Longitudinal Neuroimaging Data Classification for Early Detection of Alzheimer's Disease using Ensemble Learning Models

This paper was downloaded from TechRxiv (<https://www.techrxiv.org>).

LICENSE

CC BY 4.0

SUBMISSION DATE / POSTED DATE

03-03-2022 / 08-03-2022

CITATION

Tripathi, Satvik; Augustin, Alisha; Kim, Edward (2022): Longitudinal Neuroimaging Data Classification for Early Detection of Alzheimer's Disease using Ensemble Learning Models. TechRxiv. Preprint.
<https://doi.org/10.36227/techrxiv.19295120.v1>

DOI

[10.36227/techrxiv.19295120.v1](https://doi.org/10.36227/techrxiv.19295120.v1)

Longitudinal Neuroimaging Data Classification for Early Detection of Alzheimer's Disease using Ensemble Learning Models

Satvik Tripathi
Drexel University

Alisha Isabelle Augustin
Drexel University

Edward Kim
Drexel University

Abstract—This paper applies Ensemble Learning models for the early detection of Alzheimer's disease in elderly adults. The publicly available dataset from the Open Access Series of Imaging Studies (OASIS) Database is used. A novel longitudinal MRI data-based machine learning model is proposed in the paper, which takes account of features like- Mini-Mental State Examination (MMSE) score and years of education to make a generalized classifier. Our proposed model achieved a 5-fold cross-validation area under the curve (AUC) score of 89.93% and accuracy of 94.64%. We show that our results quantitatively outperform the state-of-the-art in Alzheimer's disease detection. We then compared our results to other previous state-of-the-art research and our model's metrics surpasses them.

■ **ALZHEIMER'S DISEASE** (AD) is an inevitable neurodegenerative disease that contributes to a gradual loss of memory and other mantle functions ultimately fatal in elderly people around the world. It is the type of dementia that is most prevalent. After 65 years old, the prevalence of AD is estimated to be about 5 percent and in developing countries, and a staggering 30 percent for more than 85 years old. It is predicted that about 0.64 billion individuals will be diagnosed with AD by 2050.

In the last decade, various attempts have been made to build computer-aided models that use

machine learning techniques on MRI images to decode the disease states [1], [2], [3], [4]. Early diagnosis and analysis of medical images and the discovery and creation of new treatments can be assisted by machine learning through the application of several high-dimensional data sources [5]. An efficient machine learning model successfully diagnosed self-detected Alzheimer's disease and mild cognitive impairment converter or non-converter during pre-stages [6]. Support vector machine (SVM), artificial neural network (ANN), and deep learning are the most extensively used classification approaches. The nature

of the optimization problem is the key distinction between SVM and ANN. SVM provides a globally optimum solution, while ANN provides a locally optimal one. Feature extraction is a key stage in both SVM and ANN [7]. Shi et al. [8] proposed that combining neural networks and intelligent agents may be beneficial for medical picture processing. Deep learning, on the other hand, includes the feature extraction procedure into the learning model itself [9]. Deep learning has been proven to be beneficial for huge datasets, particularly picture data [9]. Some researchers also used ensemble methods to improve the classification accuracy for Alzheimer's [10].

In recent years, academics have offered analyses on the work done for Alzheimer's utilizing machine learning. Litjens et al. [11] published a study of deep learning approaches for medical image processing in 2017. Although deep learning models are considered "black boxes," several statistical approaches may be utilized to evaluate the network's uncertainty. Shen et al. [9] conducted a survey on deep learning for Alzheimer's disease [12]. It also reinforced the concept that deep learning models forecast with uncertainty. Jose et al. published a review of neuroimaging approaches for brain illnesses in 2018. Machine learning approaches are said to be beneficial for determining the underlying neurological reasons for brain illnesses. From 2006 to 2016, Pellegrini et al. published 111 publications on machine learning algorithms for dementia and cognitive impairment [4]. It emphasized the creation of unique machine learning models using an interdisciplinary approach. Rathore et al. [13] also presented an overview of Alzheimer's disease and its prodromal phases.

Prediction of AD at an early stage is a recent research analysis and can be tackled using machine learning algorithms. The presented research focuses on the use of features from the Open Access Series of Imaging Studies (OASIS) 2 neuroimaging dataset in developing novel machine learning models for unbiased classification of data points [14]. The signs of dementia is very recognisable through an series of analysis of the cognitive study and neuroimaging data, and the use of machine learning not only enhances these processes but help develop more novel systems.

Related Works

Numerous studies showed that different machine learning algorithms have been implemented in the early detection of Alzheimer's disease. Trambaiolli et al. [15] have applied a support vector machine in order to extract and classify EEG patterns because of the model's robustness to process high dimensional data. Machine learning techniques and quantitative MRI metrics have been used together to identify patients with Alzheimer's from elderly people [16]. These same techniques also predicted disease progression. Another approach for Alzheimer detection was multi-modal, multi-atlas based through machine learning [17]. Collected data from the ADNI database was divided base on the LONI Probabilistic Brain Atlas (LPBA40) and Automated Anatomical Labeling (AAL) which are two well-known atlases. Classification was performed with support vector machines based on features extracted from each atlas.

Other studies have used voxel-based MRI image feature extraction with machine learning algorithms for Alzheimer detection [18]. The proposed method consists of 3-D structural brain MR images separating the white and grey matter MR images, extracting 2D slices in the coronal, sagittal and axial directions and selecting the key slices from them to do feature extraction. This approach can also be used with pattern recognition models as well. Images were preprocessed using statistical parametric mapping to individually map voxels and then they were passed through six pattern recognition models, some of which were ensemble classifiers based on stochastic searches.

Methods

This study proposes a novel technique for the early detection of Alzheimer's disease in older adults. The dataset is generated by data obtained from brain MRI images, collected from the publicly available database of OASIS-2. This set consists of a longitudinal collection of 150 subjects aged 60 to 96 for a total of 373 imaging sessions [19]. The exploratory data analysis (EDA) stage was based on investigating the relationship between the various aspects of the MRI assessments and the patient's dementia rating. In the data preprocessing stage, the dataset was preprocessed by applying feature selection and

feature extraction methods to remove any of the unwanted noise or missing values. The dataset was then split into three data sets namely training, validation, and testing. Also, feature scaling was applied to bring all the features to the same level. In the Model Implementation step, six machine learning models, Logistic Regression (w/ imputation), Logistic Regression (w/ dropna), SVM, Decision Tree, Random Forest, AdaBoost, were trained and tested by the cleaned dataset and 5-Fold Cross-Validation was implemented. Finally, in the Analysis of Models stage, all models were evaluated on a score of the area under the receiver operating characteristic curve (AUC) score, Accuracy, and Recall of each model.

Figure 1. A few example of the MRI sequences from which the longitudinal dataset is derived. The three columns describes scans of patients with Moderate Dementia, Very Mild Dementia, and Non-Dementia ratings.

Results and Discussion

Through the Data Exploratory stage, we analyzed the medical history of patients and the correlation of features with the degree of Clinical Dementia Rating (No dementia = 0 CDR, Very mild AD = 0.5 CDR, Mild AD = 1 CDR) [20]. The results derived from the explorations are described in Table 2.

A Boxplot (Figure 3) was also plotted to represent the correlation between the data in various attributes of the database and Clinical

Figure 2. Correlation between CDR and age distribution

Figure 3. A Boxplot representation of correlation between CDR with each feature. In the box plot, female and male groups of patients are represented through group 0 (blue) and group 1 (orange) respectively.

Dementia Rating (CDR). Through a series of graph analysis, we drew various conclusions: 1. The MMSE score was much higher in Non-demented group than the Demented group of patients 2. The brain volume is greater in Non-demented group than the Demented group of patients. This conclusion holds true either way because AD directly results in the shrinking of brain tissues 3. The concentration of age group from 70 and older is much higher in Demented group than Non-demented group of patients, thus we can also establish that AD's prognosis is dependent on aging. 4. There is very low frequency of patients from age group 90 and

Table 1. Description of demographic, clinical, and derived imaging measures present in dataset.

Feature	Description	Citation
Age	Age at time of image acquisition (years)	-
Gender	Gender (M or F)	-
Education	Years of education	-
SES	Socioeconomic status as assessed by the Hollingshead Index of Social Position and classified into categories from 1 (highest status) to 5 (lowest status)	Hollingshead, 1957
MMSE	Mini-Mental State Examination score (range is from 0 [worst] to 30 [best])	(Folstein, Folstein, & McHugh, 1975)
CDR	Clinical Dementia Rating. (0 = no dementia, 0.5 = very mild AD, 1 = mild AD, 2 = moderate AD)	(Morris, 1993)
ASF	Atlas scaling factor (unitless). A computed scaling factor that transforms native-space brain and skull to the atlas target (i.e. the determinant of the transform matrix)	(Buckner et al., 2004)
eTIV	Estimated total intracranial volume (cm ³)	(Buckner et al., 2004)
nWBV	Normalized whole brain volume, expressed as a percent of all voxels in the atlas-masked image that are labeled as gray or white matter by the automated tissue segmentation process	(Fotenos et al., 2005)

Table 2. Sample characteristics of subjects. Mean values given $\pm$ SD. Values in parentheses represent the range

Attribute	CDR 0	CDR 0.5	CDR 1
Number	86	51	13
Female/male	60/26	21/30	7/6
Age, y	75.8 $\pm$ 8.2 (60–93)	74.8 $\pm$ 6.3 (62–90)	75.7 $\pm$ 8.7 (61–96)
Education, y	15.2 $\pm$ 2.7 (8–23)	13.6 $\pm$ 2.8 (6–20)	14.0 $\pm$ 3.2 (8–20)
MMSE	29.1 $\pm$ 0.8 (27–30)	26 $\pm$ 3.1 (17–30)	23.0 $\pm$ 3.3 (19–30)
Prescriptions, n	2.9 $\pm$ 2.1 (0–9)	3.2 $\pm$ 2.4 (0–11)	2.5 $\pm$ 2.4 (0–7)
Systolic BP, mmHg	135.5 $\pm$ 20.3 (98–192)	143.5 $\pm$ 19.4 (118–188)	143.4 $\pm$ 24.9 (90–188)
Diastolic BP, mmHg	72.8 $\pm$ 10.2 (50–100)	77.1 $\pm$ 10.1 (58–98)	76.9 $\pm$ 9.2 (60–88)
Reported HBP, %	54.6	46	53.3
Diabetes, %	9.3	14	13.3

older, but we can't conclude that the disease has a lower survival rate at that age group because the cause of death could have other factors as well. 5. The education level represent a crucial relation, patients with higher education tend are less likely to have Dementia. 6. Male patients are more likely with Dementia than the female patients' group. Using the above conclusions, the machine learning models were successfully trained to discriminate between data points.

In the Analysis of Models, the Random Forest Classifier achieved the highest accuracy and 5-fold cross-validation area under the curve (AUC) score of 89.93% and an accuracy of 94.64% which outperformed all other models in discriminating between Demented and Non-demented patient groups as shown in Table 3.

Furthermore, we also compared our results with the previous state-of-the-art researches (shown in Table 4), and our proposed model's

Table 3. Classification metrics results amongst various models trained

Models	Accuracy	Sensitivity	AUC
Logistic Regression (w/ imputation)	76.31	68.41	76.67
Logistic Regression (w/ dropna)	80.56	75.63	75.00
SVM	82.58	70.25	82.31
Decision Tree	81.89	65.77	82.50
Random Forest	94.64	89.83	91.22
AdaBoost	86.48	76.30	86.50

Table 4. Comparison of proposed approach with state of the art techniques

Approaches	Modality	Accuracy	sensitivity
SK SVM	MRI/PET	84.40	84.64
MK SVM	MRI/PET	86.42	84.98
Liu et al.	MRI/PET	87.76	88.57
Cuingnet et al.	ADNI	88.58	81.00
Hinrichs et al.	MRI/PET	82.00	85.00
Our proposed model	OASIS	94.64	89.83

accuracy, sensitivity, and AUC came out to be highest amongst all of them.

Conclusion

The work introduces meta-learning and ensemble learning-based models for the early detection of AD in older adults, utilizing various

Figure 4. A Box Plot representation of correlation between CDR with each feature. We drew various conclusions: 1. The Non-demented group got much higher MMSE scores than Demented group 2. Non-demented group has a higher brain volume ratio than the Demented group. This is assumed to be because the diseases affect the brain to be shrinking its tissue. 3. There is a higher concentration of 70-80 years old in the Demented patient group than those in Non-demented patients. 4. Patients who suffer from AD have a lower survival rate thus there are fewer individuals more than 90 years old 5. Demented patients were less educated in terms of years of education than Non-demented.

features of longitudinal brain MRI data. Specifically, the author integrated features like MMSE score, Education, and Socioeconomic status for a non-biased classification. Meanwhile, various data exploratory and analysis methods were applied to establish correlations between features and also to find trends in the data. Shrinking of brain volume, higher risk in 70-80-year-old adults, and lower risks in patients with high education levels are some of the outcomes established through the explorations. Random Forest Classifier achieved an accuracy of 94.64% and a 5-fold cross-validation area under the curve (AUC) score of 89.93% in classifying between Demented and Non-demented patient groups. The extensive explorations on the OASIS-2 dataset demonstrate that the proposed models and methodology signif-

icantly helps in the classification of Alzheimer's Disease at an early stage with high accuracy and, also, vast feature selections helped in creating a more generalized model.

Acknowledgements

Data were provided by OASIS: Longitudinal: Principal Investigators: D. Marcus, R. Buckner, J. Csernansky, J. Morris; P50 AG05681, P01 AG03991, P01 AG026276, R01 AG021910, P20 MH071616, U24 RR021382

REFERENCES

1. HI Suk. Latent feature representation with stacked auto-encoder for ad/mci diagnosis, 2015.
2. Satvik Tripathi. Artificial intelligence: A brief review. Analyzing Future Applications of AI, Sensors, and Robotics in Society, pages 1–16, 2021.
3. Elaheh Moradi, Antonietta Pepe, Christian Gaser, Heikki Huttunen, Jussi Tohka, Alzheimer's Disease Neuroimaging Initiative, et al. Machine learning framework for early mri-based alzheimer's conversion prediction in mcisubjects. *Neuroimage*, 104:398–412, 2015.
4. Enrico Pellegrini, Lucia Ballerini, Maria del C Valdes Hernandez, Francesca M Chappell, Victor González-Castro, Devasuda Anblagan, Samuel Danso, Susana Muñoz-Maniega, Dominic Job, Cyril Pernet, et al. Machine learning of neuroimaging for assisted diagnosis of cognitive impairment and dementia: a systematic review. *Alzheimer's Dementia: Diagnosis, Assessment Disease Monitoring*, 10:519–535, 2018.
5. Monika A. Myszczyńska. Applications of machine learning to diagnosis and treatment of neurodegenerative diseases, 2020.
6. Rashmi Kumari. Machine learning technique for early detection of alzheimer's disease, 2020.
7. Halil Bisgin, Tanmay Bera, Hongjian Ding, Howard G Semey, Leihong Wu, Zhichao Liu, Amy E Barnes, Darryl A Langle, Monica Pava-Ripoll, Himansu J Vyas, et al. Comparing svm and ann based machine learning methods for species identification of food contaminating beetles. *Scientific reports*, 8(1):1–12, 2018.
8. Zhenghao Shi, Lifeng He, Kenji Suzuki, Tsuyoshi Nakamura, and Hidenori Itoh. Survey on neural networks used for medical image processing. *International journal of computational science*, 3(1):86, 2009.
9. Dinggang Shen, Guorong Wu, and Heung-Il Suk. Deep learning in medical image analysis. *Annual review of biomedical engineering*, 19:221–248, 2017.

10. Claudia Plant, Stefan J Teipel, Annahita Oswald, Christian Böhm, Thomas Meindl, Janaina Mourao-Miranda, Arun W Bokde, Harald Hampel, and Michael Ewers. Automated detection of brain atrophy patterns based on mri for the prediction of alzheimer's disease. *Neuroimage*, 50(1):162–174, 2010.
11. Geert Litjens, Thijs Kooi, Babak Ehteshami Bejnordi, Arnaud Arindra Adiyoso Setio, Francesco Ciompi, MohsenGhafoorian, Jeroen Awm Van Der Laak, Bram Van Ginneken, and Clara I Sánchez. A survey on deep learning in medical image analysis. *Medical image analysis*, 42:60–88, 2017.
12. José María Mateos-Pérez, Mahsa Dadar, María Lacalle-Auriales, Yasser Iturria-Medina, Yashar Zeighami, and Alan C Evans. Structural neuroimaging as clinical predictor: A review of machine learning applications. *NeuroImage: Clinical*, 20:506–522, 2018.
13. Saima Rathore, Mohamad Habes, Muhammad Aksam Iftikhar, Amanda Shacklett, and Christos Davatzikos. A review on neuroimaging-based classification studies and associated feature extraction methods for alzheimer's disease and its prodromal stages. *NeuroImage*, 155:530–548, 2017.
14. Satvik Tripathi and Thomas Heinrich Musiolik. Fairness and ethics in artificial intelligence-based medical imaging. In *Ethical Implications of Reshaping Healthcare With Emerging Technologies*, pages 71–85. IGI Global, 2022.
15. Fraga FJ Kanda PA Anghinah R Nitrini R. Trambaiolli LR, Lorena AC. Improving alzheimer's disease diagnosis with machine learning techniques, 2011.
16. Xiaojing Long, Lifang Chen, Chunxiang Jiang, Lijuan Zhang, and Alzheimer's Disease Neuroimaging Initiative. Prediction and classification of alzheimer disease based on quantification of mri deformation. *PloS one*, 12(3):e0173372, 2017.
17. Yousra Asim, Basit Raza, Ahmad Kamran Malik, Saima Rathore, Lal Hussain, and Mohammad Aksam Iftikhar. A multi-modal, multi-atlas-based approach for alzheimer detection via machine learning. *International Journal of Imaging Systems and Technology*, 28(2):113–123, 2018.
18. Srinivasan Aruchamy, Amrita Haridasan, Ankit Verma, Partha Bhattacharjee, Sambhu Nath Nandy, and SivaRam Krishna Vadali. Alzheimer's disease detection using machine learning techniques in 3d mr images. In *2020 National Conference on Emerging Trends on Sustainable Technology and Engineering Applications (NCETSTE)*, pages 1–4, 2020.
19. Daniel S. Marcus. Open access series of imaging studies: longitudinal mri data in nondemented and demented older adults, 2010.
20. John C. Morris. The clinical dementia rating (cdr): Current version and scoring rules, 1993.

Satvik Tripathi , is currently a freshman at Drexel University and an active researcher in the field of AI in Medicine. His main areas of concentration are Artificial Intelligence, Neuroscience, Psychology, Radiology, and Mathematics. He is currently working as a Research Assistant at various labs at Drexel University and Drexel School of Medicine. Alongside, he is also serving as the Vice President at Drexel AI and the Student Officer at the Medical Intelligence Society. He is well experienced with neuroradiological imaging and developing as well as implementing Deep Learning techniques for clinical use. His main research interests include AI in Medicine, Computation and Quantitative Neuroscience, Cognitive neuroscience, and psychoanalysis. Recently, he received a grant from Drexel Undergraduate Research Fund and Pennoni Honors College for his project in medical imaging. Contact him at st3263@drexel.edu.

Alisha Isabelle Augustin, is currently an undergraduate student at Drexel University. Her research interests include: artificial intelligence, machine learning, computational neuroscience, bioinformatics, biomedical signal processing and medical imaging. She is an active researcher at Drexel University as well as the President of Drexel AI.

Dr. Edward Kim , is an Associate Professor in the Department of Computer Science at Drexel University. He graduated from Lehigh University in 2013 with a Ph.D. in Computer Science. Dr. Kim performs research in the area of Computer Vision, Sparse Coding, Neuromorphic Computing, Medical Image Processing, Artificial Intelligence, and Game Development. Kim was the recipient of the 2019 NSF CAREER Award in Robust Intelligence.