# Differentiating Alzheimer's Disease from Cognitively Normal Individuals Using Convolutional Neural Networks: A Reproducible Study

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**Abstract.** Alzheimer's disease (AD) is a progressive neurodegenerative disorder that affects millions of individuals worldwide. Early and accurate diagnosis is crucial for effective intervention and patient care. This study aims to develop a reproducible deep learning model based on convolutional neural networks (CNNs) to differentiate between AD patients and cognitively normal participants using brain MRI scans.
The chosen CNN model is not able to appropriately differentiate AD patients from cognitively normal (CN) participants. The attribution maps associated to the trained network highlighted regions known to be affected by the disease (medial temporal regions).
This reproducible study questions the potential of convolutional neural networks in differentiating Alzheimer's disease patients from cognitively normal individuals based on brain MRI scans and a possible clinical application. The open-source code used in this study is made available to facilitate further research and ensure transparency and reproducibility in the field of neuroimaging-based AD diagnosis.

**Keywords:** Alzheimer's disease · Deep Learning · Magnetic Resonance Imaging.

## 1 Introduction

Alzheimer's disease (AD) affects over 20 million people worldwide. Neuroimaging provides useful information to identify AD, such as the atrophy due to gray matter loss with anatomical magnetic resonance imaging (MRI). A major interest is then to analyze those markers to identify AD at an early stage. Machine learning and deep learning methods have the potential to assist in identifying patients with AD by learning discriminative patterns from neuroimaging data [1].

As the most widely used architecture of deep learning, convolutional neural networks (CNN) have attracted huge attention thanks to their great success in image classification. Contrary to conventional machine learning, deep learning allows the automatic abstraction of low-to-high level latent feature representations. Thus, one can hypothesize that deep learning depends less on image preprocessing and requires less prior on other complex procedures, such as feature selection, resulting in a more objective and less bias-prone process.

The purpose of this paper is to explain the results of a deep learning network trained to differentiate Alzheimer's disease patients from cognitively normal participants. The source code for the experiments and models described in this paper will be made available on GitHub and is attached to this submission during the review process.

## 2 Data set

The data used for this research were sourced from the UK Biobank dataset, which is a comprehensive cross-sectional collection of health and genetic data obtained from over 500,000 participants. This dataset encompasses a diverse range of individuals spanning various age groups and health conditions.

For the purposes of this study, our focus was directed towards a specific subset of the UK Biobank data, which consisted of individuals aged between 18 and 96 years. Within this subset, we included participants who exhibited two distinct cognitive states: those who were cognitively normal (CN) and those who had received clinical diagnoses of very mild to moderate Alzheimer's disease (AD). To differentiate the CN group, we divided it into two subcategories based on age: the "old" group, which encompassed individuals aged 62 years and older (in accordance with the minimum age of AD participants within this dataset), and the "young" group, which consisted of all participants below the age of 62 years.

For each subject, we selected the average of the motion-corrected co-registered individual T1-weighted MR images, which were resampled to 1 mm isotropic voxels. These images were located in the `PROCESSED/MPRAGE/SUBJ_111` subfolder of the dataset. Following a rigorous preprocessing pipeline, we randomly selected 10 participants from each age group whose images had successfully passed the quality check procedure (see section 3.1 for more details on the preprocessing steps).

This approach allowed us to work with a well-defined subset of the UK Biobank data, ensuring that the selected images met the necessary quality criteria for our study.

## 3 Methods

### 3.1 Preprocessing of T1-weighted MRI

The transformation of the UKBioBank data into the Brain Imaging Data Structure (BIDS) format was computed with Clinica (v0.7.6) [2]. Subsequently, the

T1-weighted MR images underwent preprocessing via Clinica's `t1-linear` pipeline, which serves as a wrapper for the ANTs software. For bias field correction, we applied the N4ITK method. An affine registration to MNI space was conducted using ANTs. Further adjustments were made by rescaling the registered images based on minimum and maximum intensity values. Subsequently, the images underwent cropping to eliminate extraneous background information, resulting in image dimensions of 169×208×179, featuring 1 mm isotropic voxels. In order to ensure the reproducibility of our results, we set the random seed of ANTs to the enigmatic number 42.

Quality control was meticulously carried out on the post-preprocessing outputs using a deep learning-based framework devised by Fonov et al. [3], and this framework was integrated into ClinicaDL (v1.5.0) [4]. This software generates a probability score reflecting the accuracy of the registration. Scans with probabilities below 0.5 were excluded from further analysis, and we conducted a visual assessment of scans with probabilities lower than 0.70. Consequently, we excluded a total of 39 scans from our dataset.

### 3.2 Deep learning network

Our network takes the whole 3D image as input and produces a numerical value for each label (AD and CN). These values can be interpreted as probabilities, representing the likelihood of belonging to each respective class, after the application of a SoftMax function.

*Hyperparameter search & values* We employed the random search method from ClinicaDL to optimize the network hyperparameters. Some parameters remained fixed throughout this process like the kernel size, the padding and the stride. The first convolutional layer has a number of channels of 16. Others parameters were subject to variation during the random search including the number of convolutional blocks, the type of normalization layer, the activation function, the number of fully-connected (FC) layers and the learning rate.

*Architecture* Our CNN architecture was discovered through an exhaustive process of 50 random search runs. It comprises 4 convolutional blocks and 2 FC layers. Each convolutional block is composed of a single convolutional layer with a kernel size of 3, a stride of 1, and padding of 1. Additionally, it includes an instance normalization layer, a leaky ReLU activation function, and a max-pooling layer with a kernel and stride of 2. We have also inserted a leaky ReLU activation function between the two fully connected layers.

*Computational setup* It's important to note that the runtime represents an average duration across all the runs conducted in the random search, with larger architectures requiring more time compared to smaller ones. This process, conducted on a computing cluster equipped with 10G of memory, took approximately 6 hours and 15 minutes per job. Additionally, the explainability method lasted 3 hours and 34 minutes.

### 3.3 Evaluation strategy

*Validation procedure* The test dataset comprised 200 individuals randomly selected to match in terms of age and gender, with 100 individuals belonging to each diagnostic class (i.e., 100 individuals with normal cognitive function and 100 individuals diagnosed with Alzheimer's disease). The remaining data was designated as the training/validation dataset. Using the ClinicaDL software, we ensured that the age and gender distributions in the training/validation and test datasets did not exhibit statistically significant disparities.

The process of model selection, which encompassed the selection of model architecture and the fine-tuning of training hyperparameters, was exclusively conducted using the training/validation dataset. To achieve this, a 5-fold cross-validation technique was employed, resulting in one fold (equivalent to 20% of the data) for validation, while the remaining data was used for training. It should be noted that this 5-fold data partitioning was executed only once across all experiments, thus ensuring that all experiments were relying on the exact same set of individuals for training and validation.

### 3.4 Implementation details

The deep learning models were built using the PyTorch library. Throughout the experiment, we leveraged the ClinicaDL software, which played a central role in various stages, including the creation of the train/test/validation sets, the random search for hyperparameters, and ultimately computing the performance of the networks.

Upon acceptance, we plan to make all of our code available to the community. This code will encompass comprehensive implementation details, providing a transparent and accessible resource for replicating and understanding our work.

## 4 Results

The performance of the network is lower when considering only the old population compared to using the whole CN group. Indeed 8 old CN participants on 10 are classified as AD patients (see Table 1).

Table 1: Confusion matrix of the CNN.

| | AD | CN |
|---|---|---|
| AD | 90 | 10 |
| CN (young) | 5 | 95 |

Both clinical scores are correlated with the probability of the diagnosis. However the strongest correlation is with age (correlation coefficient = 0.87). The sex is not correlated with the diagnosis.

Figure 1 displays the attribution map found with the first fold of the network. For all folds, we observed that the regions known to be atrophied by Alzheimer's disease were highlighted by the attribution map.

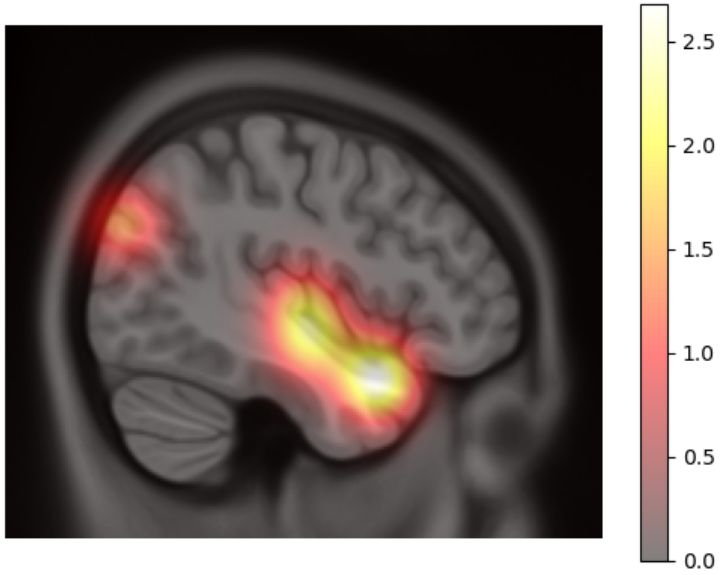


Fig. 1: Attribution map generated from the network trained on the first fold of the cross-validation.

## 5 Conclusion

In this paper we showed that the application of a deep learning network trained to detect AD on the ADNI data set cannot be directly applied to UKbioBank. Though the result of the network is correlated to the clinical scores used to diagnose dementia (MMSE and CDR), and the attribution map is highlighting regions that are known to be affected by the disease, we found that the strongest correlation is with the age, which is a healthy cause for brain atrophy. Future work will investigate why other regions than the medial temporal ones are included in the attribution map, and how they could be correlated with age detection.

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