Multimedia Tools and Applications
https://doi.org/10.1007/s11042-023-16413-7

Comparative analysis of different brain regions using machine learning for prediction of EMCI and LMCI stages of Alzheimer's disease

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Received: 22 August 2022 / Revised: 24 May 2023 / Accepted: 24 July 2023

Abstract
For early diagnosis of dementia and slowing the progression of Alzheimer's disease (AD), detection of Mild Cognitive Impairment (MCI), which is the first stage of AD, in the early or late stages is crucial. The progression from Early Mild Cognitive Impairment (EMCI) stage to Late Mild Cognitive Impairment (LMCI) stage is not reversible and means that the cognitive condition of the patient gets worse significantly. Therefore, distinguishing the stages of MCI is very important for treatment possibilities. In this paper, it has been aimed to specify which brain regions are affected higher during the progression from EMCI to LMCI. Detection of EMCI stage gives an important opportunity to control the progression and results of the disease. Unfortunately, it is a very challenging classification problem because the changes in the values of biomarkers are generally low during the EMCI and LMCI stages. As a result of this study, we detect and present a combination of features which are the most effective ones for distinguishing the stages of MCI. Atrophy values obtained by magnetic resonance imaging (MRI) are considered as the powerful diagnostic biomarkers for the detection of AD. In this work, atrophy values of 90 EMCI, 38 LMCI and 14 MCI patients have been used. Volume information of 13 different brain regions for each patient were obtained from the ADNI dataset. By using the results of classification algorithms, the mostly affected brain regions on transition process from EMCI to LMCI are determined. Moreover, the classification results indicate the combination of the most effective features. This feature combination can be used as a pattern in the researches about the stages of MCI. Focusing on the brain regions which have more impact on the progression of AD can provide more sensitive analysis of the stages of AD and make possible to control and smooth the effects of it.

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Published online: 03 August 2023

Keywords Alzheimer's Disease · EMCI · LMCI · Machine Learning

1 Introduction

Alzheimer's Disease (AD) is the most common neurodegenerative disorder. It constitutes approximately 60% of dementia diseases and incidence rate of AD is increasing rapidly due to the aging population [17]. Alzheimer's Disease International (ADI) has reported in World Alzheimer's Report (2018) that approximately 50 million people suffer from AD worldwide and this number will approximately double every 20 year [3]. It is expected that the number of patients will reach to 152 million till 2050. As a result of the prevalence of the disease, it is becoming more and more important and popular to develop new and effective methods for early diagnosis and treatment of AD.

The main indicator of AD is typically thought as forgetfulness, but even in the first stages of the disease, regression in many neurological functions (movement, speech etc.) begins to be seen simultaneously [50]. In the early stages of the disease, it is possible to observe a slight decrease in cognitive abilities, reasoning abilities and memory. These symptoms indicate that the patient is in mild cognitive impairment (MCI) stage of the disease. Once a person is diagnosed with MCI, the risk of developing Alzheimer's disease increases. Clinical and neuroimaging based researches have reported some important differences between MCI and healthy elderly normal control (NC) groups [36, 40]. As it is emphasized by many studies the grading of patients with MCI by revealing the different features of early MCI (EMCI) and late MCI (LMCI) groups is an important and challenging procedure [28, 41, 48].

Detection of AD is possible with deep analysis at every stage of the disease. For this purpose, many studies have focused on the detection of biomarkers using neuroimaging techniques [26, 29, 45, 46, 49, 51]. The analysis of brain MRIs indicate that the neuronal losses (atrophy) in the brain can be thought as a significant biomarker for AD [13, 34, 37, 42, 44]. Neuronal losses are observed with the volumetric reduction in different brain regions. By analyzing the structural and functional brain MR images with machine learning methods, information about the course of specific neurodegenerative diseases such as schizophrenia [9, 39], AD [5, 7, 8, 10, 20, 47] or obsessive–compulsive disorders [43] is obtained. Using this technique for diagnosis of AD, evaluation of disease progression and potential treatments gives an opportunity to clinicians for control outcomes at the first stages.

Several studies have investigated the effectiveness of focusing on localized MRI areas for classification purposes in distinguishing between EMCI and LMCI diagnostic groups [4, 14, 18, 25, 31, 52]. In our study, a data set of EMCI and LMCI groups was created by evaluating the atrophy values of 142 patients from the ADNI database. The features were extracted by examining the atrophy values of each group. These features consist of brain areas that are affected in the course of the disease, so that which region will be affected how much with the progression of the disease is analyzed. The 13 brain regions whose effect values were planned to be measured for AD analysis were semantically labeled to perform diagnostic classification.

Classification between AD, MCI, and NC groups using neuroimaging is an issue that has been explored in the previous studies [1, 6, 11, 12, 15, 18, 25, 35, 53, 54]. In a research focusing on the differences between AD and MCI groups [50], the best result obtained with the SVM method was 66.78%. In the study presented by Gray et al. [15], 88% classification

accuracy has been obtained for classification of AD and NC. A 82.19% classification accuracy has been obtained by López et al. [25]. The authors performed classification between non-convertible MCI (a sub-group of the MCI with mild cognitive loss but no transition to Alzheimer's) and NC groups. Rodrigues and Silveira reported in their research [35] that the classification accuracies between AD and NC groups are 96.7% with neural networks (NN) and 89.52% with support vector machine (SVM) classifiers respectiveley. Nozadi and Kadoury [28], on the other hand, obtained classification results with rates changing between 65 to 79 % respectively using the regions chosen for MCI through SVM and kNN (k-nearest neighbors) techniques. Using the same method, an accuracy of 85% was also obtained for AD versus NC [1]. In the study presented by Zhang et al. [54], the distinction between AD and MCI has been classified with the accuracy of 91.5%. Generally, most researches have aimed to classify AD, MCI (single class) and NC. Because there is always an important difference at atrophy values of an Alzheimer's patient and a healthy individual, it is normal to obtain high classification performances. However, classification of EMCI and LMCI stages, is particularly a difficult problem especially when MRI is used. If it can be distinguished, it provides the opportunity for early diagnosis.

Enhanced MRIs can be more helpful for detecting the atrophies at different brain regions. More details cause to better detection performances. Liu et al. [23] presented a dual domain deep network for reconstructing the MRIs from under sampled data. Results of their method looks promising for brain MRIs. Another deep learning (DL) based MRI reconstruction method is proposed by Liu et al. [22]. They reconstructed the images from incomplete k-space data using a new DL algorithm which is called KV-Net. The study presented by Zhao et al. [55] has introduced a new learning based data augmentation method to synthesize the medical images. Application of their method to brain MRIs for segmentation is succesfull and promising.

In this research, the diagnostic performance of MRI on MCI stages and the general early diagnosis potential of MRIs have been obtained by using the atrophy values calculated from the cortical and subcortical regions of the brain with the help of machine learning (ML) methods. We obtained the volumes of 13 different brain regions and analyzed the potentials of them as the biomarkers of the progression of MCI stages. Analysis of volumetric data seen in Fig. 1 showed that the volumes of 10 regions decreased, 1 region increased and 2 regions unchanged with the transition from EMCI to LMCI. Their potentials as the biomarkers were specified with the help of ML methods and discussed in section III.

The main contribution of this study is to form a feature pattern that can be used while diagnosing the progression of AD from EMCI stage to LMCI stage. By using the results of this work, mainly effected parts of the brain at this progression stage can be specified and tracked in future researches and diagnosing processes.

2 Material and method

2.1 Study design and participants

Within the scope of this study, a data set was created by using the database of the Alzheimer's Disease Neuroimaging Initiative (ADNI). The chosen data from the database were distributed as; EMCI (n = 90; 62.94%), MCI (n = 14; 9.79%), and LMCI (n = 39; 27.27%). The chosen data were distributed depending on gender as; female (n = 61; 42.66%) and

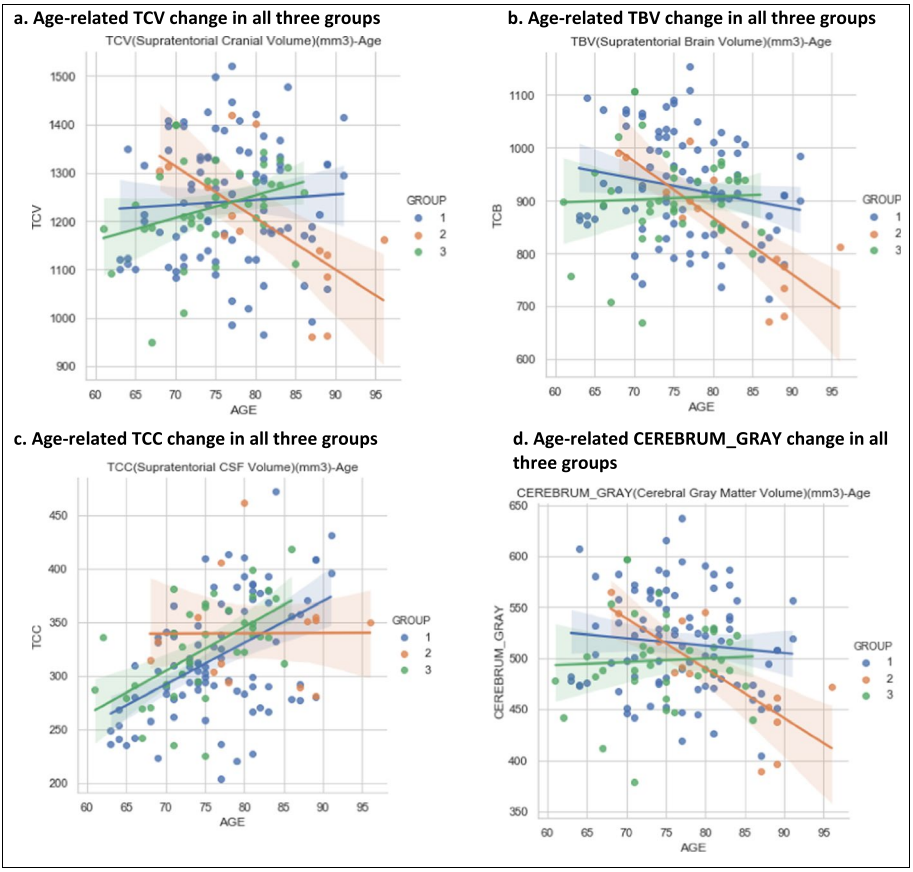

Fig. 1 Volumetric analysis of different brain regions (a, b, c, d) (Group 1 = EMCI, Group 2 = MCI, Group 3 = LMCI). The points in the figures represent the volume values (mm^3 and cm^3)

male (n = 82; 57.34%). All of them consist of T1-weighted MR images of the patients in NIFTI format. Data distribution according to gender, age and diagnosis is given in Table 1.

2.2 Features of the data

Within the scope of the study, 16 features were created for using in the analysis of different brain regions. The features represent the commonly used brain regions for AD diagnosis.

1. TCV (Supratentorial Cranial Volume),
2. TBV (Supratentorial Brain Volume),
3. TCC (Supratentorial CSF Volume),
4. CEREBRUM_GRAY (Cerebral Gray Matter Volume),
5. CEREBRUM_WHITE (Cerebral White Matter Volume),
6. HIPPOCAMPUS_L (Left Hippocampal Volume),

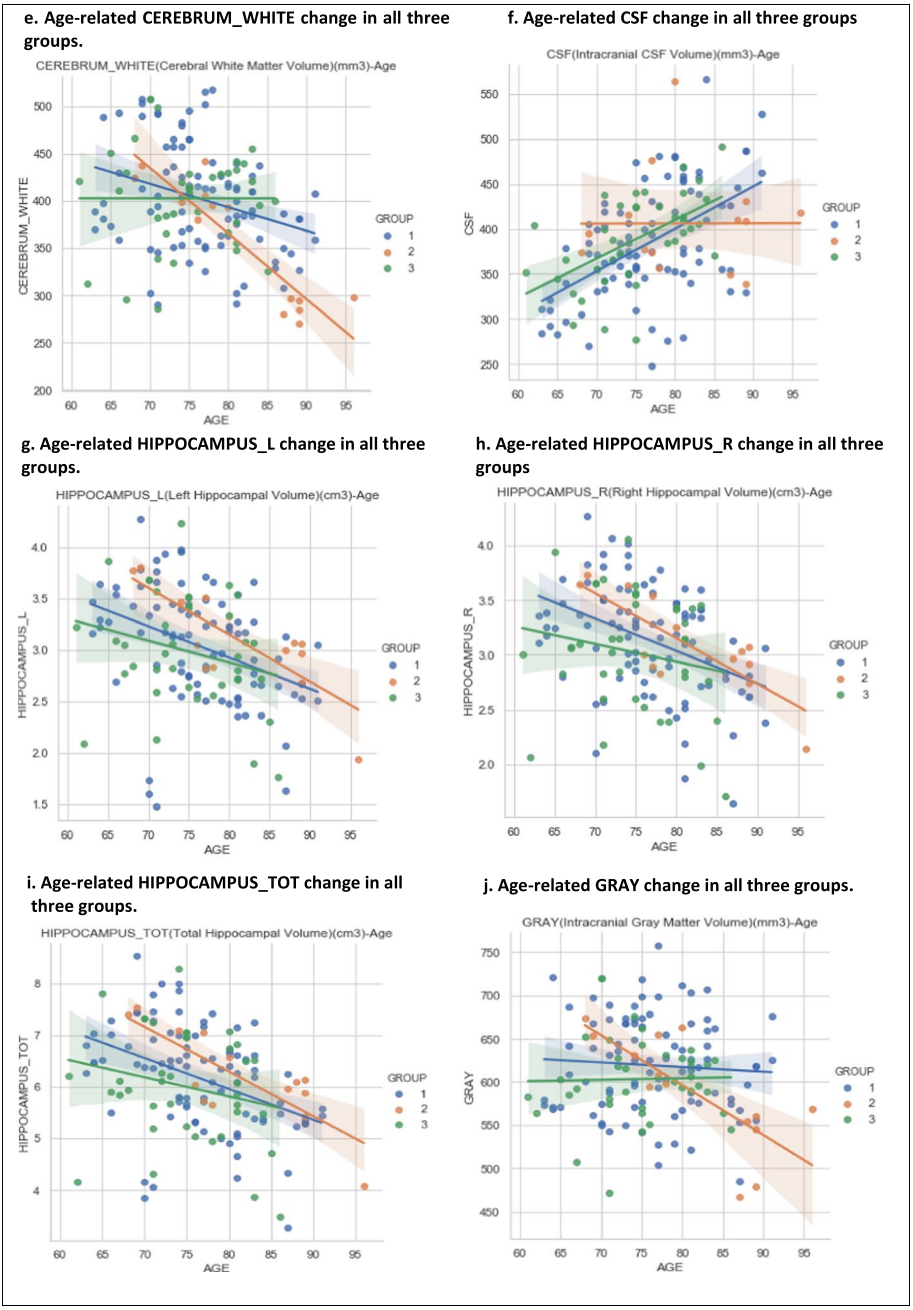

Fig. 1 (continued)

7. HIPPOCAMPUS_R (Right Hippocampal Volume),
8. HIPPOCAMPUS_TOT (Total Hippocampal Volume),
9. CSF (Intracranial CSF Volume),

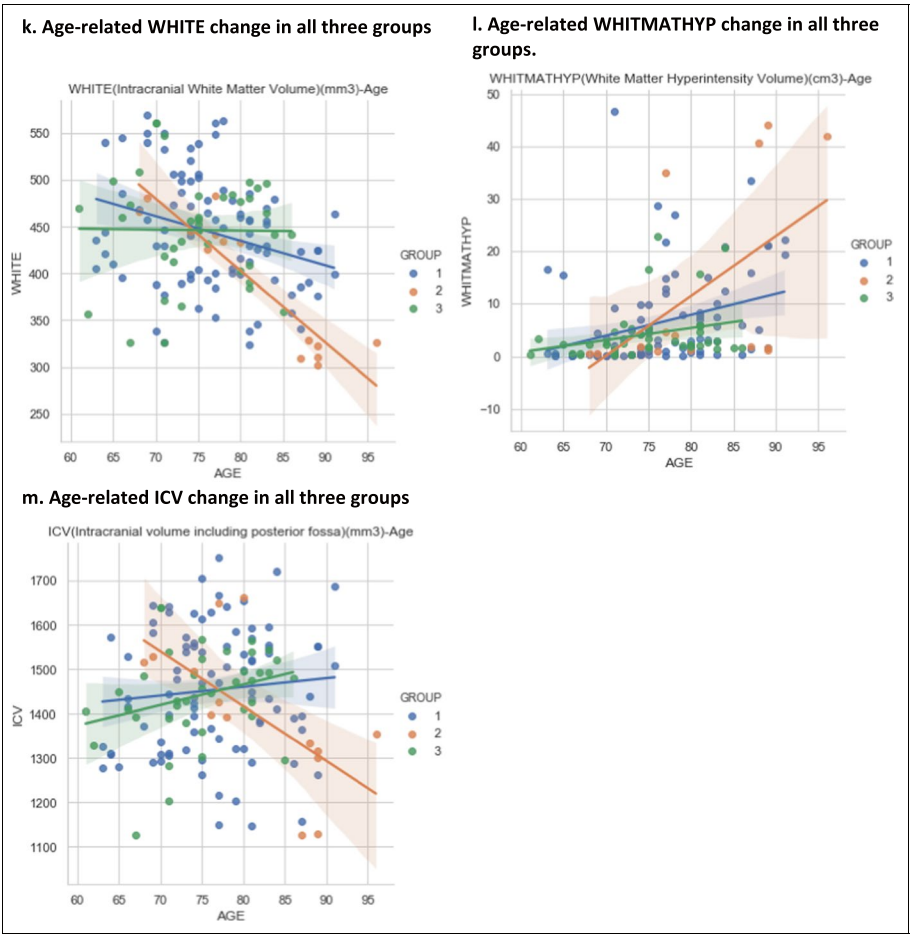

Fig. 1 (continued)

Table 1 The Distribution of The Data

n = 143	Number of EMCI		Number of MCI		Number of LMCI		
Age	Female	Male	Female	Male	Female	Male	Total
60–64	5	-	-	-	2	-	7
65–69	4	5	-	2	3	2	16
70–74	9	14	1	-	5	6	35
75–79	7	13	-	4	4	4	32
80–84	5	16	-	1	2	9	33
85–89	7	5	4	1	2	-	19
90–96	-	-	1	-	-	-	1
Total	37	53	6	8	18	21	143

10. GRAY (Intracranial Gray Matter Volume),
11. WHITE (Intracranial White Matter Volume),
12. WHITMATHYP (White Matter Hyperintensity Volume),
13. ICV (Intracranial Volume İncluding Posterior Fossa),
14. AGE,
15. GENDER,
16. GROUP (Diagnostic Groups: EMCI, MCI, LMCI).

2.3 Feature selection

In order to increase the classification success of the machine learning algorithm, the features in the data set are eliminated. Thus, the prediction accuracy of the algorithm is improved. For this purpose, 6 features that are expected to increase the prediction accuracy among the 15 features in the data set were selected using the SelectKBest() function and the ExtraTreesClassifier() function from the Python scikit-learn library. The evaluation results of these two functions are given in Table 2.

2.4 Machine learning algorithms

Machine learning algorithms are divided into categories, each designed for a different purpose. In this paper, the 6 most common classification models in supervised machine learning algorithms are used and their performances are evaluated.

2.4.1 Logistic regression

Logistic Regression algorithm is generally used in binary classification problems. The probability of the dependent variable entering one of the two response categories is expressed with a value between 0 and 1 [33].

Table 2 Feature Selection Scores

Features	Score of SelectKBest ()	Score of ExtraTreesClassifier()
TCV	0.937	0.064
TBV	3.122	0.083
TCC	1.218	0.078
CEREBRUM_GRAY	3.405	0.076
CEREBRUM_WHITE	4.048	0.075
HIPPOCAMPUS_L	0.215	0.064
HIPPOCAMPUS_R	0.749	0.049
HIPPOCAMPUS_TOT	0.382	0.061
CSF	0.891	0.072
GRAY	2.439	0.082
WHITE	4.451	0.069
WHITMATHYP	4.433	0.085
ICV	0.895	0.043
AGE	4.305	0.077
GENDER	0.085	0.024

2.4.2 K-Nearest neighbors

The K-Nearest Neighbors (KNN) algorithm makes classification by controlling the degree of similarity of the data [2]. Based on the distance between samples, it is measured with the nearest neighbor distance function and the sample is assigned to the class of its nearest neighbor. In our study, the distance function "minkowski" was chosen by evaluating the distribution of our data and the classification algorithm was created accordingly.

2.4.3 Support vector machines

Support vector machines (SVM) make it possible to separate classes with the hyperplane created at the decision boundary for binary classification of the data [19]. SVM maximizes the distance of the margin hyperplane and creates an n-dimensional hyperplane; thus, it performs the classification by dividing the data into the two best categories [30, 56].

2.4.4 Decision tree

The decision tree is visualized as diagrams, often similar to flowcharts, used for classification and regression. In a decision tree, the top box of the diagram is the root node and its internal nodes represent the state of the variable and the final nodes or leaves are the final decision of the algorithm [19]. In the classification process, a well-formed decision tree classifies data efficiently by performing a root query, not until it reaches a particular node [16].

2.4.5 Random forest

Random forest (RF) removes the instability of predictions with a large number of multiple decision trees put together [27]. The RF model is generally more advantageous than the individual decision tree because of the randomness and less sensitivity to outliers in the dataset [32].

2.4.6 Gaussian naive bayes

Naive Bayes classifiers work based on Bayes' theorem (Thomas Bayes (1701–1761)), which defines the probability of a previously known event for a conditional event, thereby calculating the probability of an item falling into a particular category and classifying it. It is characterized as a powerful classifier due to the versatility and accuracy of the algorithm, assuming that all features in the dataset are equally important and independent [21].

Naive Bayes algorithms basically have three models. Multinomial Naive Bayes makes classification mostly by looking at the frequency of a categorical nominal data. Bernoulli Naive Bayes is similar to multinomial classification, but in this algorithm the predictions are boolean variables (like yes or no values). Gaussian Naive Bayes, on the other hand, provides classification of numerical or categorical data with a gaussian distribution, which is preferred within the scope of the study.

2.5 Performance evaluation of classification algorithms

For performance evaluation, estimated values are compared with the actual values in the system. The purpose of the evaluation is to investigate and measure the performance of the classification algorithm in order to determine its accuracy. Confusion or error matrix is frequently used to evaluate the performance of classification models used in machine learning. The confusion matrix, which is described in Table 3, contains four classification performance parameters: true positive (TP), false positive (FP), false negative (FN), and true negative (TN).

Performance measurement models are formed with the parameters obtained from the confusion matrix. Accuracy rate is a measure of how close the measured or predicted value to the true value and it is expressed in (1).

$$\text{Accuracy Rate} = \frac{TP + TN}{Total} \times 100 \tag{1}$$

Specificity is a measure of how much of the data with a negative true state can be predicted correctly. This ratio is expressed by (2):

$$\text{Specificity} = \frac{TN}{TN + FP} \times 100 \tag{2}$$

Sensitivity is a measure of how much of the data with a positive true state can be positively predicted. This ratio is expressed by (3):

$$\text{Sensitivity} = \frac{TP}{TP + FN} \times 100 \tag{3}$$

3 Results and discussions

Estimating the conversion of the EMCI stage to LMCI and MCI is significant to understand the developmental process of the disease and it allows early intervention. The volumetric distributions of each diagnostic groups (group1 = EMCI, group2 = MCI, and group3 = LMCI) according to age and gender can be seen in Fig. 1. With the help of Fig. 1, volumetric changes at different brain regions can be analyzed related with the progression stages of MCI. It is seen that the volumes of some regions decrease and some of them increase with progression of the disease.

As it can be seen in Fig. 1, TCV (Supratentorial Cranial Volume) value decreases depending on age in the MCI group, while the volume values increase in the EMCI and LMCI groups. This is not normally expected, but since the data are from different patients, not from the same patient, it is normal to see volumetric differences in

Table 3 Confusion Matrix

Actual Class	Predicted Class	
	Positive	Negative
Positive	True Positive (TP)	False Negative (FN)
Negative	False Positive (FP)	True Negative (TN)

interpersonal brain areas. Because, in brain studies, there are cases where atrophy in the brain of a cognitively healthy elderly person is parallel to the atrophy in the brain of a patient with Alzheimer's disease. This difference is characterized as a condition caused by brain plasticity.

For the patients with Alzheimer's disease, when CSF does not enter the circulation and causes accumulation in the skull, TCC and CSF values increase, which is consistent with our results. The volumetric decrease in the white and gray areas of the cerebral cortex, that is, the decrease in the thickness of the cerebral cortex, is an important biomarker in Alzheimer's studies. So the age-related decrease in TBV, CEREBRUM_GRAY and CEREBRUM_WHITE values are consistent with our results. However, an interesting result of our study is that this decrease is very sharp in the MCI group.

Studies show that the limbic lobe is the first and most affected area in Alzheimer's patients, and when we look at our results, HIPPOCAMPUS_L, HIPPOCAMPUS_R and HIPPOCAMPUS_TOT values have significantly been decreased in each patient group. The hippocampus in the limbic lobe, also known as the cognitive ability and memory lobe, is the brain region most affected in the Alzheimer's process, as we have observed in our previous studies [45, 46].

When we look at the GRAY and WHITE values, the static volume in the LMCI and EMCI groups in these regions is an unexpected situation. This stable situation can be explained by focusing on the effect of these regions on cognitive ability. While the WHITMATHYP value increases slightly for the LMCI and EMCI groups, it shows a significant increase in the MCI group.

The absence of parallel effects in the brain regions of the diagnostic groups may be due to the narrowness of the data class, individual differences, or brain plasticity as previously noted. While age-related atrophy increased for each diagnosis group, more atrophy occurred especially in the MCI group compared to the other groups. Already MCI is considered as the transition period to cognitive loss in Alzheimer's.

At the classification process, 6 classification models which are the most widely used among supervised machine learning algorithms have been used and the performances of the algorithms have been evaluated depending on the results. All classification models were trained by separating the training and test data at a rate of 33%-67%. At this stage, all regions (each feature) for each observation class were analyzed separately and their effect on classification success was examined. Confusion matrix was used to evaluate the performance of the model and the obtained accuracy score and correct known values (TP + TN) are summarized in Table 4.

When each observation class is used separately for classification, the prediction performance of diagnosis is between 41 and 60%. Considering the performance of each classification model by using all the features, 68% accuracy is obtained with the logistic regression model. The feature selection was made using the SelectKBest() function and features with a score above 3 were included in the classification algorithm (TBV = 3.122, CEREBRUM_GRAY = 3.405, CEREBRUM_WHITE = 4.048, WHITE = 4.451, WHITMATHY = 4.433, AGE = 4.305 or 2,4,5,11,12,14). In the classification of diagnosis made with effective values, 75% estimation accuracy was achieved with the KNN algorithm. This result shows that priority areas should be focused on disease analysis. In the analysis with another feature selection function, ExtraTreesClassifier() (TBV = 0.083, TCC = 0.078, CEREBRUM_GRAY = 0.076, CEREBRUM_WHITE = 0.075, CSF = 0.072, GRAY = 0.082, WHITMATHYP = 0.085, AGE = 0.077 or 2,3,4,5,9,10,14) were included in the algorithm and diagnosis prediction was made with a success rate of 68.8%.

Table 4 Diagnosis Performances of Classification Algorithms for the EMCI, MCI, and LMCI Diagnostic Groups (Best results are underlined)

	1-TCV	2-TCB	3-TCC	4-CER-EBRUM GRAY	5-CER-EBRUM WHİTE	6-HIPPOCAMPUS_L	7-HIPPOCAMPUS_R	8-HIPPOCAMPUS_TOT	9-CSF
	ACCURACY SCORE /TP+TN								
LR	0.604/29	0.604/29	0.604/29	0.625/30	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29
KNN	0.500/24	0.542/26	0.479/23	0.458/22	0.417/20	0.500/24	0.667/32	0.417/20	0.542/26
SVM	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29
GNB	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29	0.584/28	0.563/27	0.604/29
DT	0.500/24	0.542/26	0.479/23	0.458/22	0.417/20	0.500/24	0.688/33	0.417/20	0.542/26
RF	0.500/24	0.542/26	0.479/23	0.479/23	0.375/18	0.500/24	0.708/34	0.479/23	0.542/26
	10-GRAY	11-WHITE	12-WHITMATHYP	13-ICV	14-AGE	15-GENDER	ALL	[3, 29, 36, 40, 46, 49]	[3, 26, 36, 40, 46, 50, 51]
	ACCURACY SCORE /TP+TN								
LR	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29	0.604/29	<u>0.688/33</u>	0.625/30	0.666/32
KNN	0.479/23	0.521/25	0.542/26	0.563/27	0.521/25	0.479/23	0.646/31	<u>0.75/36</u>	<u>0.688/33</u>
SVM	0.604/29	0.646/31	0.604/29	0.604/29	0.604/29	0.604/29	0.666/32	0.666/32	0.666/32
GNB	0.604/29	0.625/30	0.646/31	0.604/29	0.542/26	0.604/29	0.479/23	0.375/18	0.563/27
DT	0.479/23	0.521/25	0.542/26	0.563/27	0.542/26	0.604/29	0.604/29	0.542/26	0.604/29
RF	0.479/23	0.542/26	0.563/27	0.583/28	0.417/20	0.604/29	0.604/29	0.604/29	0.563/27

Comparison of the diagnosing accuracies of proposed method with some other methods in literature can be seen in Table 5. Accuracy of our approach looks lower than other methods. This is normal because we have preferred to focus on the stages of MCI and we have tried to classify them. Distinguishing the stages of MCI is a more challenging and harder problem because of the lower changes during the progression process. However, the volumetric reductions are more evident between MCI – AD, MCI – NC and AD – NC. Therefore, having high classification accuracies for these classes is a normal and expected situation. Accuracy of our approach is acceptable for distinguishing the stages of MCI, but it is still possible to improve the method for obtaining higher accuracies.

4 Conclusions

There is no definitive cure for AD yet, whereas active research groups are seeking more effective treatments for early MCI with the aim of slowing the progression of the disease. This means that there is a great urgency to develop sensitive biomarkers to detect and monitor changes in the brain. Early diagnosis of AD provides a significant advantage in interfering with the course of the disease. Thus, it is expected to have a major impact in reducing the cost of long-term care.

The unexpected result of our study is that, although the hippocampus atrophy values are considered as a very important biomarker in AD under normal conditions and the results support this when analyzed individually, it does not show the expected predictive success on algorithms when combined with other brain regions. The reason for this may be inconsistency in results due to individual differences, since the atrophy values of each region are taken from different people. Otherwise, when the analysis is done with only the hippocampus values, a sharp decrease in the atrophy value due to age is observed, as expected.

In this study, we preferred to use common and classical learning methods. Essentially, we aimed to specify the most significant parts of the brain while the AD progressing from EMCI stage to LMCI stage. Diagnosing of different stages of MCI is very difficult procedure with classical methods because of the low volumetric changes in brain regions. This difficulty has decreased the prediction results of our study. As it can be seen in Table 4, the accuracy results obtained with classifications of 13 brain regions separately is not enough. There are not significant differences between ML methods. Only the changes at the volume of the right hippocampus produce promising classification results for distinguishing the

Table 5 Comparison of the Proposed Method with the Other Methods

Research	Classes	Method	Diagnosing Accuracy
Westman et al. [50]	MCI – AD	SVM	66,78%
Gray et al. [15]	MCI—AD	FDG-PET, SVM	88,4%
López et al. [25]	MCI—NC	PCA—SVM	82,19%
Rodrigues and Silveira [35]	AD—NC	Neural Network	96,7%
Nozadi and Kadoury [28]	EMCI—LMCI	kNN	79%
Zhang et al. [54]	NC – (MCI/AD)	SVM	91,5%
Proposed method	EMCI – MCI—LMCI	kNN	75%

EMCI, MCI and LMCI stages. The best classification ratio is 70,8% and it is achieved by using the random forest classifier with right hippocampus. However, we determined the combination of the most important brain regions for following the progression of the disease in this research. We specified that the combination of the features numbered as (2, 4, 5, 11, 12, 14) produces the best accuracy result. By using this combination, 75% prediction accuracy has been achieved with KNN algorithm.

A feature pattern has been obtained in this work. This pattern can be used directly in the researches about the stages of MCI. Usage of this feature pattern can accelerate the future research and can orientate the researchers to focus on significant parts. The results of this work have confirmed that it is possible to obtain high prediction results for diagnosis by using the extracted features of the specified brain areas. In future, the analysis of the most effective brain regions with more data of relatively younger patients will be performed to observe and improve the potentiality of the early diagnosis. Also, deep learning methods are getting more useful and successful at MRI based diagnosing researches. Especially, new and promising deep learning algorithms like transformer [38] and LSTM [24] will be examined and employed in our next researches.

Acknowledgements The authors would like to thank to the Alzheimer's Disease Neuroimaging Initiative (ADNI) for sharing MRI data and volume information used in this work.

Author contributions G.U. carried out the simulations, analyzed the results and wrote the paper; M.O. analyzed the results and wrote the paper.

Data availability The MR images and brain volume information used in this work were taken from the website of the Alzheimer's Disease Neuroimaging Initiative (ADNI) (https://adni.loni.usc.edu/) with permission. All of the data and material used in this work belong to ADNI and they are publicly available at the website of ADNI.

Declarations

Ethics approval The experiments and data collection were approved by the local ethics committee as mentioned in ADNI data sharing website (https://adni.loni.usc.edu/). The authors of this work have accepted the ethics rules agreement of ADNI and obeyed them during the research.

Consent for publication The publisher has the permission from the authors to publish the paper.

Information sharing statement The MR images and volume information of patients with AD are publicly available at the website of the Alzheimer's Disease Neuroimaging Initiative (ADNI) (https://adni.loni.usc.edu/).

Conflict of interest The authors declare that they have no conflict of interest.

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