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AI neurotechnology compatibility with Alzheimer's Disease Treatment: A Review

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Abstract. Alzheimer's Disease (AD) is one of the most ordinary kind of dementia, yet no definitive cause or cure for it is found. Currently, there are only developments in drugs or technology that can slowly help to minimize the symptoms of AD through treatment or aid in the diagnosis of this disease. The main problem is that the treatment and diagnosis of AD administered through medical professionals are prone to errors. This has created a need for methods that make the process of diagnosing AD and concluding the most effective treatment both efficient and highly accurate. This brings focus to studies in AD, more specifically neurotechnology that uses Artificial Intelligence (AI) to aid in diagnosis and process of treatment. AI has the potential to diagnose and can even work hand in hand with different AD treatments, as it is expected to analyze the best approach for individual patients for course of treatment which could lead to the cure of Alzheimer's. Studies on Neurotechnologies that use AI, such as systems like Machine Learning, Deep Learning, and have yielded promising results of the potential accuracy of these systems, proving its ability to diagnose AD with high accuracy while being more efficient. With the wide variety of potential treatments of AD, it is in these situations where AI neuro technology can play a role in the deciding factor of treatment. This paper will be a comparison on these diverse types of AI systems, and which may be the best in terms of diagnosis and treatment of AD.

Keywords: machine learning, deep learning, transfer learning, AI, Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is one of the neurodegenerative diseases [1], with over 55 million people (about twice the population of Texas) worldwide affected by AD as of 2020. Although AD is most common in ages 65 or older, it can also be found in people younger than 65. This number is predicted to double by 2040, and AD is predicted to have approximately 140 million cases in 2050 [2]. AD can cause a loss of mental, behavioral, and functional abilities, deriving symptoms such as memory loss. A more thorough diagnosis of AD would be to obtain brain imaging of the patient, namely through Magnetic Resonance Imaging (MRI), which forms images of the brain using electrically charged molecules. These scans can be done on both a macroscopic and microscopic scale. The macroscopic provides more general features that may lead to the diagnosis of AD, such as atrophy in the posterior cortex, the frontal lobe, the medial temporal lobe, which may lead to volume loss of white matter or enlargement of frontal and temporal horns. Other features of AD the macroscopic scan can observe is neuromelanin pigmentation loss in the locus coeruleus, or overall decrease in brain weight. Though,

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these features are not limited to the prognosis AD because of similar features to other diseases on the macroscopic scale. To take a deeper look into the pathology of AD, microscopic scans can be used to detect neurofibrillary tangles, amyloid plagues, eosinophilic Hirano bodies, granulovacuolar degeneration, which are factors contributing to the symptoms of AD [3]. These methods alone may not be the sole solution to Alzheimer's, as each treatment's effectiveness may vary on different patients. This introduces the compatibility of neurotechnology, AI technologies like deep learning AI. AI models have become efficient tools not only in diagnosis of Alzheimer's, but also in deciding the approach of treatment for the patient. AI learning networks are practical tools for aiding in AD because it learns through the data that is introduced to the AI. The AI can be trained to be more specific to AD by introducing substantial amounts of labeled datasets. They further optimized by separate algorithms, making it capable of learning sophisticated patterns from large imaging datasets, namely from neuroimaging, allowing for correct diagnosis of AD and even combating prognosis of AD through treatment, which is embodied through systems like Machine Learning, Deep Learning.

2. Machine Learning Biomarkers

One of the more prominent types of machine learning biomarkers is cerebrospinal fluid (CSF) since it is a better source because it directly interacts with the brain's extracellular space and can mirror biochemical changes inside the brain. In a study conducted by a team in Italy, they tested the core biomarkers of CSF to diagnose AD. Researchers used an unsupervised Gaussian mixture model for cluster analysis. The clustering algorithm generated cut-off values varying for the distribution of each core biomarker, creating 6 clusters (best number chosen by the Bayesian information criterion/BIC) to classify the 2 main cohorts, comparing AD prone patients (early MCI/dementia) versus other neurological diseases (OND) with CSF samples provided (Fig. 1).

	% AD clusters	% cluster 1	% cluster 2	% cluster 3	% cluster 4	% cluster 5	% cluster 6
AD	95	3	2	32	34	22	7
PDD	57	43	0	57	0	0	0
DLB	62	38	0	43	10	10	0
OND	7	77	15	6	0	1	0

Figure 1. Heat map GMM cluster analysis. Clusters 3-6 represent AD, Parkinson's disease with dementia, and patients with dementia with Lewy bodies. Clusters 1-3 represent other neurological diseases/conditions.

It was observed that 95% of AD patients were classified into clusters 3-6, while OND samples were in cluster 1, suggesting that AD patients have low AB42/AB40 values and high p-tau and t-tau values. Although this may be a viable option in AD diagnosis, it may be more practical for general usage in detecting neurological diseases due to other diseases and sharing similar features as AD pathology, and similarly ending up in the same clusters as AD samples. Though, some limitations of these methods are the system being biased to small sample sizes of diagnostic categories, a lack of amyloid PET, and may not be effective for detecting cases of AD misdiagnosis or underlying conditions. On the other hand, cut-off values calculated for AD clusters compared to control clusters were unchanged regarding age

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and gender matched subsets of clusters and can be helpful in situations involving massive quantities of samples, being ideal for neurodegenerative disease diagnostics [4].

In addition, there are other potential unique biomarkers such as ones that are blood-based, more specifically involving plasma, that can be used with Machine Learning. This type of biomarker was applied through the 2D3A8 antibody, found in plasma samples to predict the development of AD in mild cognitive impairment patients who would later develop AD. It has been observed that unfolded p53 plasma levels are correlated with progression of AD. The team utilized an integrated regression tree algorithm to predict the risk of AD in patients. This was done by creating 6 nodes, separated into three categories with two nodes each, with APOEe4 presence and MMSE scores < 25.5 as standards for classification, and unfolded p53 plasma levels were the most important differentiating factor to classify the types of risk of AD development. RT achieved 86.67% accuracy according to the clinical diagnosis of the subjects. Specifically, RT classified 13 subjects as high-risk, 11 (84.62%) of which would actually develop AD in a span of 4 years, 12 as medium-risk, 7 progressing to/maintaining stable MCI and the remaining 5 developing AD, and lastly classified 65 subjects as low-risk, with 62 (95.38%) of them CN or having mild MCI (Fig. 2).

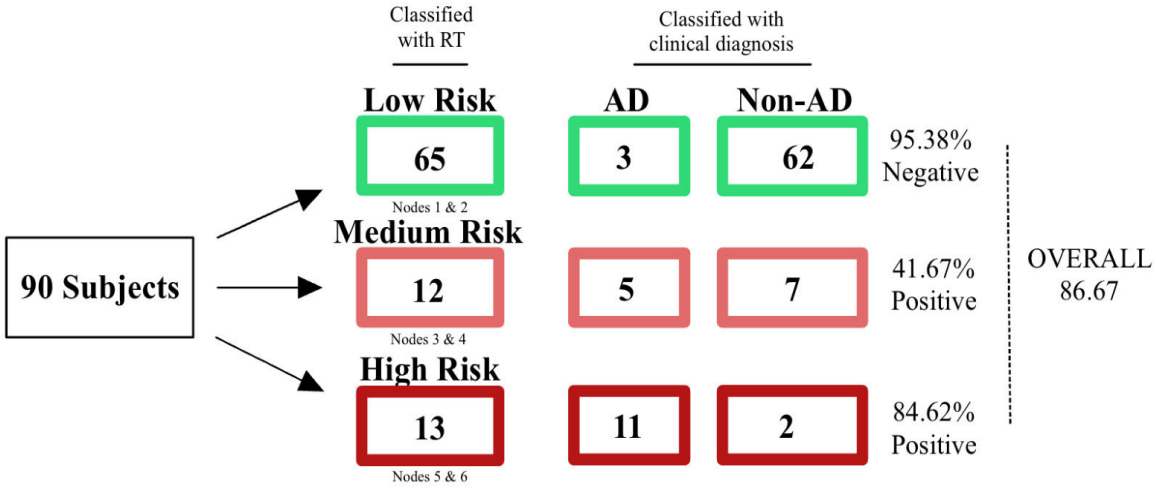

Figure 2. RT algorithm representation to predict AD risk. Structure represents 6 nodes split into 3 categories implicating risk of AD (green: low, pink: middle, red: high) classified by APOEε4, MMSE, and most importantly U-p532D3A8+ and patients classified into each category, including accuracy according to clinical diagnosis.

This process was used similarly to test the plasma samples using unfolded plasma to identify AB^+ subjects from aMCI PharmaCog/E-ADNI. Instead of having 6 nodes, this experiment would include 4 nodes separated in groups of two using the same weight of conditions and similar criteria through the RT algorithm. The algorithm yielded promising results, in terms of which AB+ aMCI subjects will develop AD within a period of 6-30 months (about 2 and a half years). Overall, this blood-based biomarker's strength in distinguishing non-AD patients has the potential to be effective in early detection, helping in primary care settings. Compared to CSF and PET scans, misdiagnosis rates may exceed 20%, providing a well-rounded solution; in addition, unfolded p53 levels specifically could be compatible with CSF or plasma [5].

Another type of biomarkers is the N-Methyl-D-Aspartate Receptor-Mediated biomarker. This is a brain-based biomarker based on the N-Methyl-D-aspartate receptor along with glutamate, both important in synaptic plasticity and excitatory neurotransmissions. In this study, Chang et al. tested SVM, logistic regression, random forest, and naive Bayes using D-glutamate levels and MMSE scores to build predictive models for classifying patients with AD or MCI from a healthy control. Chang et al. found the naive Bayes model and random forest model were better suited for determining MCI and AD

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vulnerability with AUC: 0.8207 and 0.7900, sensitivity: 0.8438 and 0.6997, and specificity: 0.8158 and 0.9188. On another note, the team discovered that D-glutamate is negatively correlated to cognitive functionality in AD patients, observing that glutamate levels were lower in MCI and AD patients compared to a healthy elderly control; additionally, glutamate levels significantly affected Mini-Mental State Examination scores. They suggest that glutamate may be a potential candidate in detecting MCI and AD, and similar rapid and cost-effective high-performance liquid chromatography (HPLC) biomarkers paired with machine learning can benefit the diagnosis of MCI and AD in outpatient clinics [6].

3. Deep Learning

Other benefits that deep learning can provide is the ability to diagnose AD remotely. By establishing a website that utilizes CNN architectures where the patient/doctor uploads MRI images. The CNN architecture tested was a VGG19 model with 19 layers with fine-tuning applied (fine-tuned VGG19). For the multi-classification of NC, AD, early mild cognitive impairment, and late mild cognitive impairment, the fine-tuned VGG19 reached an accuracy of 97%, not only diagnosing, but also determining the current state of AD that the patient has based on the AD spectrum. Then, the website can advise the patient on their course of action regarding their condition. This will be helpful in the future, as the population of elderly people is projected to significantly increase, many of which have limited mobility. By making the process of diagnosis more remote, removing the hassle of coming in for a personal appointment, systems like these can make the medical field more available to all types of people [7].

Convolution Neural Networks are typically an effective tool in AD diagnosis, but due to the fully connected layer's limitations in only inputting 1D data, the study proposes shallow 3D-CNN networks. In addition, the team implemented a bidirectional long short-term memory which has two inputs to control information flow, stacked with the LSTM becoming a stacked Bi-LSTM (SBi- LSTM) to enhance spatial information from the 3D-CNN, and further enhanced with the FC layer to increase accuracy by enhancing connection between the output nodes of SBi-LSTM, finally becoming a fully stacked bidirectional LSTM (FSBi-LSTM). The researchers wanted to compare the efficacy of AD diagnosis of this model by comparing it with other machine and deep learning models, such as Fisher vector (FV), support vector machine (SVM), FSBi-RNN (recurrent neural network), FSBi-GRU (gated recurrent unit), 2D-CNN with SBi-GRU, and so on by calculating various metrics of these models' performance in classifying AD vs. Normal control, progressive MCI vs. NC, and stable MCI (sMCI) vs. NC. Overall, the FSBi-LSTM dominated the statistics, showing particularly high performance in AD vs. NC and pMCI vs. NC classifications. According to the researchers, despite enhanced accuracies in these categories, it was more challenging for the FSBi-LSTM system to detect sMCI, and the team suspects it is due to the intricate anatomical changes of sMCI, therefore making it harder to observe. Furthermore, brain lesion structure can only be procured by shielding the brain area and not directly obtained due the lack of signal/imaging sampling employed in the algorithm; additionally, the utilization of longitudinal MRI data can be complementary. In short, FSBi-LSTM is more practical for the regular diagnosis of AD due to the high accuracy displayed by the system in classifying AD vs. NC patients using MRI and PET [8].

Transfer learning has demonstrated superior effectiveness compared to training models from scratch. Building on previous research, this study delves into the comparison between stable Mild Cognitive Impairment (sMCI) and progressive Mild Cognitive Impairment (pMCI). The research aims to enhance classification efficiency by transferring learned visual representations from an Alzheimer's Disease (AD) versus Normal Control (NC) model to the pMCI versus sMCI classification model. The study utilizes the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, applying convolutional autoencoder (CAE)-based unsupervised learning for AD vs. NC classification, and supervised transfer learning for differentiating pMCI from sMCI.

Transfer learning has proved to be a more effective choice than models trained from scratch. Related to the previous study, this study will go into depth about sMCI, comparing sMCI to pMCI which

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researchers believe employing a transfer learning procedure will be more efficient in identifying by transferring visual representation by classifying AD vs. NC to the pMCI vs. sMCI learning model to enhance classification capabilities. The team proposed using convolutional autoencoder-based unsupervised learning for classifying AD vs. NC and for pMCI vs. SMCI using the Alzheimer's Disease Neuroimaging Initiative database. Transfer learning was employed by initializing the layers of the 3D-CNNs using pretrained weights of the AD vs. NC model to establish the pMCI vs sMCI model and reached a peak of a 73.94% accuracy (10% better than other models tested). Some limitations of the study include the number of training subjects to be small which may limit performance (although proves the potential of learning models despite lack of data), and gender difference may have impacted performance/outcomes of the study. Despite these limitations, not only did the transfer learning model produce better results, but by implementing this type of system would allow for less effort for training, which would save time being an efficient option [9].

4. Conclusion

As technology continues to improve, these AI systems categories like machine learning and deep learning will improve along with new developments. These AI systems have the capabilities to become especially useful as they are developed, potentially becoming an everyday tool aiding with the diagnosis of AD, which will become particularly important in the future as AD cases increase. With no current developments in a cure for AD, these AI systems will become crucial in helping with the process of treatment, the current best option to take for a patient to improve mentally. As these AI systems are continually developed, it will revolutionize the medical world, making diagnosis and treatment of disease more efficient and accurate, while also making it more convenient for doctors and patients alike.

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