Classifying Early and Late Mild Cognitive Impairment Stages of Alzheimer's Disease by Analyzing Different Brain Areas

Gokce UYSAL
Department of Biomedical Engineering
Institute of Graduate Studies
Istanbul University-Cerrahpasa
Istanbul, Turkey
gokceuysal375@gmail.com

Mahmut OZTURK
Department of Electrical and Electronics Engineering
Engineering Faculty
Istanbul University-Cerrahpasa
Istanbul, Turkey
mahmutoz@ıstanbul.edu.tr

***Abstract*— Early detection of the stage of mild cognitive impairment (MCI) is very important for early diagnosis of dementia and slowing down the progression of Alzheimer's disease. Atrophy values obtained by magnetic resonance imaging (MRI), one of the neuroimaging techniques, are considered to be a fairly powerful diagnostic biomarker used in the detection of Alzheimer. Since the transition from early mild cognitive impairment (EMCI) to late mild cognitive impairment (LMCI) is irreversible and implies a significant change in a patient's condition, we focus on to the classification of these two stages in this work. In this study, atrophy values of 13 brain areas of 90 early mild cognitive impairment, 38 late mild cognitive impairment, 14 mild cognitive impairment participants were used in the diagnosis of the disease. Diagnosis groups have been classified with an accuracy of 68.8% as a result of data estimations obtained using classification algorithms. When the classification has been made only by taking effective values, an accuracy rate of 75% has been achieved and this means a significative improvement. The deep analysis of the disease and the focusing on the brain regions where it has more impact in order to distinguish the stages early, show the potential of utilizing MRI features to improve cognitive assessment.**

Keywords— Mild Cognitive Impairment, Alzheimer's Disease, Classification Algorithms, Machine Learning

I. INTRODUCTION

Alzheimer's disease (AD) constitutes approximately 60% of dementia and it is one of the neurodegenerative disorder types whose incidence is rapidly increasing due to the population aging in developing countries [1]. According to the World Alzheimer's Report (2018) published by Alzheimer's Disease International (ADI) and dementia statistics of the World Health Organization; worldwide, there are approximately 50 million adults living with dementia and this number is projected to reach 82 million in 2030 and 152 in 2050 [2]. With the increasing incidence of the disease, researches on its treatment and early diagnosis are becoming very important.

Although the main symptom of AD is expressed as memory lapses due to decline in mental function, dysfunctions such as motor skill disability, problems using language and doing activities, they can be seen with the early stages of the disease [3]. In the mild cognitive impairment (MCI) stage, which is one of the early stages of Alzheimer's, there is a slight but noticeable and measurable decline in a person's cognitive abilities, including memory and reasoning abilities. A person diagnosed with MCI has an increased risk of developing AD. Clinical and neuroimaging studies have shown differences between MCI and normal controls (NC) [4]. The importance of staging patients diagnosed with MCI by revealing the differences between early MCI (EMCI) and late MCI (LMCI) groups has been emphasized in many studies [4-8]. Each stage of the disease is analyzed to detect AD at an early stage. For this purpose, by analyzing the brain images obtained by magnetic resonance imaging in many studies, it is stated that the volumetric reduction in some parts of the brain -atrophy- can be used as an important biomarker for AD [8-12]. Machine learning techniques can be used to predict diagnosis using structural and functional brain images in specific neurodegenerative diseases such as schizophrenia [13-14], Alzheimer's [15-19] and obsessive-compulsive disorders [20]. Even if appropriate treatment cannot be provided with current findings, slowing the disease gives clinicians the chance to control the results at an early stage.

A. Related Works

There are a limited number of studies to investigate the effectiveness of focusing on localized MRI areas to differentiate and classify EMCI and LMCI groups [6,7,15-19]. In a study focusing on AD and MCI separation [21], groups were distinguished using support vector machine (SVM) algorithm with 66.78% success, and Gray et al. [22] classified AD and NC with a classification accuracy of 88% in their study. López et al. [18] achieved a 65% classification accuracy between non-convertible MCI (MCI group with mild cognitive loss but not conversion to Alzheimer's) and NC. In the study performed by Rodrigues and Silveira [23] between AD and NC groups, it is seen that neural networks (NN) and SVM classifiers achieved accuracy results of 96.7% and 89.52%, respectively. Nozadi and Kadoury [7] reached classification results varying between 65% and 79% on the regions selected for MCI using SVM and kNN algorithms. An accuracy of 85% for NC and AD was also achieved using the same method [24]. In the study conducted by Zhang and Shen [25], the AD and MCI distinction could be classified with 91.5% success. Generally, most studies have compared AD, MCI (single class) and NC, it is very normal for

"978-1-7281-8073-1/20/$31.00 ©2020 IEEE"

their classification performances to be high as there will already be a significant difference in atrophy between the individual with Alzheimer's disease and the healthy individual. EMCI and LMCI classification is a particularly difficult problem. But its distinction allows early intervention.

In this study, the diagnostic efficiency of MRI on the MCI stages; The diagnostic potential of MR images was evaluated by using atrophy values obtained from cortical and subcortical regions in the diagnostic classification. For this purpose, it is aimed to classify the diagnostic groups on the data set containing EMCI and LMCI. We aim to measure the effect values of the examined brain areas on the course of the disease by using features obtained from semantically tagged MR images to perform diagnostic classification. Data from 143 patients from the ADNI database were analyzed and 13 labeled brain regions were evaluated for the diagnosis of MCI.

II. METHODOLOGY

A. Distribution of Data Set

The data used in the preparation of this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).The data set analyzed within the scope of the study was from T1-weighted MR images in NIFTI format of patients diagnosed with EMCI (n = 90; 62.94%), MCI (n = 14; 9.79%), LMCI (n = 39; 27.27%) (n = 143). It consists of the atrophy values obtained. 61 (42.66%) of these data belong to female and 82 (57.34%) to male patients in the whole group. 16 features were created by evaluating the data set: TCV (Supratentorial Cranial Volume), TBV (Supratentorial Brain Volume), TCC (Supratentorial CSF Volume), CEREBRUM_GRAY (Cerebral Gray Matter Volume), CEREBRUM_WHITE (Cerebral White Matter Volume), HIPPOCAMPUS_L (Left Hippocampal Volume), HIPPOCAMPUS_R (Right Hippocampal Volume), HIPPOCAMPUS_TOT (Total Hippocampal Volume), CSF (Intracranial CSF Volume), GRAY (Intracranial Gray Matter Volume), WHITE (Intracranial White Matter Volume), WHITMATHYP (White Matter Hyperintensity Volume), ICV (Intracranial Volume İncluding Posterior Fossa), AGE, GENDER, GROUP (EMCI,MCI,LMCI) .

B. Feature Extraction for Classification

Feature extraction is the process of selecting and finding the most useful features within the dataset. This process greatly affects the performance of the machine learning model. Feature extraction was applied to improve the accuracy scores of the predictive values of the classification algorithms of the features in the used dataset or to increase their performance in very high dimensional dataset. SelectKBest () function was chosen from the Python scikit-learn library to extract features that are expected to show the highest performance for classification algorithms among 16 features of the dataset. In the feature selection made using the SelectKBest () function, the highest scored 5 features: 1-TBV, 3-CEREBRUM GRAY, 4-CEREBRUM WHITE, 9-HIPOCAMPUS TOT, 11-AGE.

C. Brief Description of Classification Algorithms Used

Classification is a process of predicting a qualitative response, and classification algorithms are machine learning models used for estimating categorical data [26]. Within the scope of the study, 3 most common classification models were used and their performances were evaluated. In this work, we analyzed the data by using the Logistic Regression (LR), K-Nearest Neighbors (KNN), Support Vector Machines (SVM).

The logistic regression model is included in the linear regression class, which is a classification algorithm that classifies the relationship between the most basic regression model, the y variable and the x attributes, based on a linear prediction function. When classifying with the logistic regression method, this probability is expressed with a value between 0 and 1 by looking at the probability of whether an observation is part of a certain class or not. A probability close to 1 means that the observation is likely to be part of this category [27].

The K-Nearest Neighbors algorithm is one of the simplest machine learning algorithms used to categorize test data by checking the degree of similarity found among a certain amount of training data [28]. It makes the classification of the sample whose category is unknown by measuring the distance between the training sample and the unknown sample.

Support vector machines are considered as one of the most effective models in binary classification of high dimensional data used for data classification and regression [26]. The separation of classes is possible with the hyperplane created at the decision boundary. SVM performs a classification that separates the data into two categories in the best way by maximizing the distance, ie margin, of the hyperplane and creating an n-dimensional hyperplane [29].

III. RESULTS

The transformation from the EMCI phase to MCI and LMCI is important in terms of monitoring AD and providing early diagnosis. Accordingly, when looking at the atrophy values in the most analyzed brain regions for the disease, a consistent regression, that is, volumetric reduction, is expected due to the advancement of age. The volumetric decline observed in each diagnostic group (group 1 = EMCI, group 2 = MCI, group 3 = LMCI) and age-related distribution graphs of the data are summarized in Figure 1. When looking at the results in the table, the age-related increase seen in TCC (Supratentorial CSF Volume) and CSF (Intracranial CSF Volume) values is the expected situation. Due to the advancement of age, cerebrospinal fluid (CSF) may not participate in the circulation and cause accumulation in the skull, which is associated with AD and hydrocephalus. Increasing evidence that Alzheimer's biomarkers can be traced in CSF has increased Alzheimer's studies in which CSF amount and content are analyzed. Age-related decrease in TBV (Supratentorial Brain Volume), CEREBRUM_GRAY (Cerebral Gray Matter Volume) and CEREBRUM_WHITE (Cerebral White Matter Volume) values is expected. The fact that volumetric decreases seen in the white and gray regions of the cerebral cortex caused cognitive loss made cerebral cortex thickness an important biomarker in Alzheimer's studies. What draws attention in the experimental findings is that this decrease is very sharp in the MCI group. HIPPOCAMPUS_L (Left Hippocampal Volume), HIPPOCAMPUS_R (Right Hippocampal Volume) and HIPPOCAMPUS_TOT (Total Hippocampal Volume) values are the only brain region where a net reduction is experienced for each group. Our previous studies [30,31] showed that the first and most affected area in the presence of dementia is the hippocampus. Our experimental findings were also in line with these studies, and significant atrophy was observed as the age advanced.

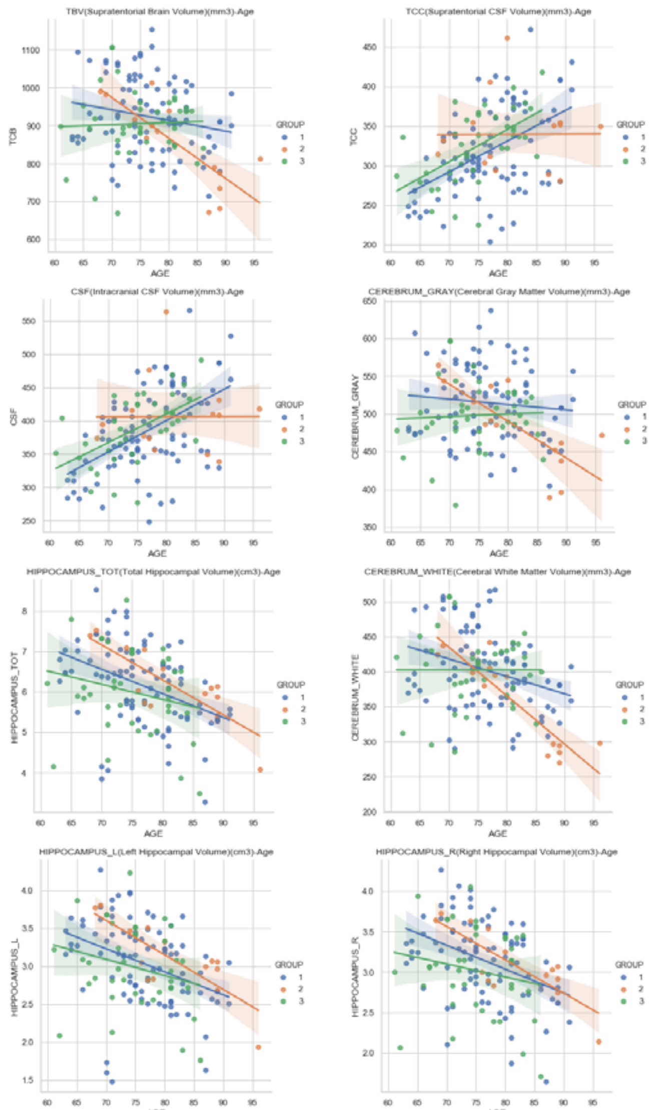

Fig 1. Analysis of observation classes (TBV, TCC, CSF, Cerebrum Gray, Cerebrum White, Hippocampus Total, Hippocampus Right, Hippocampus Left).

When the observation classes considered within the scope of the study are evaluated, age-related volumetric reduction increases for each diagnostic group, while a sharper change is observed especially in the MCI group. The acceptance of MCI as the transition phase of the disease to cognitive loss confirms this observation.

A. *Comparative Diagnosis Performances of Classification Algorithms*

While establishing the classification algorithms, which is the other stage of the study, training and test data were divided into 33% -67%. First of all, each observation class was included one by one and individual effect values were measured by diagnostic classification. Afterwards, the diagnosis classification was made according to the new observation groups created by taking the SelectKbest() scores into consideration. Performance evaluation of classification algorithms is summarized in Table I according to accuracy score and true values (TP + TN) obtained from confusion matrix.

Table I. Performance Evaluation of Classification Algorithms.

ACCURACY SCORE /TP+TN

	LOGISTIC REG.	KNN	SVM
1-TBV	0.604/29	0.542/26	0.604/29
2-TCC	0.604/29	0.479/23	0.604/29
3-Cerebrum Gray	0.625/30	0.458/22	0.604/29
4-Cerebrum White	0.604/29	0.417/20	0.604/29
5-Hippocampus_L	0.604/29	0.500/24	0.604/29
6-Hippocampus_R	0.604/29	0.667/32	0.604/29
9-Hippocampus_Tot	0.604/29	0.417/20	0.604/29
10-CSF	0.604/29	0.542/26	0.604/29
11-Age	0.604/29	0.521/25	0.604/29
All	0.688/33	0.646/31	0.666/32
SelectKBest()[1,3,4,9,11]	0.625/30	0.75/36	0.666/32

By using each observation class individually in classification, the diagnosis prediction success varies between 41% and 60%. The fact that the observation classes have very close values has a negative effect on the prediction success. When the diagnosis is estimated by including all observation classes, 68,8% success performance is obtained with the logistic regression model. In the feature selection made by using the SelectKBest () function, the highest scored 5 features (1-TBV, 3-CEREBRUM_GRAY, 4-CEREBRUM_WHITE, 9-HIPPOCAMPUS_TOT, 11-AGE) are included in the classification algorithm and 75% prediction success has been achieved with the KNN algorithm. This value indicates which areas should be focused primarily in the analysis of the disease.

IV. Discussions

The lack of a definitive cure for Alzheimer's disease increases the importance of studies to slow the progression of the disease. The main focus of this study is to observe and compare the levels of damage occurring in different areas of the brain at each stage of the MCI, which is considered to be the transition stage to Alzheimer's disease. In particular, analyzing markers in brain regions to differentiate EMCI from LMCI may be the answer to why the disease has progressed. In order to observe the effect levels of the brain areas at the stage of the disease, the volume values obtained from the MR images were used and the diagnosis estimation based on these values was made using machine learning algorithms.

The second focus of this study is to determine which area of the brain changes most at the developmental stage of MCI to decide which region to focus on in the analysis of the disease. Analyzing the progression of atrophy that occurs in brain regions at different stages of the disease may slow or even prevent the progression of AD conversion by providing appropriate treatment and clinical measure. Although a holistic approach to the brain is effective in neurodegenerative diseases, determining the area where the disease affects the most can be helpful in understanding the disease. However, when the experimental results are observed, although it is thought that the sharp transitions between EMCI, MCI, and LMCI will be interpreted by looking at the hippocampus atrophy values, it is seen that the effect of the cerebrum volumes is more when the success of the classification models is considered. This result can be evaluated by the fact that the values measured from the groups are very close to each other due to the low number and variety of data, thus making it difficult to distinguish the groups. Moreover, it is known that the brain creates new neuronal pathways and increases brain plasticity as a result of the effective use of the brain in Alzheimer's analysis due to the advancement of age. This causes elderly people with atrophy but no cognitive loss, and makes it difficult to perform Alzheimer's analysis by looking at structural MRI data.

The ability to diagnose and classify AD and MCI at an early stage enables clinicians to make more informed decisions at later stages for clinical intervention and treatment planning. The study results also confirm that successful results will be obtained in diagnosis prediction by focusing on the correct brain areas. Future studies can focus only on the analysis of these active groups by increasing the number of data by obtaining more homogeneous data distribution.

References

[1] J. Hardy, “Alzheimer's disease: the amyloid cascade hypothesis—an update and reappraisal,” *Journal of Alzheimer's Disease*, vol. 9, no. 3 supplement, pp. 151–153, 2006.

[2] Alzheimer’s Disease International (ADI), 2009-2018, World Alzheimer Report.

[3] E. Westman, A. Simmons, J.-S. Muehlboeck et al., “AddNeuroMed and ADNI: Similar patterns of Alzheimer's atrophy and automated MRI classification accuracy in Europe and North America,” *NeuroImage*, vol. 58, no. 3, pp. 818–828, 2011.

[4] G. Román and B. Pascual, “Contribution of Neuroimaging to the Diagnosis of Alzheimer's Disease and Vascular Dementia,” *Archives of Medical Research*, vol. 43, no. 8, pp. 671–676, 2012.

[5]M. W. Weiner, D. P. Veitch, and P. S. Aisen, “2014 update of the alzheimer’s disease neuroimaging initiative: a review of papers published since its inception,” *Alzheimer’s & dementia*, vol. 11, no. 6, pp. e1–e120, 2015.

[6]N. Smailagic, M. Vacante, C. Hyde, S. Martin, O. Ukoumunne, and C. Sachpekidis, “18F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI),” *Cochrane Database of Systematic Reviews*, 2015.

[7]Nozadi, S. H., & Kadoury, S. (2018). *Classification of Alzheimer’s and MCI Patients from Semantically Parcelled PET Images: A Comparison between AV45 and FDG-PET. International Journal of Biomedical Imaging, 2018,1–13.*

[8]Risacher, S.L., Saykin, A.J., West, J.D., Shen, L., Firpi, H.A., McDonald, B.C., ADNI, 2009, Baseline MRI Predictors of Conversion from MCI to Probable AD in the ADNI Cohort, Current Alzheimer Research, 6, 347-361.

[9]Rowland, D.C., Moser, M.B., 2013, Time finds its place in the hippocampus, Neuron, 78 (6), 953-954.

[10]Sontheimer, H., 2015, Aging, Dementia, and Alzheimer Disease, Diseases of the Nervous System, 4, 99–131.

[11] J. Stoeckel and G. Fung, “SVM feature selection for classification of SPECT images of Alzheimer's disease using spatial information,” in Proceedings of the 5th IEEE International Conference on Data Mining, ICDM 2005, pp. 410–417, USA, November 2005.

[12]Fox, N. C., Freeborough, P. A., & Rossor, M. N. (1996). Visualisation and quantification of rates of atrophy in Alzheimer’s disease. The Lancet, 348(9020), 94–97. doi:10.1016/s0140-6736(96)05228-2

[13] Shen, L., Ford, J., Makedon, F., Saykin, A., 2003. Hippocampal shape analysis: surface-based representation and classification. Proceedings of SPIE, 5032, pp. 253–264.

[14] Demirci, O., Clark, V.P., Calhoun, V.D., 2008. A projection pursuit algorithm to classify individuals using fMRI data: application to schizophrenia. NeuroImage 39 (4), 1774–1782.

[15] Batum, K., Çınar, N., Şahin, Ş., Çakmak, M. A., & Karşıdağ, S. (2015). The Connection Between Mcı And Alzheimer Disease: Neurocognitive Clues. Turkısh Journal Of Medıcal Scıences, 45, 1137–1140. doi:10.3906/sag-1404-179

[16] Angelucci, F., Spalletta, G., Iulio, F., Ciaramella, A., Salani, F., Varsi, A., … Bossu, P. (2010). *Alzheimers Disease (AD) and Mild Cognitive Impairment (MCI) Patients are Characterized by Increased BDNF Serum Levels. Current Alzheimer Research, 7(1), 15–20.*

[17] Wu, L., Rowley, J., Mohades, S., Leuzy, A., Dauar, M. T., … Shin, M. (2012). Dissociation between Brain Amyloid Deposition and Metabolism in Early Mild Cognitive Impairment. PLoS ONE, 7(10), e47905. doi:10.1371/journal.pone.0047905

[18] López, M., Ramírez, J., Górriz, J. M., Álvarez, I., Salas-Gonzalez, D., Segovia, F., … Gómez-Río, M. (2011). *Principal component analysis-based techniques and supervised classification schemes for the early detection of Alzheimer’s disease. Neurocomputing, 74(8), 1260–1271.* doi:10.1016/j.neucom.2010.06.025

[19] Hinrichs, C., Singh, V., Mukherjee, L., Xu, G., Chung, M. K., & Johnson, S. C. (2009). *Spatially augmented LPboosting for AD classification with evaluations on the ADNI dataset. NeuroImage, 48(1), 138–149.* doi:10.1016/j.neuroimage.2009.05.056

[20] Soriano-Mas, C., Pujol, J., Alonso, P., Cardoner, N., Menchn, J.M., Harrison, B.J., Deus, J., Vallejo, J., Gaser, C., 2007. Identifying patients with obsessive–compulsive disorder using whole-brain anatomy. NeuroImage 35, (3).

[21] C. Cabral and M. Silveira, “Classification of Alzheimer's disease from FDG-PET images using favourite class ensembles,” Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference, vol. 2013, pp. 2477–2480, 2013.

[22] K. R. Gray, R. Wolz, R. A. Heckemann, P. Aljabar, A. Hammers, and D. Rueckert, “Multi-region analysis of longitudinal FDG-PET for the classification of Alzheimer's disease,” NeuroImage, vol. 60, no. 1, pp. 221–229, 2012.

[23] F. Rodrigues and M. Silveira, “Longitudinal FDG-PET features for the classification of Alzheimer's disease,” in Proceedings of the 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014, pp. 1941–1944, USA, August 2014.

[24] H. Aidos, J. Duarte, and A. Fred, “Identifying regions of interest for discriminating Alzheimer’s disease from mild cognitive impairment,” in Proceedings of the 2014 IEEE International Conference on Image Processing, ICIP 2014, pp. 21–25, 2014.

[25]D. Zhang, Y. Wang, L. Zhou, H. Yuan, and D. Shen, “Multimodal classification of Alzheimer's disease and mild cognitive impairment,” NeuroImage, vol. 55, no. 3, pp. 856–867, 2011.

[26] Khan, N., Abdullah, J., Khan, A.S., 2017, Defending Malicious Script Attacks Using Machine Learning Classifiers, Wireless Communications and Mobile Computing, 1–9.

[27] Raschka, S., 2016, Giving Computers the Ability to Learn from Data, Python Machine Learning, In: Olson, R.S. (ed.), Chapter 1, Packt Publishing Ltd., Birmingham, UK, 3-10.

[28] Altman, N.S., 1992, An İntroduction To Kernel And Nearest-Neighbor Nonparametric Regression, The American Statistician, 46(3), 175–185.

[29] Z. Zhou, Ensemble Methods Foundations and Algorithms, CRC Press, 2012.

[30]G. Uysal and M. Ozturk, "Using Machine Learning Methods for Detecting Alzheimer's Disease through Hippocampal Volume Analysis," 2019 Medical Technologies Congress (TIPTEKNO), Izmir, Turkey, 2019, pp. 1-4.

[31] Uysal, G., & Ozturk, M. (2020). Hıppocampal Atrophy Based Alzheımer’s Dısease Dıagnosıs Vıa Machıne Learnıng Methods. Journal of Neuroscience Methods, 108669. doi:10.1016/j.jneumeth.2020.108669