Predicting Rate of Cognitive Decline at Baseline
Using a Deep Neural Network with Multidata Analysis

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Abstract
This study investigates whether a machine-learning-based system can predict the rate of cognitive decline in mildly cognitively impaired (MCI) patients by processing only the clinical and imaging data collected at the initial visit. We build a predictive model based on a supervised hybrid neural network utilizing a 3-Dimensional Convolutional Neural Network to perform volume analysis of Magnetic Resonance Imaging (MRI) and integration of non-imaging clinical data at the fully connected layer of the architecture. The analysis is performed on the Alzheimer’s Disease Neuroimaging Initiative (ADNI) dataset. Experimental results confirm that there is a correlation between cognitive decline and the data obtained at the first visit. The system achieved an area under the receiver operator curve (AUC) of 66.6% for cognitive decline class prediction.

Keywords: Computer-aided detection/diagnosis, Alzheimer’s Disease in the early stages, Cognitive decline, Mild cognitive impairment, Baseline Visit

1. Introduction
Mild Cognitive Impairment (MCI) is an intermediate stage between Cognitively Normal (CN) and Alzheimer’s Disease (AD) [1]. The patients in the MCI phase have a varied prognosis such that the cognitive functions of some MCI patients remain stable, without progression to AD [2][3]. While there has not been any successful treatment to reverse cognitive decline, to date, therapy to decelerate its progression is likely to be most beneficial if it is applied early [4][5]. In this study, we investigate whether a machine learning-based system can predict the rate of cognitive decline in patients with diagnosed MCI by processing only the clinical and imaging data obtained at the initial visit.

Prior studies have reported on biomarkers and the prediction of MCI-to-AD conversion [6][7][8][9]. However, in our study, we investigate the feasibility of predicting the “rate of cognitive decline” in MCI patients at their first visit by processing only the baseline MRI and routinely collected clinical data. We use a deep-learning-based predictive model that integrates imaging and non-imaging clinical data (demographic information) in the same neural network architecture. The analysis is performed on publicly available Alzheimer’s Disease Neuroimaging Initiative (ADNI) dataset (c.f., Section 2.1).

To that end, we build a predictive model based on a supervised neural network. The model predicts the patients’ cognitive condition as slowly deteriorating/stable or rapidly deteriorating. The model processes the clinical data obtained at the baseline visit, and it contains 3 main components: 1) MRI brain images, 2) scalar volumetric features, and 3) demographics. MRI brain scans are provided as input to the network as sequential DICOM images. Scalar volumetric features represent selected brain substructure volume data as extracted using FreeSurfer methods [10]. The scalar volume features included in the neural network architecture are total intracranial volume, whole-brain volume, and regional volumes of the hippocampus, entorhinal cortex, fusiform gyrus, medial temporal lobe. The demographic information are age, gender, years of education, ethnicity, and race. The proposed model is illustrated in Figure 2. We supervise the predictive model with the change in Mini-Mental State Examination (MMSE) scores [11][12]. The MCI subjects are grouped clinically according to (i) slow cognitive decline over 3 years, and (ii) fast cognitive decline over 3 years. The neural network architecture is a fully-automated, deep-learning-based, hybrid model containing 3-Dimensional Convolutional Neural Network (3D-CNN) to perform volume analysis of MRI and integration of non-imaging clinical data at the fully connected layer of the architecture.

2. Materials and Methods

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1 Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at [http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)
2.1. Data

The data used in this study were obtained from the ADNI database [13], which is an ongoing multi-center study. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. The subjects in the dataset were diagnosed as AD, MCI, Significant Memory Loss, or Cognitively Normal (CN) based on Mini-Mental State Examination (MMSE) scores. The enrolled subjects are being followed up to 3 years with visits at 3, 6, 12, 18, 24, and 36 months. For our research, we utilize data on ADNI patients who were clinically diagnosed as MCI at their baseline visits. A total of 569 subjects are used. The demographics of the subjects are summarized in Table 1.

![Table 1: Characteristics of the study subjects. MMSE: Mini-Mental State Examination. MCI - Mild Cognitive Impairment.](image)

We use the rate of decline in MMSE scores to supervise the system. The MMSE, which is a 30-point test, is a cognitive assessment tool [11][12]. Changes in MMSE scores in follow-up visits demonstrate the patients condition in terms of cognitive capabilities. A decrease in MMSE score reflects deterioration in cognitive capabilities; if a patients cognitive capability is stable, the MMSE scores remain relatively stable.

We model the change in MMSE scores by fitting a line to the scores obtained at follow-up visits. The slope of the line indicates the rate of the cognitive loss. A patient who has faster cognitive deterioration would have a higher absolute value of slope. A slope close to zero indicates that the cognitive decline is stable. In this document, the Rate of Cognitive Decline term will refer to the slope of decline. The predictive model is binary. Therefore, the rate of cognitive decline is converted to binary variables using a threshold of -0.05 points/month, such that progressive rapidly deteriorating level of cognition is defined as a rate of decrease exceeding 0.6 points/year. The rate of cognitive decline distribution of the study subjects is shown in Figure 1.

![Figure 1: Rate of cognitive decline distribution of the study subjects](image)

2.2. The System Pipeline

The predictive model learns the mapping function from input data to the target output. Let $V$ be the imaging sequence, $D$ be the corresponding clinical data, $y$ be the target class, and $f(.)$ represent the mapping function between input data and output labels. The model can be formulated as

$$y_i = f(V_i, D_i)$$

for each subject $i \in N$, where $N$ is the number of patients with MCI in the training data. Clinical data include age, gender, baseline MMSE score, education, ethnicity, and race. We also use brain volumes as supporting scalar features, which are computed with an open-source library (FreeSurfer) for analyzing and visualizing structural and functional neuroimaging data [10]. We use whole-brain volume and regional volumes of the hippocampus, entorhinal cortex, fusiform gyrus, and medial temporal lobe as scalar features. The brain volumes of each subject are available in the ADNI dataset [13]. We pose the problem as a supervised classification task, with training subjects classified into two groups based on their MMSE score changes (c.f., Figure 1). Therefore, the output variable $y \in (0, 1)$ denotes the target classes, 0 represents “slowly deteriorating/stable” class, and 1 represents “rapidly deteriorating” class. The proposed system is illustrated in Figure 2.

![Figure 2: System pipeline](image)

2.3. Pre-processing

We apply pre-processing techniques to each MRI volume $V$ and corresponding clinical data $D$ before the training. The MRI sequences are skull-stripped, which includes removal of non-cerebral tissue (calvarium, scalp, and dura) [14]. The skull-strip algorithm, that is based on a U-Net architecture [15] trained on skull-stripping datasets [16], reduces the processing size of volumes, hence increasing the computational speed during the training.

The scalar regional volume features are divided by each subject whole-brain volume size for normalization. The demographic data contains categorical values (e.g., such related to gender and ethnicity) that are converted into numeric data. The neural networks require the inputs to be scaled in a consistent way. Therefore, we normalize the images, scalar volumetric features, and clinical data into the range between 0 and 1.

2.4. Model Configuration of the Neural Network

The learning algorithm is based on a supervised neural network that has a hybrid architecture with three main compo-
Figure 2: An illustration of the hybrid prediction system

2.5. Addressing Overfitting

The voxel-based convolutional neural networks are prone to over-fitting due to high dimensional data, a large number of parameters and a relatively small number of cases to optimally train the system [21, 14, 22]. To address the data-scarcity, we accumulate the training data with augmentation strategies. We flipped MRI volumes such that left and right hemispheres are reversed [14], and randomly tilted at a degree less than 5°. We have also employed the regularization techniques dropout [19] and weight decays [20] in order to increase the generalization capacity of the model.

3. Experiments

3.1. Implementation Details

The dataset used in the study consists of 569 subjects with MPRAGE (MRI) scans and corresponding clinical data (c.f., Section 2.1). We perform 5-fold cross-validation to reduce the performance differences due to relatively small size datasets and to provide more robust generalization performance. At each fold, 60% of the dataset is used to train the model, 20% is used for model selection, and 20% of the dataset is used to test the model. The processing dimension of each MPRAGE volume is resized into $116 \times 130 \times 83$ voxels. We train using Adam optimization [23], which provides faster convergence due to the velocity component in addition to the acceleration component. The learning rate is $0.00001$, hyper-parameters $\beta_1 = 0.9, \beta_2 = 0.999$, and $\epsilon = 10^{-8}$. The categorical cross-entropy is employed as a loss function. As regularization, we use dropout regularization at the fully connected layer with keep rate 0.5. We also use...
Formula

| Metric   | Formula                  |
|----------|--------------------------|
| Accuracy | $\frac{(TP + TN)}{(TP + FP + FN + TN)}$ |
| PPV      | $\frac{TP}{(TP + FP)}$   |
| Sensitivity | $\frac{TP}{(TP + FN)}$   |
| Specificity | $\frac{TN}{(FP + TN)}$   |
| NPV      | $\frac{TN}{(FN + TN)}$   |

Table 2: FN=True Negatives, FP=True Positives, NPV=Negative Predictive Value, PPV=Positive Predictive Value, TN=True Negatives, TP=True Positives

early stopping [24] to prevent overfitting by monitoring the validation loss and stop the training if generalization error starts to increase over 20 iterations. The system is developed in Python using Tensorflow Keras API and trained on the Nvidia Quadro GV100 system with 32GB graphics cards with CUDA/CuDNN v9 dependencies for GPU acceleration.

3.2. Evaluation

We built 3 models: (i) an imaging model based on a 3D-CNN component that takes into account information from whole brain MRI, (ii) a hybrid model that combines the 3D-CNN component with brain-volume scalar data and demographic information, and (iii) a simple model that processes brain-volume scalar data and demographic information data. We assess the models’ prediction performance in terms of accurately classifying cognitive decline on a test dataset at each test fold and average the evaluation metric scores across all the models. The performance metrics used in the study are Sensitivity, Specificity, Accuracy, PPV, NPV, and AUC. Table 2 lists the performance metrics.

3.2.1. The imaging module prediction performance

The correlation between the morphological changes in the brain (e.g., parenchymal volume loss) and AD is known [25][26]. Based on a prior study [27], (i) MCI subjects have medium atrophy of hippocampus; (ii) the brain morphology in non-converters is similar to brain morphology in CN; converters are more similar to AD, and (iii) converters have more severe deterioration of neuropathology than non-converters. Due to the correlation between the pathological changes in brain morphology and the AD stages, we first measured how much we could predict the pace of the cognitive decline of patients by processing only the MRI scans through a 3D-CNN. The system achieved 64.8% AUC for predicting cognitive-decline class. The Receiver Operator Characteristic (ROC) curve is shown in Figure 3 (Top).

3.2.2. The hybrid model prediction performance

The hybrid model processes the MRI sequences, brain volume scalar data, and demographic information (age, gender, years of education, ethnicity and race). Table 2 lists the performance scores obtained with the proposed system in terms of mean and standard deviation across the cross-validated folds. The system achieved an Accuracy of 61.1%, with a PPV of 55.1%, Sensitivity of 51.8%, Specificity of 68%, and NPV of 65.5% at threshold 0.5. The average AUC is 66.6%. Adding the brain volume and demographic information as scalar values to

Figure 3: The plots depicting the system performance for predicting cognitive-decline class. Top) The predictive model processed only MRI sequences with 3D-CNN; average AUC = 64.8%. Middle) The hybrid predictive model is based on MRI sequences with 3D-CNN, brain-volume scalar data and non-imaging clinical data; average AUC = 66.6%. Bottom) The predictive model processes only scalar data (brain-volume and non-imaging clinical data); average AUC = 66.6%. (ROC: Receiver Operator Characteristic) (AUC: Area Under the Curve)
the system increased the system performance from 64.8% AUC to 66.6% AUC as shown in Figure 3Middle.

3.2.3. The brain volume scalar data and non-imaging clinical data prediction performance

The voxel-based convolutional neural networks are prone to over-fitting due to high dimensional data, a large number of parameters, but lack of annotated subject to optimally train the system [21][14][22]. Although we utilize several regularization techniques, we still observed over-fitting due to the 3D-CNN module of the hybrid system. In this experiment, we remove the 3D-CNN module of the hybrid model and run the experiments only using brain—volume scalar data with non-imaging clinical data. The system achieved 66.6% AUC for cognitive decline class prediction as shown in Figure 3Bottom.

4. Conclusions and Discussion

In this study, we investigate whether a machine learning-based system can predict cognitive decline in MCI patients at the initial visit by processing the clinical data routinely collected. Unlike other studies that focus on predicting MCI-to-AD conversion or AD/CN/MCI classification, we approach the problem as an early prediction of cognitive decline rate in MCI patients. The ability to identify an individual’s cognitive decline rate potentially helps the clinician to develop early preventive treatment strategies.

We observed the performances of 3 models for the prediction of cognitive-decline class. Our results confirm that there is a correlation between cognitive decline and clinical data obtained at the first visit; the imaging model achieved 64.8% AUC. By adding brain volume and demographic information as scalar values to the system, the performance increased to 66.6% AUC. Processing brain volumes (from FreeSurfer brain data) and demographic information as scalar values provide similar results as the hybrid module performance. Even though patient’s cognitive condition is mostly decided based on non-imaging clinical data (e.g., MMSE score, patient age) at the clinical visit, and MRI scans are generally collected to exclude other brain pathology, our results show that the structural MRI provides useful information related to the patient’s cognitive condition and may further contribute to the clinical evaluation and follow-up of patients with MCI.

A similar study [27] trains a convolutional neural network with regional patches extracted from the hippocampus and combines the extracted information with FreeSurfer brain data. Our results are compatible in that combining CNN features with scalar brain data features obtained with the FreeSurfer library increases the prediction performance. However, our study has differences, since our model (i) does not predict the MCI-to-AD conversion probability but rather predicts the rate of cognition-deterioration in MCI patients based on first-visit data; (ii) identifies patterns within the whole brain MRI instead of only the hippocampus, and (iii) uses limited FreeSurfer brain data compared the brain data used in [27].

Our system performance is lower compared to the published studies that investigate MCI-to-AD conversion or AD/CN classification. However, predicting cognitive decline is more challenging than AD/CN classification due to the subtle nature of pathological changes [27]. Moreover, our system processed only data that is routinely collected at the first visit and therefore makes predictions based on much less information compared to studies that incorporate follow-up data through time-sequence analysis. Therefore, the system’s ability to identify an individual’s cognitive decline rate with 66.6% AUC is comparable to the performance of analogous models in the published literature.

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Conflict of interest: The authors declare that they have no conflict of interest. Human Participants: This article does not contain any studies with human participants or animals performed by any of the authors. This article does not contain patient data.
Table 3: The hybrid model prediction performance. Training: 60%, Validation: 20%, Test: 20% of ADNI baseline set. (FN = False Negatives, FP = False Positives, NPV = Negative Predictive Value, PPV = Positive Predictive Value, TN = True Negatives, TP = True Positives)

| Metric th = 0.2 | Metric th = 0.3 | Metric th = 0.4 | Metric th = 0.5 | Metric th = 0.6 | Metric th = 0.7 | Metric th = 0.8 | Metric th = 0.9 |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Accuracy       | 0.600 ± 0.042  | 0.588 ± 0.040  | 0.591 ± 0.042  | 0.611 ± 0.027  | 0.612 ± 0.020  | 0.600 ± 0.016  | 0.568 ± 0.029  | 0.530 ± 0.044  |
| PPV            | 0.625 ± 0.245  | 0.532 ± 0.120  | 0.534 ± 0.077  | 0.551 ± 0.036  | 0.542 ± 0.020  | 0.525 ± 0.015  | 0.500 ± 0.020  | 0.478 ± 0.022  |
| Sensitivity    | 0.549 ± 0.138  | 0.322 ± 0.142  | 0.41 ± 0.0117  | 0.541 ± 0.110  | 0.641 ± 0.085  | 0.739 ± 0.071  | 0.833 ± 0.073  | 0.918 ± 0.059  |
| Specificity    | 0.865 ± 0.105  | 0.788 ± 0.102  | 0.726 ± 0.101  | 0.680 ± 0.087  | 0.591 ± 0.071  | 0.495 ± 0.066  | 0.369 ± 0.090  | 0.237 ± 0.117  |
| NPV            | 0.606 ± 0.028  | 0.609 ± 0.030  | 0.622 ± 0.030  | 0.655 ± 0.029  | 0.689 ± 0.030  | 0.720 ± 0.036  | 0.759 ± 0.074  | 0.836 ± 0.105  |

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