Diagnosis of Alzheimer’s disease and Mild Cognitive Impairment using Rethinking and Deep Neural Networks

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***Abstract*—The early diagnosis of Alzheimer’s Disease (AD) and its prodromal stage, Mild Cognitive Impairment (MCI), are important for doctors to treat patients as soon as possible. In this paper we focus exclusively on the use of EEG for the Machine Learning based diagnosis of MCI and AD. The choice of EEG is made because this modality is relatively inexpensive, non-invasive and easily available even outside the clinical environment. Unlike the majority of ML algorithms for AD diagnosis which treat EEG as an 1-D signal we propose a 2-D approach. We first split the EEG channel signals into fixed length segments and then we reshape them into 2-D images used to train a powerful VGG-16 deep Convolutional Neural Network model. In order to improve the performance of the VGG-16 model and avoid overfitting, we employed a powerful pruning method called Rethinking.We study two experimental tasks: (a) classifying segments into AD/MCI or Health Control (HC) categories (b) classifying subjects (patients and healthy individuals) into the same categories. Our results showed that the proposed method can be used as a tool to diagnose AD at early stages with accuracy over 98.8.**

I. Introduction

Alzheimer’s disease (AD), is a progressive neurological disorder that causes the brain to shrink (atrophy) and brain cells to die. It mainly affects individuals over 65 years, and the rate of occurrence increases exponentially at the age of 65 years [1]. Currently, there exists no cure for AD and the existing medicines could only temporarily slow the brain degradation in patients. In recent years many researchers have tried to create techniques, and testing procedures to predict or diagnose AD in the very early stages of the disease [2]. These standards are an advancement in the previous guidelines, which had been developed in 1984 by the National Institute of Neurological And Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) [3].

The widespread adoption of machine learning can be mostly attributed to the availability of extremely large datasets and the improvement of computational techniques, which reduce over fitting and improve the generalization of trained models. These two factors have been the driving force to the rapid popularization and adoption of machine learning in almost every field today. This coupled with the increasing prevalence of interconnected devices or the Internet of Things (IoT) has created a rich infrastructure upon which to build predictive and automated systems [4].

Machine learning is a primary method of understanding the massive influx of health data today. An infrastructure of systems to complement the increasing IoT infrastructure will undoubtedly rely heavily on these techniques. Many use cases have already show enormous promise.

EEG is a technology that can record the electrical activity of the cerebral cortex over time by measuring the postsynaptic potentials of a large number of neurons that have the same spatial orientation. EEG’s spatial resolution refers to the number and location of electrodes on the scalp cite [5]. Several methods have been created to analyze the complexity of EEG in the past years.

In this study we propose a new pruning technique for CNN networks called “Rethinking”, transform EEG signals to heatmaps and use CNN to classify patients to one of the categories : Healthy, MCI, AD.

A. *Previous work*

The studies by Esteva et al. (2017) [6] and Simonyan and Zisserman (2014) [7] demonstrate the potential of deep neural networks (DNNs) for image classification tasks, including skin cancer and large-scale image recognition. These successes in image classification suggest that DNNs could also be effective in analyzing EEG signals for Alzheimer’s disease (AD) diagnosis. Cao et al. (2015) [8] proposed a feedback CNN for capturing top-down visual attention, which could be useful for analyzing attentional deficits in AD patients. Additionally, Sperling et al. (2011)[9] proposed using biomarkers, such as EEG signals, for early detection of AD. Therefore, the use of DNNs for analyzing EEG signals could be a promising approach for AD diagnosis. However, the challenge of obtaining

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large datasets for training DNNs remains a significant hurdle in this field.

The article titled ”Regional coherence evaluation in mild cognitive impairment and Alzheimer’s disease based on adaptively extracted magnetoencephalogram rhythms” [10] as conducted by J. Escudero and colleagues and aimed to investigate changes in brain connectivity in patients with mild cognitive impairment and Alzheimer’s disease using magnetoencephalography (MEG). The study involved analyzing MEG recordings of brain activity from 37 subjects, including healthy controls, individuals with mild cognitive impairment, and patients with Alzheimer’s disease. The researchers used an adaptive algorithm to extract rhythmic patterns in the MEG signals and then calculated coherence, a measure of synchronization, between different brain regions. The results showed that patients with mild cognitive impairment and Alzheimer’s disease had decreased coherence in certain brain regions compared to healthy controls.

Sarica et al. (2017)[11] conducted a review of the use of machine learning algorithms, including random forest classifiers, for the classification of neuroimaging data in AD. They found that random forest classifiers were effective for distinguishing between AD patients and healthy controls. However, the potential of DNNs for this task has not been extensively explored. The study by LeCun et al. (2015) [12] provides an overview of DNNs, including convolutional neural networks (CNNs), and their applications. This study emphasizes the importance of large datasets for training DNNs, which is a challenge in the field of AD diagnosis. Additionally, the work by Zhou et al. (2016)[13] proposes a method for learning deep features for discriminative localization in images, which could be adapted for the analysis of EEG signals to identify the specific regions of the brain affected by AD. Finally, Han et al. (2021)[14] proposed a method for compressing DNNs by pruning and quantization, which could be useful for reducing the computational requirements of DNNs for AD diagnosis. Evaluating the performance of DNNs for AD diagnosis could be done using cross-validation and bootstrap methods for estimating the accuracy of machine learning models, as proposed by Kohavi (1995)[15]. In conclusion, DNNs have great potential for the diagnosis of AD from EEG signals. However, there are challenges that need to be addressed, such as the availability of large datasets and the computational requirements of DNNs. The studies reviewed in this literature review provide insights and approaches that could be adapted for the analysis of EEG signals in AD diagnosis.

II. Research Methodology

In this section we describe our methodology which includes data collection, preprocessing, feature extraction, model architecture, and cross-validation techniques. The proposed study uses the EEG signal to diagnose AD and MCI against Healthy Control condition. Suggest that a deep CNN network architecture is learned to analyze multichannel human EEG signals and that increases the efficiency of classification.

A. Data collection

The dataset was provided by the “Greek Association of Alzheimer’s Disease and Related Disorders” and it consists of EEG recordings from 54 subjects: 18 healthy control individuals (HC), 18 patients affected by Mild Cognitive Impairment (MCI), and 18 patients affected by Alzheimer’s Disease (AD). The EEG signals were collected through a set of 21 electrodes, with the use of Nihon 274 Kohden Neurofax J921A, following the 10-20 international reference system (F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2) at 500Hz. Each patient had around 15 minutes of recorded data. During this 15-minute period, the eyes of the subject were closed for at least 5 minutes. Figure 1 shows the positions that the electrodes. For the experiments, only

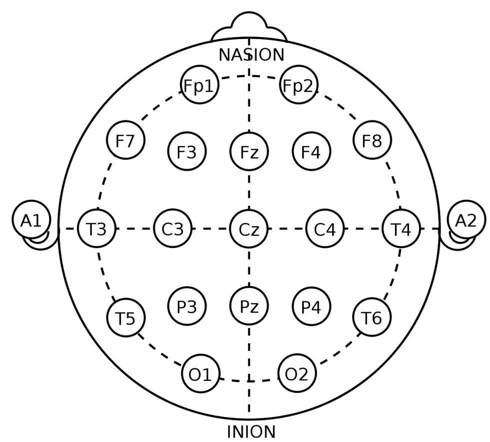

Fig. 1. EEG Electrodes placement

the 5-minute, eyes-closed session was used, without having artificial artifacts being involved in the process, as recorded in the annotations of the EDF files. For each subject, the 5 minute-session is segmented into non-overlapping epochs of 2 seconds, sequentially producing 150 segments for each subject and 8100 segments in total. We exclude Fp1, Fp2 electrodes signals because they are affected by eye movement.

B. Pre-processing

During pre-processing we first split each EEG channel signal into non-overlapping 2 seconds segments and tag them with the patient’s condition (AD/MCI/HC). Then we convert these segments into heatmaps using temperatureMap algorithm [16]. Each EEG recording consists of 19 channels, with heatmaps representing a 2-second segment from a specific channel as a 2-dimensional image of size 19x200 pixels. These heatmaps serve as visual representations of the information in the form of 2-D color images. The EEG data was collected using a sampling rate of 100 Hz. In our case, the image rows represent the 2 seconds data from an EEG segment, and the columns represent the 19 electrode channels. The temperature is mapped to colors.

C. Model

For the experiment we applied the VGG-16 convolutional neural model [7]. More specifically, we propose two different approaches: (a) using a classic VGG-16 model and (b) using a VGG-16 model with the “Rethinking” technique [8].

VGG-16 is a convolutional neural net (CNN) which was used to win the ILSVR (Imagenet) competition in 2014. It is considered to be one of the excellent vision model architecture to date. Instead of having a large number of hyper-parameters the authors focused on having convolution layers of 3x3 filters with a stride 1 and always used same padding and max-pooling layer of 2x2 filters of stride 2. This arrangement of convolution and max pooling layers are followed consistently throughout the whole architecture. In the end it has 2 fully connected layers followed by a softmax output layer [17]. The number 16 in VGG-16 refers to the fact that it has 16 layers. This model is a quite large network having about 138 million trainable parameters [18].

Rethinking is a pruning method that has been introduced for CNN models [8]. It is a feedforward and feedback mechanism that gets the working idea from selectivity in biased competition theory. The general idea of Rethinking is adding 1 or more rethinking layers after a hidden layer or an entire network and then calculate neuron enabling values with an specific selection algorithm. These values are used to reconfigure our network or hidden layer. After that, the methods sends back the output image as input to the hidden layer or network and the process maybe repeated.

The Rethinking layer is using binary neuron activation values to set the neurons as enabled or disabled. The algorithm takes as input an image and a neural module (e.g. a layer or a whole network) with learned parameters $\mathbf{w}$, and optimizes the module output by joint inference on binary neuron enabling values over all the hidden layers. In our work a Rethinking Layer is applied on top of each ReLU layer, changing ReLU and softmax behavior (re-interpreting the behavior of the layers employing a set of binary enabling variables $z \in \{0, 1\}$ for each neuron) and update the last rethinking layers according to the sign of the gradient of each neuron. After that, in each rethinking layer use the gradient ascent algorithm to update the hidden variables through all layers simultaneously and perform a back propagation step to send back the gradients.

The Rethinking Feedback loop works as follows:

1st iteration
: all neuron enabling values z_i are set to 1. The given information is processed and neurons in rethinking hidden layers update their enabling status to maximize the confidence of target output neuron.

2nd iteration
: Eliminate signals with minor contributions in making decisions, deactivate the relevant neurons. Then process the information again.

We could have more than 2 loops with same functionality.

The process of rethinking techniques used in data modeling can lead to significant improvements in both accuracy and the issue of overfitting. By critically evaluating and potentially modifying existing approaches, it is possible to create a more robust model that better captures the underlying patterns and relationships within the data. This can result in more accurate predictions and a reduced likelihood of overfitting, which occurs when a model is overly complex and performs well on the training data but poorly on new, unseen data. Thus, rethinking techniques can be an effective way to optimize data models and improve their overall performance.

III. Implementation

In this work, the ML models were trained and tested 10 times by applying 5-fold cross validation. The test performance of the methods is estimated by the average performance from all 10 experiments.

We use the VGG-16 models with and without rethinking for the automatic classification of normal and abnormal EEG signals. We study two types of classification problems:

(a) the classification of EEG signals into 3 categories: Health Control (HC), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD)

(b) the pairwise classification of EEG signals in
  - (b1) HC vs. AD
  - (b2) HC vs. MCI
  - (b3) MCI vs. AD

We also separate two different study cases: classifying signal segments into the proper categories or classifying the whole EEG of a subject into the proper category. In the first case, referred to as classification "per segment", it is possible to have segments from the same subject in both the training and test sets, thus achieving better performance compared to the second case, referred to as classification "per subject" in which all the segments of an EEG belong either in the training or the test set. The "per segment" scenario is not practical but it is studied because it commonly appears in the literature as a benchmark case.

There are 54 subjects in the EEG collection and each EEG is split to 150 segments of duration 2 seconds. The segments were transformed to heatmaps, as described in the pre-processing section. After that we randomly split the dataset into 80% used as training data and 20% as validation data.

For the "per segment" experimental design, the training dataset is composed of 80% of the total data, which corresponds to 54 patients multiplied by 150 segments per patient. This means that the training dataset contains 6480 segments, while the remaining 20% of the data, which corresponds to 1620 segments, is used as the test set.

For the "per subject" experimental design, the segments for each subject are kept together in either the training or test set. Specifically, all segments for a particular subject are included either in the training set or the test set, but not both. This means that if a subject has 150 segments, then all 150 segments are included in either the training or test set.

IV. Results

The results of classification for the VGG-16 trained model per subject are shown in Tables I, II and Figure 3. After processing all of the subject's EEG segments, we use the majority of our predictions to decide the class to assign to the subject.

The results of classification for the VGG-16 trained model per segment are shown in Tables III, II and Figure 4.

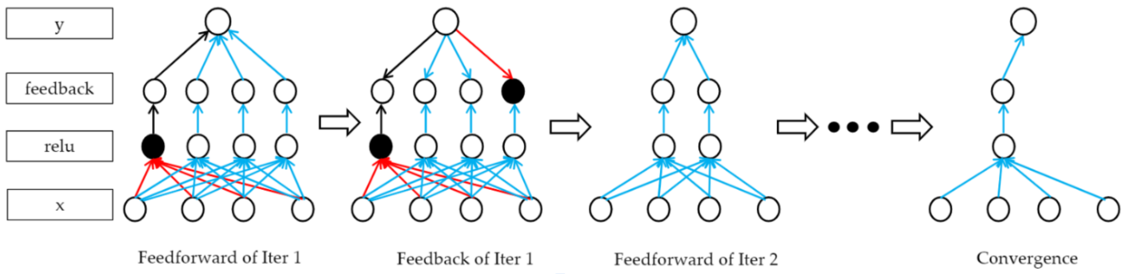

Fig. 2. Rethinking Example: Illustration of a model and its inference process. At the first iteration, the model performs as a feed-forward neural net. Then, the neurons in the feedback hidden layers update their enabling status to maximize the confidence output of the target top neuron. This process continues until convergence

TABLE I. PER SUBJECT CLASSIFICATION RESULTS FOR THE HC/MCI/AD CLASSIFICATION TASK.

Model	VGG-16	VGG-16 with Rethinking
Avg. Acc.	73.1	**74.2**
Max Acc.	81.3	**82.4**
Min Acc.	63.6	**64.1**

TABLE II. PER SUBJECT RESULTS FOR THE PAIRWISE CLASSIFICATION TASK. COLUMNS WITH HEADER “V” AND “V+R” CORRESPOND TO THE VGG-16 MODEL AND THE VGG-16 MODEL WITH RETHINKING, RESPECTIVELY.

Type	AD/MCI		MCI/HC		AD/HC	
Model	V	V+R	V	V+R	V	V+R
Avg. Acc.	84.5	**85.3**	58.7	**59.3**	88.1	**89.4**
Max Acc.	91.1	**92.7**	64.8	**65.3**	94.2	**95.1**
Min Acc.	67.3	**68.1**	54.4	**55.2**	79.6	**80.1**

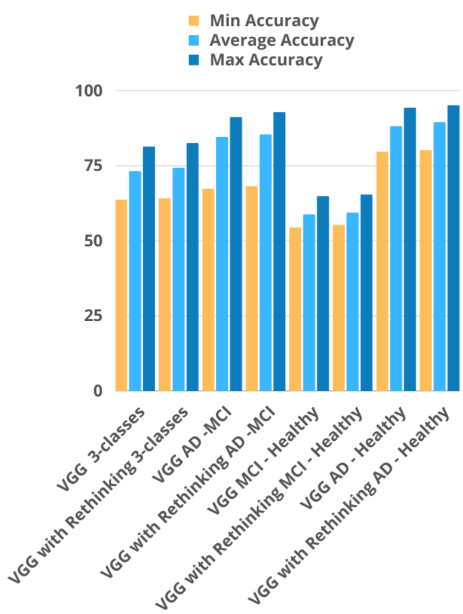

Fig. 3. Per Subject results diagram

TABLE III. PER SEGMENT RESULTS FOR THE HC/MCI/AD CLASSIFICAITON TASK.

Model	VGG-16	VGG-16 with Rethinking
Avg. Acc.	93.7	**95.2**
Max Acc.	95.4	**96.1**
Min Acc.	91.7	**92.8**

TABLE IV. PER SEGMENT RESULTS FOR THE PAIRWISE CLASSIFICATION TASK.

Type	AD/MCI		MCI/HC		AD/HC	
Model	V	V+R	V	V+R	V	V+R
Avg. Acc.	90.3	**91.1**	87.2	**88.9**	98.7	**99.3**
Max Acc.	91.1	**92.7**	89.3	**90.5**	99.2	**99.5**
Min Acc.	87.4	**88.3**	81.1	**82.2**	89.5	**98.8**

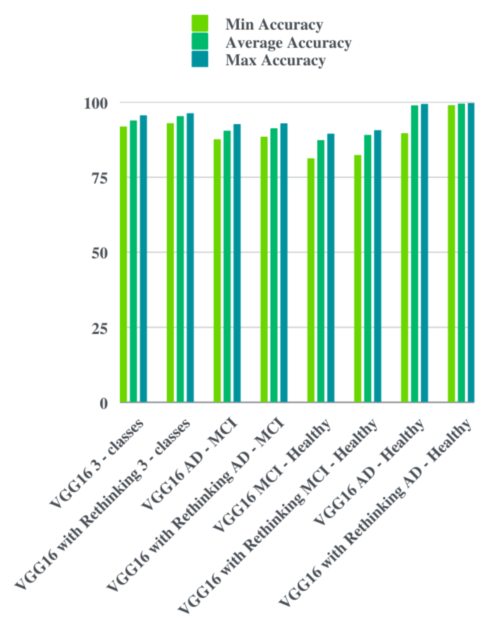

Fig. 4. Per Segment Results Diagram

A. Discussion

It is easily observed that the accuracy difference between classification by segment and classification by subject is significant. This is clearly because in the "per segment" scenario we use segments from the same subject in both training and test sets. Moreover, "Rethinking" improves all measurement (Min, Max and Average) of the accuracy by 1.5% - 3%.

One of the results that attracts attention, is that the AD vs MCI classification model achieves the highest accuracy. That means we could use this model with the rethinking technique to predict with high accuracy if a patient has AD or not. Using majority voting to classify the results for each subject, leads to a more stable and accurate classification.

Conclusions

This study investigates the potential of using electroencephalogram (EEG) data to classify patients as having Alzheimer's disease (AD), Mild Cognitive Impairment (MCI), or being healthy. The study employs a high-performance classification model that transforms EEG data into heatmaps and feeds them into a VGG-16 convolutional neural network (CNN) with Rethinking. The results demonstrate that this approach can be reliable enough to serve as a diagnostic tool for AD and MCI. The study stands out from previous research by separating subject EEG segments only into train or test sets. EEG data are useful for assessing brain activity, and previous studies have shown that EEG signals differ between individuals with AD, MCI, and healthy individuals. This study builds on that research, suggesting that using EEG data with deep learning techniques has great potential for improving the diagnosis of AD and MCI, which are major health concerns. Overall, this study provides valuable insights into the potential of using EEG data to identify individuals with AD or MCI.

Our future work will focus on classifying groups that transition from MCI to AD, an area that has not been extensively studied.

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