Using Machine Learning Methods for Detecting Alzheimer's Disease through Hippocampal Volume Analysis

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***Abstract*—Alzheimer's disease (AD) is a neurodegenerative disorder that gradually destroys memory and thinking skills. It is the most common cause of dementia and the incidence of the disease increases with age. As the elderly population increases, the incidence of the disease is expected to increase further in the coming years so developing new treatments and diagnostic methods is getting more important. The work presented in this paper assesses the utility of image processing on the Magnetic Resonance Imaging (MRI) scans to estimate the probability of early diagnosis of dementia in Alzheimer's Disease. We analyzed the data diagnosed by the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol. The analyzed data were T1-weighted magnetic resonance images of 159 patients with Alzheimer's disease, 217 patients with mild cognitive impairment and 109 cognitively healthy older people. Within the scope of the study, 3-dimensional modeling of the hippocampus, considered to be one of the first and most affected brain regions of dementia, was calculated by means of semi-automatic segmentation software. Then, a data set was formed based on age, gender, diagnosis, right and left hippocampal volume values. The diagnosis via hippocampal volume information was made by using machine learning techniques. By using this approach, we conclude that brain MRIs can be used to separate the patients with Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI) and Cognitive Normal (CN); while most of the researches were only be able to separate AD with CN. Results revealed that our approach improves the performance of the computer-aided diagnosis of the Alzheimer's disease.**

Keywords—Alzheimer's Disease, Hippocampal Atrophy , Models of Classification, Machine Learning

I. INTRODUCTION

Nowadays, age-related diseases are becoming more common because the elderly population is increasing rapidly. The data of the Turkish Statistical Agency shows that 8.7% of the population were older than 65 years at 2018 while it was 4.7% at 1980.This ratio is expected to be 25.6% in 2080. Age-related diseases such as Alzheimer's disease increase as a result of increased aging of the population. According to World Alzheimer's Report(2018) published by Alzheimer's Disease International (ADI) it is stated that there are approximately 50 million dementia patients worldwide. In addition, the number of patients with Alzheimer's disease is expected to increase approximately twice as every 20 years and to about 152 million by 2050. As a result of the growth of this problem, developing new and effective methods for early diagnosis and treatment of AD is getting more important and popular. With the rapid development of neuroimaging techniques, it is possible to diagnose or detect biomarkers in the early stage of AD and then to give a chance to control and slow down the results, even if it does not yet provide treatment.

In recent years, several new studies have been conducted to develop effective methods for the diagnosis of AD from neuroimages. Researchers, by analyzing the magnetic resonance (MR) images of the patient's brain, said that the volumetric reduction in some parts of the brain can be used as a biomarker for AD [1-4]. Neuronal losses in the brain and atrophy of large cortical neurons were observed in AD patients. Approximately 50% of cells and synapses are lost in the cortex and hippocampus [5-8]. Neuropathologic examinations of brain tissue have concluded that the brain cortex is thinner than normal. Using volumetric atrophy measurements, the hippocampus was the most affected anatomical region [9-11].

II. METHODOLOGY

The main objective of this study is to diagnose AD clinically as early as possible, to speed up the diagnostic process, and to minimize the human factor in the diagnosis by using machine learning methods. In this study, we suggest that brain MRIs can be used to differentiate AD, MCI and CN diagnosed groups. We recommend focusing on hippocampal atrophy in the brain. Using the volume information of the hippocampus with age and gender of the patients, we have showed that it is very possible to diagnose AD from MRI.

Many studies have shown that the tau increase and the amyloid plaque deposition which are accepted as the biomarkers of the neuronal damage are associated with hippocampal atrophy. Early-stage dementia researches show that the hippocampal

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atrophy prevalance increases with age and is commonly transformed from AD to MCI [9-13].

A. Calculation of Hippocampus Volume

At this stage, three-dimensional image models of the right and left hippocampus were obtained and their volumes were calculated using segmentation tools of ITK-SNAP. This tool was prepared by the protocol between the University of Pennsylvania - Image Computing and Science Laboratory and the University of Utah - Institute for Scientific Computing and Imaging. ITK-SNAP provides semi-automatic segmentation to analyze medical images and to obtain three-dimensional models.The MR image data selected from ADNI is transferred to the ITK-SNAP software based on imaging protocols, age, gender and diagnostic criteria. On the ITK-SNAP the anatomical localization is defined by matching the patient's anatomical coordinates to the coordinates of the segmentation tool. Three-dimensional model of left hippocampus can be seen in Figure 1. For this sample, volume of the left hippocampus was calculated as 2513,30 mm^3.

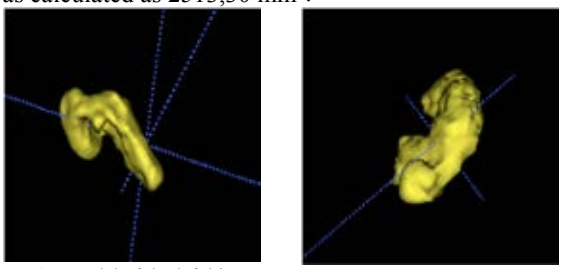


Fig.1. 3D model of the left hippocampus.

B. Using Machine Learning for Diagnosis of AD

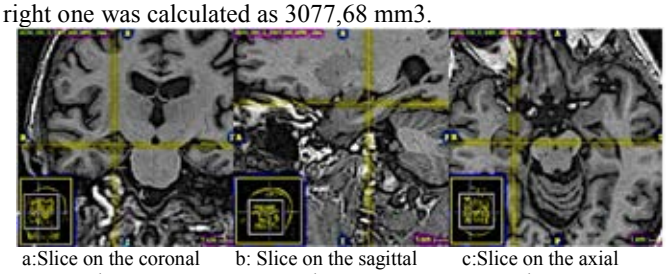
Machine learning algorithms are divided into three categories according to learning methods: supervised, unsupervised, and semi-supervised algorithms. The main purpose of supervised learning is to obtain a learning model from the tagged educational data that enables us to predict unknown or future data. In this study, the supervised data corresponds to a group of pre-labeled samples for estimation. Classification or regression models were created according to the data class used. Within the scope of this study, while analyzing the volume, age and gender data with the machine learning algorithms, the data analyzed were divided into 66,6% as education and 33,3% as test data like generally accepted in the literature.

In this work, we analyzed the data by using the Logistic Regression (LR), K-Nearest Neighbors (KNN), Support Vector Machines (SVM), Decision Tree (DT), Random Forest (RF), and Gaussian Naive Bayes (GNB).

III. RESULTS

Image data analyzed in this study consist of T1-weighted MR images in NIFTI format of 485 patients diagnosed as AD (n=159, 31,8%), MCI (n=217, 44,7%), CN (n=109, 22,5%) of these data. Although, all of the available data were included in the study, there were not enough data in the age group of 90 and over in all categories and in the 55-69 age group in CN category.

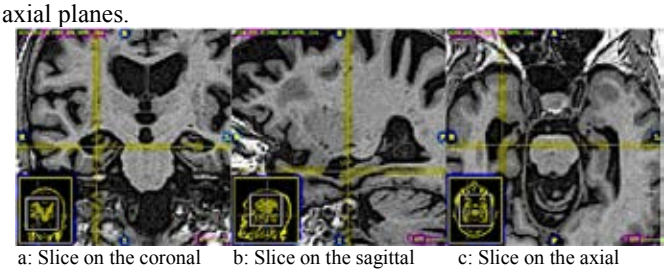
Right and left hippocampus volumes of all patients included in this work are calculated using ITK-SNAP semi-automatic segmentation software and significant atrophy differences were observed. For example, at Figure 2 right and left hippocampus slices of a 73 years old Cognitively Normal woman can be seen on the coronal, sagittal and axial planes . Left hippocampus volume of this patient was calculated as 2858,74 mm^3, and the right one was calculated as 3077,68 mm3.



a:Slice on the coronal plane. b: Slice on the sagittal plane. c:Slice on the axial plane.

Fig.2. Hippocampus slices on three planes of the cognitively normal woman.

By using same calculation techniques, left and right hippocampus volumes of an 87 years old woman with AD were calculated 846,12 mm^3 and 592,83 mm^3 respectively. Hippocampal atrophy can be clearly observed at the MR images of this patient showed in Figure 3 on the coronal, sagittal and axial planes.



a: Slice on the coronal plane. b: Slice on the sagittal plane. c: Slice on the axial plane.

Fig. 3. Hippocampus slices on three planes of the patient with Alzheimer's disease.

In the two samples examined, it is seen that the right and left hippocampus volumes of the patient with AD have decreased approximately 2000 mm^3 compared to the healthy elderly.

For all data included in this work, averages of the right and left hippocampus volumes were obtained separately with respect to the age period and gender can be seen in Table 1.

Table 1. Average volume values of right and left hippocampuses for all examined samples.

	Average volume of right hippocampus (mm^3)		**Average volume of left hippocampus (mm^3)**	
n:109 CN	***Female***	***Male***	***Female***	***Male***
55-65	-	2582,91	-	2648,66
66-79	2518,00	2570,75	2447,81	2521,80
80-95	2423,80	2481.96	2392,47	2414.13
n:217 MCI	***Female***	***Male***	***Female***	***Male***
55-65	2211,92	2414,78	2197,13	2392,48
66-79	1927,75	2005,49	1887,26	1946,36
80-95	1863.26	1726,41	1833,51	1731.57
n=159 AD	***Female***	***Male***	***Female***	***Male***
55-65	1871,75	1774,66	1763,64	1741,10
66-79	1474.19	1506,26	1390.07	1378,68
80-95	1291,49	1361,68	1212,56	1339,09

When the data of the cognitively healthy elderly in Table 1 are examined, it is seen that the amount of hippocampal atrophy in

the aging process of cognitively healthy elder people is much lower than the other groups.

When the mean volume data of the patients with MCI are examined, it is seen that the hippocampus volume of male patients decreases rapidly due to aging, but the hippocampus volume of the female patients does not decrease with the same rate. In addition, hippocampal atrophy in male patients with MCI appears to be approximately twice that of female patients

In parallel with our findings, there are some studies showing that men's atrophy rate is higher than women. however, the fact that the cause of hippocampal atrophy in male patients is twice as high as female patients is thought to be due to the distribution of sample data.

When the volume data of AD patients given in Table 1 are examined, the fact that hippocampal atrophy has less difference compared to the MCI group despite the more cognitive impairment is due to the evaluation of the diagnostic group itself. Even when the hippocampus volume values of the 55-65 year old AD and MCI diagnostic groups are compared, a volume difference of approximately 500 mm^3 is seen.

To clarify the findings, changes in the hippocampus volume at different levels depending on the age in each diagnostic group are given in Figure 4 for the left hippocampus and Figure 5 for the right hippocampus. Although the main effect of age on regional gray matter volume, particularly on the hippocampus, is known, it is important as long as the initial differences in the volume of the diagnosis are evaluated.

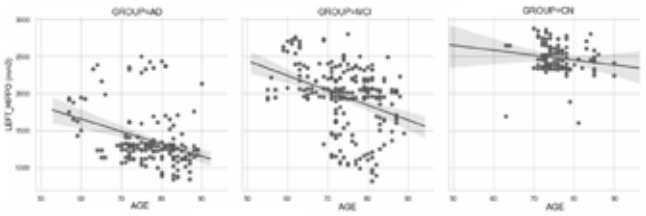


Fig. 4. Age-related change of left hippocampus volume for each diagnostic group.

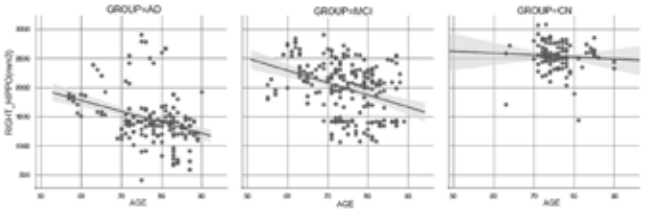


Fig. 5. Age-related change of right hippocampus volume for each diagnostic group.

A. Comparative Diagnosis Performances of Classification Algorithms

The right hippocampus volume and left hippocampus volume calculated from the image data of each diagnostic group in the study were made taking into consideration the age and gender criteria of the individuals and the diagnosis was estimated by classification algorithms. In each classification model, double and triple diagnostic groups were analyzed in single and multiple parameters. The predictive performances of the classification models were measured by looking at the accuracy, sensitivity and specificity values read on the confusion matrix.

In Table 2, all diagnostic groups were included in the common data set and their classification performances were measured. For each model, 482 data were divided into 160 (33.2%) test data and 322 (66.8%) training data.

Estimation performances were evaluated by classification among all diagnostic groups. Since the left hippocampus volume value yielded more successful estimation results than the right hippocampus in each model, a new domain was examined by adding age and gender parameters to which the right hippocampus value was not included. success rate increased. In this case, the most successful prediction algorithm was KNN with 80% accuracy when all parameters were evaluated, and GNB with 82% accuracy with the exclusion of right hippocampus volume value. Age and gender have positive effects for each algorithm. When all of the findings are evaluated, it is seen that a significant diagnostic estimate can be made with hippocampus volume information and hippocampal volume differences between ages and genders are effective in the diagnosis decision.

Table 2. Diagnosis performance of classification algorithms for AD, MCI and CN diagnostic group.

Diagnosis Performances	**Effect sizes of investigated parameters**					
	RHV	*LHV*	*RHV+LHV*	*RHV+LHV+A*	*RHV+LHV+A+G*	*LHV+A+G*
LR						
%Acc.	0.67	0.71	0.71	0.72	0.74	0.78
%Sen.	0.85	0.87	0.87	0.87	0.86	0.87
%Spe.	0.67	0.51	0.62	0.67	0.71	0.74
KNN						
%Acc.	0.56	0.70	0.69	0.77	0.80	0.78
%Sen.	0.63	0.72	0.80	0.80	0.83	0.80
%Spe.	0.51	0.77	0.59	0.77	0.77	0.77
SVM						
%Acc.	0.58	0.69	0.69	0.70	0.76	0.79
%Sen.	0.35	0.76	0.65	0.59	0.72	0.80
%Spe.	0.54	0.44	0.62	0.67	0.74	0.79
GNB						
%Acc.	0.65	0.77	0.74	0.74	0.74	0.82
%Sen.	0.77	0.87	0.89	0.89	0.87	0.87
%Spe.	0.74	0.90	0.85	0.87	0.87	0.95
DT						
%Acc.	0.56	0.69	0.68	0.76	0.74	0.80
%Sen.	0.63	0.72	0.76	0.78	0.74	0.87
%Spe.	0.51	0.77	0.56	0.67	0.79	0.77
RF						
%Acc.	0.57	0.71	0.71	0.78	0.78	0.78
%Sen.	0.61	0.74	0.80	0.87	0.80	0.85
%Spe.	0.56	0.77	0.69	0.74	0.77	0.69

IV. DISCUSSIONS

The main focus of this study is to use the MR imaging technique for early diagnosis of Alzheimer's disease and then to estimate the diagnosis by machine learning techniques. Since atrophy caused by the disease is an important biomarker, MRI is used as the main technique in structural imaging.

The second focus of this study is the selection of the main anatomic localization affected by the disease. According to

recent research, a holistic approach to the brain is effective in neurodegenerative diseases. When the memory is evaluated, it is seen that the whole brain is related to memory and learning. Furthermore, the increase in age-related plasticity allows new neuronal pathways to be made, thereby preventing loss of function to the age-related orate in the individual. there are even cases where AD biomarkers are observed but there is no cognitive loss. In dementia research, it is thought that the stress level of the living conditions of the individual and even the nutrition style will affect the memory and learning level.
In this study, the effect of hippocampal atrophy on dementia in Alzheimer's disease was investigated and it was emphasized that the possibility of early diagnosis is possible. On the other hand, the findings of this study confirmed this approach and clearly demonstrated the increase in age-related atrophy. The parallelism of the hippocampal atrophy comparisons with the literature studies also provided continuity of the study.

As a result of the findings, it was focused on the prediction of diagnosis by using machine learning techniques, considering that the interpretation of atrophy should contribute to the clinician in practical life in order to reach the diagnostic speed. Many studies in the literature, machine learning based systems have been compared to human decision making process and performance evaluation has been made. Machine learning practices are seen as key components of future clinical decision-making and monitoring systems. In this way, it is aimed for clinicians to diagnose more quickly.
In this study, classification models were used to estimate the diagnosis in terms of right and left hippocampal volume, age and gender parameters in the data obtained from ADNI. Significant achievements were obtained according to the performance evaluations made with the confusion matrix. In the presence of the obtained results, it was seen that the parameters evaluated, combinations of biomarkers, provided a more successful estimate than the individual evaluation of biomarkers. Even the gender criteria that we ignore in the hippocampal volume calculation has been shown to play an active role in increasing success. In this case, it has been shown that gender, not particularly atrophy values, can affect the diagnostic decision, especially in the detection of Alzheimer's disease. It was also found that the left hippocampus volume, which is directly linked to analytical thinking skills, leads to more accurate estimates in many classification algorithms. The left side of the brain that is known is about analytical thinking ability. Whether the left side of the brain is a decisive criterion in the presence of Alzheimer's disease is a new research topic, and it is recommended to investigate the relationship between cognitive loss on the left side of the brain and Alzheimer's disease.

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