ALZHEIMER’S DISEASE DIAGNOSTICS BY ADAPTATION OF 3D CONVOLUTIONAL NETWORK

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ABSTRACT
Early diagnosis, playing an important role in preventing progress and treating the Alzheimer’s disease (AD), is based on classification of features extracted from brain images. The features have to accurately capture main AD-related variations of anatomical brain structures, such as, e.g., ventricles size, hippocampus shape, cortical thickness, and brain volume. This paper proposed to predict the AD with a deep 3D convolutional neural network (3D-CNN), which can learn generic features capturing AD biomarkers and adapt to different domain datasets. The 3D-CNN is built upon a 3D convolutional autoencoder, which is pre-trained to capture anatomical shape variations in structural brain MRI scans. Fully connected upper layers of the 3D-CNN are then fine-tuned for each task-specific AD classification. Experiments on the CADementia MRI dataset with no skull-stripping preprocessing have shown our 3D-CNN outperforms several conventional classifiers by accuracy. Abilities of the 3D-CNN to generalize the features learnt and adapt to other domains have been validated on the ADNI dataset.

Index Terms— Alzheimer’s disease, deep learning, 3D convolutional neural network, autoencoder, brain MRI

1. INTRODUCTION
Alzheimer’s disease (AD) is a progressive brain disorder and the most common case of dementia in the late life. AD leads to the death of nerve cells and tissue loss throughout the brain, thus reducing the brain volume in size dramatically through time and affecting most of its functions [1]. The estimated number of affected people will double for the next two decades, so that one out of 85 persons will have the AD by 2050 [2]. Because the cost of caring the AD patients is expected to rise dramatically, the necessity of having a computer-aided system for early and accurate AD diagnosis becomes critical [3].

Several popular non-invasive neuroimaging tools, such as structural MRI (sMRI), functional MRI (fMRI), and positron emission tomography (PET), have been investigated for developing such a system [4,5]. The latter extracts features from the available images, and a classifier is trained to distinguish between different groups of subjects, e.g., AD, mild cognitive impairment (MCI), and normal control (NC) groups [3,6,8]. The sMRI has been recognized as a promising indicator of the AD progression [3,9].

Various machine learning techniques were employed to leverage multi-view MRI, PET, and CSM data to predict the AD. Liu et al. [10] extracted multi-view features using several selected templates in the subjects’ MRI dataset. Tissue density maps of each template were used then for clustering subjects within each class in order to extract an encoding feature of each subject. Finally, an ensemble of support vector machine (SVM) was used to classify the subject. Deep networks were also used for diagnosing the AD with different image modalities and clinical data. Suk et al. [11] used a stacked autoencoder to separately extract features from MRI, PET, and cerebrospinal fluid (CSF) images; compared combinations of these features with due account of their clinical mini-mental state examination (MMSE) and AD assessment scale-cognitive (ADAS-cog) scores, and classified the AD on the basis of three selected MRI, PET, and CSF features with a multi-kernel SVM. Later on, a multimodal deep Boltzmann machine (BM) was used [12] to extract one feature from each selected patch of the MRI and PET scans and predict the AD with an ensemble of SVMs. Liu et al. [13] extracted 83 regions-of-interest (ROI) from the MRI and PET scans and used multimodal fusion to create a set of features to train stacked layers of denoising autoencoders. Li et al. [14] developed a multi-task deep learning for both AD classification and MMSE and ADAS-cog scoring by multimodal fusion of MRI and PET features into a deep restricted BM, which was pre-trained by leveraging the available MMSE and ADAS-cog scores.

Voxel-wise, cortical thickness, and hippocampus shape-volume features of the sMRI are used to diagnose the AD [3]. The voxel-wise features are extracted after co-aligning (registering) all the brain image data to associate each brain voxel with a vector (signature) of multiple scalar measurements. Klöppel et al. [15] used the gray matter (GM) voxels as features and trained an SVM to discriminate between the AD and NC subjects. The brain volume in [16] is segmented to GM, white matter (WM), and CSF parts, followed by calculating their voxel-wise densities and associating each voxel with a vector of GM, WM, and CSF densities for classification. For extracting cortical thickness features, Lerch et al. [17] segmented the registered brain MRI into the GM, WM, and CSF; fitted the GM and WM surfaces using deformable models; deform and expand the WM surface to the GM-CSF intersection; calculate distances between corresponding points at the WM and GM surfaces to measure the cortical thickness, and use these features for classification. To quantify the hippocampus shape for feature extraction, Gerardin et al. [18] segmented and spatially aligned the hippocampus regions for various subjects and modeled their shape with a series of spherical harmonics. Coefficients of the series were then normalized to eliminate rotation–translation effects and used as features for training an SVM based classifier.

Comparative evaluations [3,6,8] revealed several limitations of the above feature extraction techniques for classifying the AD. The voxel-wise feature vectors obtained from the brain sMRI are very noisy and can be used for classification only after smoothing and clustering to reduce their dimensionality [16]. The cortical thickness and hippocampus model features neglect correlated shape vari-
adversarial voxel-wise signals, actually, the weights $W_k$ define a 3D moving-window filter convolving the union of $J$-dimensional signal spaces for each voxel within the window.

To simplify notation, let $h_{i,j,k} = T_\text{inv}(x : W_k, b_k, f(\cdot))$ denote the entire encoding of the input 3D image with $J$-vectorial voxel-wise signals with the $k$-th 3D feature map, $h_k$, such that its scalar components are obtained with Eq. (1) using the weights $W_k$ and bias vectors $b_k$ for a given voxel neighborhood. The like inverse transformation, $T_\text{inv}(\ldots)$, with the same voxel neighborhood, but generally with the different convolutional weights, $P_k$, biases, $b_{\text{inv}/k}$,
and, possibly, activation function, \(g(\cdot)\), decodes, or reconstructs the initial 3D image:

\[
\hat{x} = \sum_{k=1}^{K} T_{inv}(h_k : P_{h}, b_{h_{inv,k}}, g(\cdot))
\]

(2)

Given \(L\) encoding layers, each layer \(l\) generates an output feature image, \(h_{(l)} = [h_{(l),1} : k = 1, \ldots, K_l]\), with \(K_l\)-vectorial voxel-wise features and receives the preceding output, \(h_{(l-1)} = [h_{(l-1),k} : k = 1, \ldots, K_{l-1}]\) as the input image (i.e., \(h_{(0)} = x\)).

The 3D-CAE of Eqs. (1) and (2) is trained by minimizing the mean squared reconstruction error for \(T; T \geq 1\), given training input images, \(x^{[1]}: t = 1, \ldots, T\),

\[
E(\theta) = \frac{1}{T} \sum_{t=1}^{T} \| x^{[t]} - \hat{x}^{[t]} \|_2^2
\]

(3)

where \(\theta = [W_k; P_k; b_k; b_{h_{inv,k}} : k = 1, \ldots, K]\), and \(\| \ldots \|_2^2\) denote all free parameters and the average vectorial \(\ell_2\)-norm over the \(T\) training images, respectively. To reduce the number of the free parameters, the decoding, \(P_{h}\), and encoding, \(W_k\), weights were tied by flipping over all their dimensions as proposed in [19]. The cost of Eq. (3) was minimized in the parameter space by using the stochastic gradient descent search, combined with error back-propagation.

2.2. AD Classification by 3D Adaptive CNN (3D-ACNN)

While the lower layers of a goal predictive 3D-CNN extract generalized features, the upper layers have to facilitate task-specific classification using those features [21]. The proposed classifier extracts the generalized features by using a stack of locally connected bottom convolutional layers, while performing task-specific fine-tuning of parameters of the fully connected upper layers. Training the proposed hierarchical 3D-CNN consists of pre-training, initial training of the lower convolutional layers, and final task-specific fine-tuning.

At the pre-training stage, the convolutional layers for generic feature extraction are formed as a stack of 3D-CAEs, which were pre-trained in the source domain. Then these layers are initialized by encoding the 3D-CAE weights [26], and, finally, the deep-supervision-based fine-tuning of the upper fully-connected layers is performed for each task-specific binary or multi-class sMRI classification.

Due to pre-training on the source domain data, the bottom convolutional layers can extract generic features related to the AD biomarkers, such as the ventricular size, hippocampus shape, and cortical thickness, as shown in Fig. 1(b). We use the Net2Net initialization [26], which allows for different convolutional kernel and pool sizes of the 3D-CNN layers, comparing to those in the 3D-CAE, based on the target-domain image size and imaging specifications, and facilitates adapting the 3D-CNN across the different domains. To classify the extracted features in a task-specific way, weights of the upper fully-connected 3D-CNN layers are fine-tuned on the target-domain data by minimizing a specific loss function. The loss depends explicitly on the weights and is proportional to a negated log-likelihood of the true output classes, given the input features extracted from the training target-domain images by the pre-trained bottom part of the network.

Our implementation of the 3D-CNN uses the ReLU activation functions at each inner layer and the fully connected upper layers with a softmax top-most output layer (Fig. 2), predicting the probability of belonging an input brain sMRI to the AD, MCI, or NC group. The Adadelta gradient descent [28] was used to update the pre-trained 3D-CAE and fine-tune the entire 3D-ACNN.

Table 1. Demographic data for 210 subjects from the ADNI database (STD – standard deviation).

| Diagnosis     | AD | MCI | NC |
|---------------|----|-----|----|
| Number of subjects | 70 | 70  | 70 |
| Male / Female  | 36 / 34 | 50 / 20 | 37 / 33 |
| Age (mean, STD) | 75.0 ± 7.9 | 75.9 ± 7.7 | 74.6 ± 6.1 |

Fig. 2. Our 3D adaptable CNN (3D-ACNN) for Alzheimer’s disease diagnosis.
3. EXPERIMENTAL RESULTS

To performance of the proposed 3D-CAES is evaluated on CADDementia as source domain, for generalized feature extraction. The data set contains structural T1-weighted MRI (T1w) scans of patients with the diagnosis of probable AD, patients with the diagnosis of MCI, and NC without a dementia syndrome [3]. To pretrain 3D-CAES on CADDementia, SMRI are preprocessed by spatially normalizing using rigid registration approach. Then skull is removed and image intensities are normalized to $[0, 1]$, resulting in sMRI of size $(200 \times 150 \times 150)$.

The classification performance of proposed 3D-ACNN is evaluated on Alzheimer’s Disease Neuroimaging Initiative (ADNI) database, as target domain, for five classification tasks: four binary ones (AD vs. NC, AD+MCI vs. NC, AD vs. MCI, MCI vs NC) and the ternary classification (AD vs. MCI vs. NC). Classification accuracy was evaluated for each task by ten-fold cross-validation. ADNI dataset without using any preprocessing and skull stripping performs the other approaches in all five task-specific cases, in spite of employing only a single imaging modality (sMRI) and performing no prior skull-stripping.

### Table 2. Comparative performance (ACC,%) of our classifier vs. seven competitors (n/a - non-available).

| Approach      | Modalities          | AD/MCI/NC | AD+MCI/NC | AD/NC | AD/MCI | MCI/NC |
|---------------|---------------------|-----------|-----------|-------|--------|--------|
| Suk et al. [11] | PET+MRI+CSF         | n/a       | n/a       | 95.9/1.1 | n/a    | 85.0/1.2 |
| Suk et al. [12] | PET+MRI             | n/a       | n/a       | 95.45/2.3 | n/a    | 85.7/5.2 |
| Zhu et al. [19] | PET+MRI+CSF         | n/a       | n/a       | 95.9/0/a | n/a    | 82.0/0/a |
| Zu et al. [30]  | PET+MRI             | n/a       | n/a       | 96.0/0/a | n/a    | 80.3/0/a |
| Liu et al. [13] | PET+MRI             | 53.8/4.8  | n/a       | 91.45/6  | n/a    | 82.14/9 |
| Liu et al. [10]  | MRI                 | n/a       | n/a       | 93.8/0/a | n/a    | 89.1/0/a |
| Li et al. [14]   | PET+MRI+CSF         | n/a       | n/a       | 91.41/8  | 70.1/2.1 | 77.4/1.7 |
| Sarraf et al. [31] | fMRI             | n/a       | n/a       | 96.8/0/a | n/a    | n/a     |
| Our 3D-ACNN     | MRI                 | 89.1/7.1  | 90.3/1.4  | 97.6/0.6 | 95.1/8 | 90.8/1.1 |

Performance of the proposed 3D-ACNN classifier, in terms of accuracy (ACC), for each task-specific classification was evaluated and compared to competing approaches [10–14, 29–31]. Table 3 presents the average results of ten-fold cross-validation of our classifier. According to these experiments, the proposed 3D-ACNN outperforms the other approaches in all five task-specific cases, in spite of employing only a single imaging modality (sMRI) and performing no prior skull-stripping.

4. CONCLUSION AND FUTURE WORK

This paper proposed a 3D-ACNN classifier, which can more accurately predict the AD on structural brain MRI scans, than several other state-of-the-art predictors. The pretraining and layer freezing were used to enhance generality of features in capturing the AD biomarkers. Three stacked 3D CAE network were pretrained on CADDementia Dataset. Then the learnt features are extracted and used as AD biomarkers detection in bottom layers of a 3D CNN network. Then three fully connected layers are stacked on top of the bottom layers to perform AD classification on 210 subjects of ADNI dataset. Classification performance was measured using ten-fold crossvalidation, and were compared to the state-of-the-art models, demonstrated the out-performance of the proposed 3D CNN. The future application of proposed 3D-ACNN include detection of lung cancer [33,36], heart failure [37], and autism detection [38].

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