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Comparison of Dimensionality Reduction Methods for Multimodal Classification of Early Stages of Alzheimer's Disease

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***Abstract*—Early diagnosis of Alzheimer's Disease (AD) is challenging due to its progressive nature. This study proposes a comprehensive comparison of four classifiers combined with different dimensionality reduction methods to discriminate normal controls (CN) from pre-mild cognitive impairment (pMCI) and early MCI (EMCI) using multimodal datasets including MRIs, PETs, SUVr, clinician amyloid visual reads, and subjects demographics. The most robust classifier for CN vs. MCI is the Mutual Information Best Percentile - Bagging Classifier combination, with 73.91% accuracy and a 4.82% standard deviation (SD). The best performance of 65.23% (11.84% SD) accuracy for CN vs. EMCI was DTC with ANOVA. In comparing CN with pMCI the best classification accuracy was ANOVA-DTC 51.06% (14.19% SD). An accuracy of 56.34% (10.67% SD) was achieved by bagging with ANOVA for multiclass classification of CN vs. pMCI vs. EMCI.**

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***Index Terms*—Alzheimer's Disease, Machine Learning, Classification**

I. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease among the elderly population. The most at-risk population for Alzheimer's dementia is the baby boomer generation (1946-1964), where approximately 61% have already reached the age of 65. In 2019 it was estimated that 5.6 million Americans over the age of 65 live with AD and that the number of affected individuals may reach a staggering 13.8 million by 2050 [1]. AD forecasts prompted a demand for research on early disease diagnosis and the development of more sophisticated methods, such as Artificial Intelligence (AI) and Machine Learning (ML) applications [2]–[6].

Recent developments in the field of AI applications in AD have demonstrated its ability to classify and predict different stages of AD using large amounts of multimodal datasets [7]. Despite these advances and new insights, early detection of

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the disease remains one of the top challenges faced in AD research.

Image processing techniques and related neuroimaging modalities are used in many recent studies diagnostic protocols such as sophisticated tumor and lesion detection algorithms to yield a higher efficiency and accuracy. Therefore, when diagnosing AD, ML methods have been adapted to include neuroimaging data, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) [8]. However, one of the challenges faced when using large scale multimodal data for ML algorithms is feature optimization to maximize the classifier's efficiency.

Most AD studies consider only three groups (CN, MCI, and AD), and some perform binary classification for the EMCI and LMCI subcategories. S. Singh *et. al.* propose a classification model for Fluorodeoxyglucose (FDG)-PET through a feed-forward deep neural network, which uses its analysis probabilistic principal components analysis (PPCA) applied on max-pooled FDG-PET data altogether with functional activity questionnaire (FAQ), demographic information (age, gender, APOE e1, and e2 alleles). Using this deep neural network with 10-fold cross-validation, they achieved an f1 accuracy of 72% for CN vs. EMCI, with 77.42% precision and 67.29% for recall. In the classification between CN and MCI, they get an f1 score of 78.30%, precision of 82.14%, and recall of 74.79%. [9].

D. Yao, V.D. Calhoun, Z. Fu, Y. Du, and J. Sui *et. al.* introduced a feature selection algorithm based on relative importance with a hierarchical grouping process for classifying four groups: CN, AD, MCI, and MCI converting to AD (cMCI). The data used in this study is comprised of measurements from MRI images (Freesurfer 5.3) and demographic and clinical information. The performance of the selected model reaches 54.38% for 4-class classification [10].

B. Jie, M. Liu, and D. Shen *et. al.* proposed a framework where the most important temporal and spatial variability features from dynamic connectivity networks (DCN) were extracted. A multi-kernel SVM classification was then performed for the NC, EMCI, and LMCI groups. The features were selected from volumetric measurements taken from resting-state functional MRI (rs-fMRI), clinical, and demographic information (MMSE, age, and gender). They acheived an accuracy of 66%, with recall 71.4% for classifying NC and EMCI [11].

Based on the efforts and results from past research, this study compares the use of different dimensionality reduction (DR) methods for multimodal feature spaces with four (4) classifiers trained for early AD detection.

The remainder of this article is divided into the following sections: Section II describes the data, proposed framework, and methods. Section III consists of the different approaches for dimensionality reduction (DR) and their respective results. Finally, Section IV provides concluding remarks and possible future research directions.

II. Methods

A. Data

All data used in this work was acquired from participants of the 1Florida Alzheimer's Disease Research Center (1F-ADRC) study. 1F-ADRC collects and maintains MRI, PET, cerebrospinal fluid (CSF), and neuropsychological tests for the diagnosis and prognosis of Alzheimer's disease [12]–[15]. The 1F-ADRC neuroimaging data was processed and accessed via the Neuroimaging Web Services Interface (NWSI) [16]. A total of 482 subjects between the ages of 49 and 106 were separated into different clinical cognitive diagnostic groups: Cognitive Normal (CN), Pre Mild Cognitive Impairment (pMCI) Clinical, Pre MCI Neuropsychological (pNP), Early MCI (EMCI), Late MCI (LMCI), and AD.

The 1F-ADRC data was filtered to only include subjects with both an MRI and a PET scan available. The PET scans were registered with their respective MRI image using the closest PET exam date within a 6 month period to ensure congruity of the brain at both timepoints. Out of the 232 matched records, 44 used Florbetapir (Amyvid/AV45) radiotracers for PET imaging (10: CN; 9: pMCI; 1: pNP; 13: EMCI; 5: LMCI, 6: AD) and 188 used Florbetaben (Neuraceq/FBB) radiopharmaceutical compound (29: CN; 16: pMCI; 14: pNP; 60: EMCI; 34: LMCI, 35: AD).

Since this study focuses on the classification of the early stages of Alzheimer's Disease, only the following groups were considered: CN, PreMCI (as a combination of pMCI and pNP), and EMCI.

The classifications used in this study consists of three binary classifiers and one multiclass classifier as follows: 1) CN vs. EMCI (29/60); 2) CN vs. MCI, where MCI is combination of PreMCI & EMCI (29/90) ; 3) CN vs. PreMCI (29/30); 4) CN vs. PreMCI vs. EMCI (29/30/60).

1F-ADRC includes PET visual read, where clinicians analyzed amyloid PET images and classified them as amyloid positive (A$\beta+$) or negative (A$\beta-$) [17]. In the AV45 records, 43.18% (19/44) were classified as amyloid positive, 56.82% (25/44) negative. Moreover, 62.23% (117/188) of the FBB records were classified as positives, and 37.77% (71/188) negatives.

Table I details the demographic and clinical data.

TABLE I
Demographic and Clinical Data

Data	Cognitive Diagnostic group			
	CN(n=29)	**EMCI**(n=60)	**PreMCI**(n=30)	**MCI**(n=90)
Gender (F|M)	8 | 21	28 | 32	9 | 21	37 | 53
VR (+|-)	2 | 27	23 | 37	3 | 27	26 | 64
Age[a]	73.17(5.49)	76.40(7.25)	74.87(7.00)	75.89(7.16)
Education[a]	16.59(2.98)	14.97(3.54)	16.20(2.83)	15.38(3.36)

[a]Values represented as mean(sd)

B. Proposed Network

Figure 1 shows the proposed framework for this study. Once the image data (MRI and PET scans) are collected and

processed, the volumetric (Vol) and cortical thickness (CoTh) are extracted from the MRI, and the Standard Uptake Value ratio (SUVr) is calculated from the PET scan. These measurements are later combined with the demographic variables and visual reads (VR) for amyloid plaque. Machine learning classifiers are then used to discriminate early AD diagnoses over a dimensionally reduced feature space.

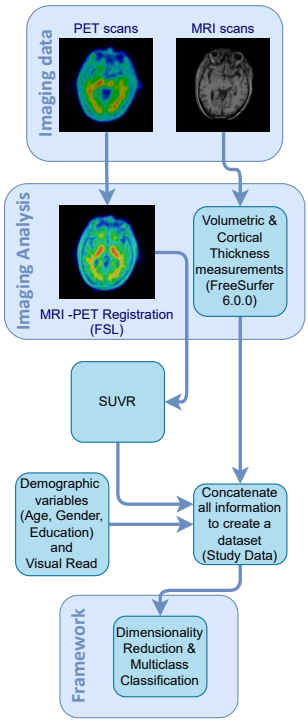

Fig. 1. General classification flowchart of the proposed framework.

C. Image Processing

Image processing for this study consists of the following stages: 1) pre-processing done during the capture of the medical images, 2) post-processing done on the T1 sequenced images by FreeSurfer (version 6.0) [18] to extract the volumetric and cortical thickness measurements of the different brain regions, 3) normalization of these values by the estimated Total Intracranial Volume (ICV), 4) processing and co-registration of the amyloid PET scans with their matched T1-weighted MRI scans using the FMRIB Software Library (FSL) toolbox [19], and 5) calculating the standardized uptake value ratio (SUVr) from the co-registered PET and T1-MRI scans.

D. Dimensionality Reduction (DR) and Classifiers

1) *Dimensionality Reduction:* Several methods for feature selection and feature extraction were implemented.
   a) *Original*: original data sample with no DR method.
   b) *VarianceThresholdDR* (Var): selects features with training-set variance greater than threshold (0.001).
   c) *CorrelationFS* (Corr): performs feature selection based on Pearson correlation greater than 65%.
   d) *MIKBest* (MI-KB): Mutual information (MI) with selection of the K (30) features with highest scores based on univariate statistical tests.
   e) *MIBestPercentile* (MI-BP): keeps features based on given percentile (16%).
   f) *FeatureImportance* (FI): executes the selection based on the evaluation of the features importance, in this framework the 30 first are selected.
   g) *ANOVA* (Analysis of Variance): selects the top 30 features with highest scores based ANOVA F-value.
   h) *LassoFS* (LASSO): selects the features that have least absolute shrinkage and selection operator (LASSO) different than 0 with $\alpha = 0.1$.
   i) *PCA* (PCA): feature extraction based on the Principal Component Analysis (PCA) with a cumulative explained variance ratio of 95%.
   j) *SVDDR* (SVD): linear DR technique which uses truncated singular value decomposition (SVD).
   k) *LDADR* (LDA): uses Bayes' rule and Gaussian density to perform Linear Discriminant Analysis (LDA) intending to get the most discriminative features.
2) *Supervised Classifiers:* four methods of classification were investigated.
   a) K-Nearest Neighbors Classifier (KNC): a non- parametric classifier where the voting system is based on the distance of the data points to fit or not a certain class.
   b) Decision Tree Classifier (DTC): a non- parametric supervised learned method. The voting process is given by simple decision rules from the features.
   c) Bagging Classifier (BAGC): fits one classifier per class, One-vs-the-rest (OvR) or one-vs-all (OvA), using bagging method which is performs DTC on random subset of the given features and vote to form final classification.
   d) Linear Support Vector Classifier (LSVC): also fits OvR, however uses a SVC with a linear kernel. This classifier is more flexible in choices of loss functions than SVC.

E. Performance Metrics:

In this study, all performance metrics follow as shown in the subsequent equations. The main metric used to evaluate performance is accuracy, which is a comparison of true labels with the predicted ones divided by the total number of labels in the sample.

1) accuracy (acc): y is the true value, $\hat{y}$ is the predicted value, and n is the number of samples.

$$acc(y, \hat{y}) = \frac{\sum_{i=0}^{n-1} 1(y = \hat{y})}{n} \tag{1}$$

2) precision (prec): TP is the number of true positives, and FP is the number of false positives.

$$prec = \frac{TP}{(TP + FP)} \tag{2}$$

3) recall (rec): TP is the number of true positives, and FN is the number of false negatives.

$$rec = \frac{TP}{(TP + FN)} \tag{3}$$

4) F1:

$$F1 = \frac{2 \times (prec \times rec)}{(prec + rec)} \tag{4}$$

The procedural flowchart of the proposed framework is shown in Fig. 2. The following steps were performed for each dataset of the framework: 1) implementation of stratified k-fold (k = 5) cross-validation to separate the training and testing samples; 2) dimensionality reduction; 3) classification; 4) extraction of the performance metrics for each DR-Classifier combination for each k-fold; and 5) averaging out of the performance metrics from the k-folds.

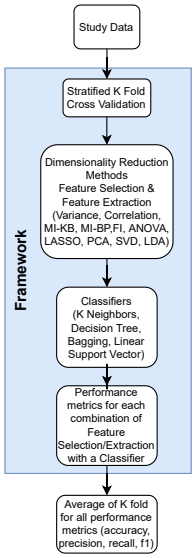

Fig. 2. Procedural flowchart of the proposed framework.

III. Results

The results of this study use the following performance metrics: accuracy, standard deviation, precision, recall, and f1 scores. Each performance metric is calculated using an average (avg) of the five (5) fold cross-validation results.

A. CN vs. EMCI (Binary classification)

The best accuracy of 64.04% for CN vs. EMCI was achieved with a combination of K-Nearest Neighbors as the classifier, and FI as the dimensionality reduction method. For the Bagging Classifier, the best accuracy was 65.16% when using SVD for DR. Furthermore, LSVC with PCA achieved 64.12%. Fig. 3 shows performance metrics for the different classifiers and their combination with different DRs methods. Table II consists of the accuracies and their standard deviation for each DR-Classifier combination. It is worth noting that the highest accuracy value of 65.23% with 11.84% of standard deviation was achieved using the ANOVA-DTC combination.

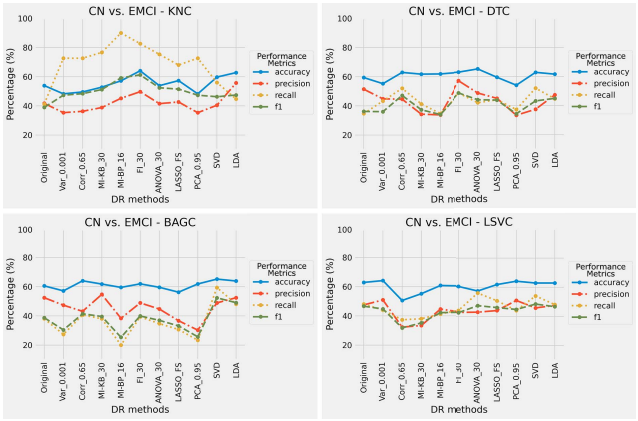

Fig. 3. Performance metrics of CN vs. EMCI

TABLE II
ACCURACY FOR CN VS. EMCI

DR methods	Classifiers			
	KNC(%)	DTC(%)	BAGC(%)	LSVC(%)
Original	53.92(16.85)	59.41(14.42)	60.52(16.28)	62.88(19.97)
Var_0.001	48.24(7.87)	55.23(16.27)	57.12(17.63)	64.12(19.73)
Corr_0.65	49.54(12.57)	62.94(8.28)	63.99(6.71)	50.52(10.84)
MI-KB_30	52.81(6.21)	61.76(12.76)	61.76(14.98)	55.16(13.80)
MI-BP_16	57.19(19.02)	61.90(9.55)	59.48(17.06)	60.78(18.61)
FI_30	64.05(19.45)	63.01(22.28)	61.90(16.62)	60.52(18.08)
ANOVA_30	53.86(17.54)	65.23(11.84)	59.54(20.56)	57.39(20.82)
LASSO_FS	57.32(19.41)	59.48(22.86)	56.21(23.62)	61.83(17.20)
PCA_0.95	48.24(7.87)	54.05(10.88)	61.83(4.24)	64.12(19.73)
SVD	59.74(12.22)	62.88(6.61)	65.16(6.06)	62.88(17.05)
LDA	62.81(21.64)	61.63(17.43)	63.86(20.45)	62.88(19.97)

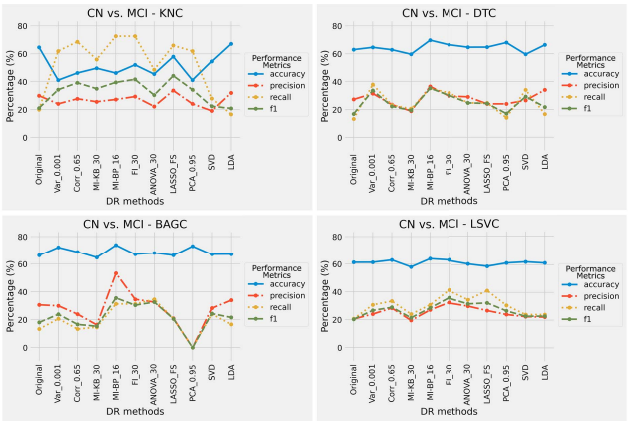

Fig. 4. Performance metrics of CN vs. MCI

TABLE III
ACCURACY FOR CN VS. MCI

DR methods	Classifiers			
	KNC(%)	DTC(%)	BAGC(%)	LSVC(%)
Original	64.71(11.22)	63.04(13.56)	66.38(12.17)	61.27(9.01)
Var_0.001	41.16(13.22)	64.67(5.82)	72.28(5.49)	61.30(5.76)
Corr_0.65	46.30(16.73)	62.97(7.22)	68.88(5.79)	62.93(11.98)
MI-KB_30	49.71(10.48)	59.75(7.71)	64.78(6.59)	57.93(5.57)
MI-BP_16	46.27(6.99)	69.82(7.76)	73.91(4.82)	63.88(1.95)
FI_30	52.14(7.26)	66.49(6.83)	67.17(5.84)	63.04(15.64)
ANOVA_30	45.51(13.66)	64.71(6.92)	68.12(3.24)	60.58(14.41)
LASSO_FS	58.01(14.03)	64.75(7.34)	66.38(10.64)	58.88(12.44)
PCA_0.95	41.16(13.22)	68.04(3.94)	73.15(4.48)	61.30(5.76)
SVD	54.64(7.87)	59.60(7.99)	67.17(7.76)	62.10(8.86)
LDA	67.21(10.83)	66.38(14.14)	67.21(12.68)	61.27(9.01)

TABLE IV
ACCURACY FOR CN VS. PREMCI

DR methods	Classifiers			
	KNC(%)	DTC(%)	BAGC(%)	LSVC(%)
Original	39.24(15.00)	50.91(6.23)	47.73(14.01)	40.61(6.35)
Var_0.001	35.30(10.23)	42.27(12.76)	45.91(16.71)	33.94(10.30)
Corr_0.65	37.12(8.83)	49.09(10.41)	43.79(18.47)	38.94(14.95)
MI-KB_30	47.12(15.50)	41.06(16.63)	40.76(11.14)	40.76(15.11)
MI-BP_16	38.79(10.53)	44.09(9.11)	43.94(17.69)	30.15(19.87)
FI_30	42.42(6.13)	47.27(8.48)	49.09(11.96)	45.76(12.50)
ANOVA_30	33.79(16.41)	51.06(14.19)	30.45(10.97)	47.27(16.74)
LASSO_FS	38.94(3.89)	37.73(16.05)	37.27(4.20)	37.27(4.20)
PCA_0.95	38.79(6.44)	47.42(12.37)	35.61(3.63)	35.45(13.31)
SVD	36.97(12.04)	49.09(10.41)	34.09(11.08)	25.30(11.53)
LDA	39.24(15.00)	40.91(18.79)	39.39(22.27)	38.94(7.06)

B. CN vs. MCI (Binary classification)

Fig. 4 depicts the performance metrics for the analysis of the comparison between CN and MCI (PreMCI and EMCI). The classification using KNC results in the highest accuracy of 67.21% combined with LDA as the dimensionality reduction method. The DTC reports an accuracy of 69.82% when using MI-BP. For LSVC, the best accuracy is obtained using MI-BP (63.88%). However, the best accuracy was achieved by the MI-BP-BAGC combination yielding a score of 73.91% (SD = 4.82%) as shown in in Table III.

C. CN vs. PreMCI (Binary classification)

The best DR method for KNC was MI-KB, scoring 47.12% accuracy as shown in Fig. 5. The Decision Tree Classifier (DTC) achieved the best accuracy score from all the classifiers with ANOVA feature selection with an accuracy of 51.06% (14.19% SD), as shown in Table IV. Moreover, the FI-BAGC reports an accuracy of 49.09% and ANOVA-LSVC a score of 47.27% accuracy.

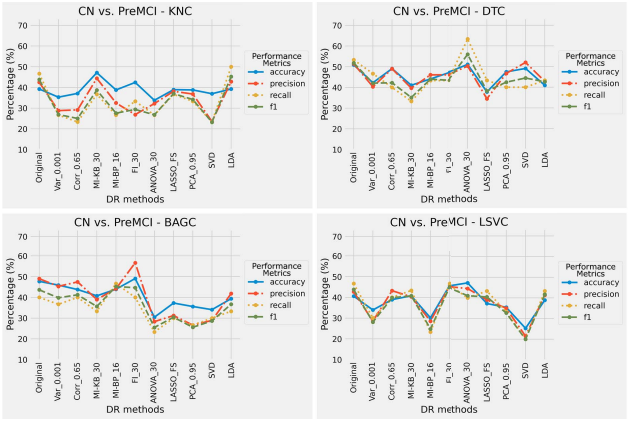

Fig. 5. Performance metrics of CN vs. PreMCI

D. CN vs. PreMCI vs. EMCI (Multiclass classification)

In the multiclass classification, the best accuracy score of all classifiers was achieved by the combination of ANOVA and BAGC with an Accuracy of 56.34% (SD = 10.67%), as shown in Table V. Fig. 6 illustrates all the performance metrics for all classifiers. The best accuracy of 47.9% for KNC was achieved with LDA dimensionality reduction. The combination of SVD and DTC resulted in an accuracy of 47.07%. Lastly, LSVC achieved its best scores when combined with LDA (45.50%).

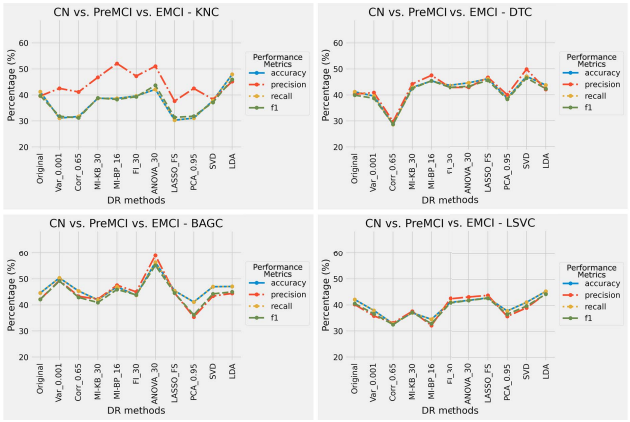

Fig. 6. Performance metrics of CN vs. PreMCI vs. EMCI

TABLE V
ACCURACY FOR CN VS. PREMCI VS. EMCI

DR methods	Classifiers			
	KNC(%)	DTC(%)	BAGC(%)	LSVC(%)
Original	41.23(7.83)	41.20(8.10)	44.57(10.98)	42.07(13.03)
Var_0.001	31.09(4.67)	39.57(9.06)	50.36(15.08)	37.86(10.00)
Corr_0.65	31.74(13.86)	28.62(12.45)	45.33(17.62)	32.79(11.23)
MI-KB_30	38.70(8.24)	42.90(11.74)	41.96(12.96)	36.96(5.25)
MI-BP_16	38.66(11.56)	45.36(10.68)	46.96(15.12)	34.49(5.72)
FI_30	39.60(12.52)	43.62(14.97)	43.70(13.34)	41.12(14.08)
ANOVA_30	42.14(9.23)	44.57(6.51)	56.34(10.67)	41.96(9.48)
LASSO_FS	30.33(9.39)	46.16(11.13)	45.43(13.86)	42.90(4.99)
PCA_0.95	31.09(4.67)	38.70(13.76)	41.12(10.95)	37.86(10.00)
SVD	37.83(7.83)	47.07(3.48)	46.99(6.97)	41.20(11.99)
LDA	47.90(12.33)	43.70(12.33)	47.07(14.55)	45.40(16.03)

IV. DISCUSSION

The proposed framework showcases the results of combining different binary/multiple classifications with different feature selection or extraction methods. From the classification's performances, it can be noticed that most classifiers achieve better results after performing at least some sort of dimensionality reduction of their input feature space.

In this study, most binary classifications have higher accuracies (CN vs. EMCI: 65.23%, CN vs. MCI: 73.91%) than the multiclass classifiers (56.34%). The binary comparison between CN vs. PreMCI obtained the lowest accuracy among all the experiments (51.06%). As an early stage in the progression of AD, PreMCI is challenging to delineate from CN. There is an absence of differences in volumetric and cortical thickness loss between these groups. The difficulty in differentiating these groups is because there is no significant difference between their demographic data, values in the measurement of volume, cortical thickness [20] and SUVr, and also requires good clinician judgment to identify a cognitive deterioration.

Future works should employ more sophisticated ML and/or Deep Learning (DL) models to tackle the complex problem of early diagnosis of Alzheimer's disease. These classifications results, especially when using the multiclass classification scenario, show that with the accuracy obtained, the ML models still contend with finding the most relevant neuroimaging features that can correlate best with the neuropsychological test scores, especially with those used for baseline diagnosis like the Mini Mental State Exam (MMSE) and the Clinical Dementia Rating (CDR). Clearly, the subtle changes expressed through neuroimaging via cortical thickness or volumetric measures of the different brain regions are not well revealed, especially in the early stages of AD. Perhaps in the initial stages, diagnosis should focus more on the disease prone areas and see how such areas correlate with SUVr measurements and the visual read for amyloid positivity, alongside with the different neuropsychological scores expressed through MMSE, CDR sum of boxes, the Montreal Cognitive Assessment (MoCA), the Loewenstein-Acevedo Scale of Semantic Interference and Learning (LASSI-L), the Rey Auditory Verbal Learning Test (RAVLT), and the Alzheimer's Disease Assessment Scale (ADAS), and other neuropsychological assessments. Determining the concordance between neuroimaging and neuropsychological measures that define the different disease states and to then capture what changes occur in its transitory stages.

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