approaches, such as *Recurrent-Neural-Networks* (RNNs) and *Transformer Models* (9), could be employed to model the *sequential* aspects of cognitive decline and brain changes. 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. Moreover, longitudinal data can be used to analyze how changes in variables like SPARE_AD interact with shifts in *cognitive reserve* (10) and other protective factors over multiple time points. Understanding these interactions will be essential for developing targeted interventions aimed at delaying the onset of cognitive decline and mitigating the impact of Alzheimer's disease.

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 NeuroLAMA system. 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.

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