# Deep Convolutional Neural Networks for Automated Diagnosis of Alzheimer's Disease and Mild Cognitive Impairment Using 3D Brain MRI

Jyoti Islam(✉) and Yanqing Zhang
for the Alzheimer's Disease Neuroimaging Initiative*

Georgia State University, Atlanta, GA 30302, USA
jislam2@student.gsu.edu

**Abstract.** We consider the automated diagnosis of Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) in 3D structural MRI brain scans. We develop an efficient deep convolutional neural network (CNN) based classifier by analyzing 3D brain MRI. The proposed model extracts features from the MRI scans and learns significant information related to Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI). We perform motion correction, non-uniform intensity normalization, Talairach transform, intensity normalization, and skull-stripping in the raw MRI scans. After that several 2D slices are generated, and center patch is cropped from the slices before passing them to the CNN classifier. Besides, we demonstrate ways to improve the performance of a CNN classifier for AD and MCI diagnosis. We conduct experiments using Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset for classification of the AD, MCI and CN (normal/healthy controls) to evaluate the proposed model. The proposed model achieves 94.97% accuracy for AD/CN classification and 91.98% accuracy for AD/MCI classification outperforming baseline models and several competing methods from other studies.

**Keywords:** Deep learning · Convolutional neural network
Alzheimer's Disease · MRI · Brain imaging

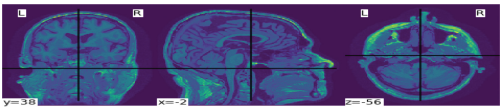
## 1 Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disease that causes people to lose their memory, mental functions and ability to continue daily activities. AD is the most prevailing type of dementia, and Mild Cognitive Impairment

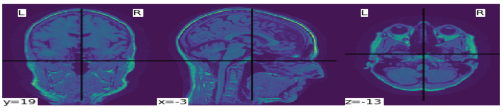
*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or 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.


S. Wang et al. (Eds.): BI 2018, LNAI 11309, pp. 359–369, 2018.
https://doi.org/10.1007/978-3-030-05587-5_34

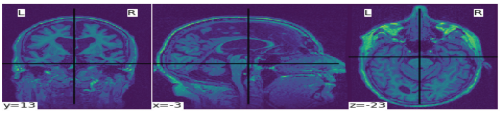
(MCI) is considered as the earlier stage of AD [1]. It is crucial to detect patient at MCI stage before the disease progress further as there is no cure for AD. Earlier diagnosis can help for proper treatment and prevent brain tissue damage. Magnetic Resonance Imaging (MRI) is a technique that creates a 3D representation of brain using magnetic fields and radio waves. Nowadays it is a standard practice to use MRI to detect changes in the brain caused by AD. Figure 1 shows some brain MRI images with different AD stages. The Hippocampus and cerebral cortex of the brain are shrunk, and ventricles are enlarged in the brain of AD patient. Hippocampus reduction causes cell loss and damages the synapses and neuron ends [21]. Structural MRI (sMRI) is helpful for measuring these progressive changes in the brain due to the AD. Deep learning technologies have achieved significant success in medical image analysis. We develop a deep convolutional neural network that learns essential features directly from the input MRI data to distinguish between CN, MCI and AD patients. We focus on the preprocessing steps and show that proper preprocessing of the data plays a vital role in accurate diagnosis. Hence, our primary contributions are two-fold: (a) We develop a deep convolutional neural network that can diagnosis MCI and AD patients from 3D MRI brain scans. (b) We devise an efficient approach to improve classification performance of an automated CNN classifier for Alzheimer's Disease diagnosis.




(a)




(b)




(c)

**Fig. 1.** Sample brain MRI images from ADNI database presenting different stages of Alzheimer's Disease. (a) normal/healthy controls (CN); (b) Mild Cognitive Impairment (MCI); (c) Alzheimer's Disease (AD).

## 2 Related Work

Researchers have been using machine learning techniques to build classifiers using imaging data and clinical measures for AD diagnosis. These studies have

identified the significant structural differences in the regions such as the hippocampus and entorhinal cortex between the healthy brain and brain with AD. Different imaging modalities, such as structural and functional Magnetic Resonance Imaging (sMRI, fMRI), Position Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), and Diffusion Tensor Imaging (DTI) scans can notice the changes causing AD due to the degeneration of brain cells. Several research works have been done using these neuroimaging techniques for AD Diagnosis. Moreover, information from multiple modalities have been combined to improve the diagnosis performance. In recent years, deep learning models specially Convolutional Neural Networks have demonstrated outstanding performance for medical image analysis. For neuroimaging data, deep learning techniques can discover the hidden representation and efficiently capture the disease-related pathologies. Gupta et al. [5] have developed a sparse autoencoder model for AD, Mild Cognitive Impairment (MCI) and healthy control (HC) classification. Payan et al. [19] trained sparse autoencoders and 3D CNN model for AD diagnosis. Brosch et al. [3] developed a deep belief network model and used manifold learning for AD detection from MRI images. Hosseini-As et al. [6] adapted a 3D CNN model for AD diagnostics. Liu et al. [16] developed a deep learning model using both unsupervised and supervised techniques and classified AD and MCI patients. Sarraf et al. [22] used fMRI data and deep LeNet model for AD detection. Suk et al. [25,26] developed an autoencoder network-based model for AD diagnosis and used several complex SVM kernels for classification. They have extracted low to mid level features from magnetic current imaging (MCI), MCI-converter structural MRI, PET data and performed classification using multi-kernel SVM. Cárdenas-Peña et al. [4] have developed a deep learning model using central kernel alignment and compared the supervised pre–training approach to two unsupervised initialization methods, autoencoders and Principal Component Analysis (PCA). Earlier we have developed several deep convolutional networks [8,10–12] to classify different stages of Alzheimer's Disease using OASIS dataset [18]. For our current work, we develop an efficient deep convolutional neural network based classifier and demonstrate better performance on the ADNI dataset [13].

## 3 Methods

### 3.1 Formalization

Let $x = \{x_i, i = 1, ..., N\}$, a set of MRI data with $x_i \in [0, 1, 2, ..., L-1]^{h*w*l}$, a three Dimensional (3D) image with L gray scale values, h * w * l voxels and $y \in \{0, 1, 2\}$, one of the stages of AD where 0, 1, 2 refers to normal/healthy control (CN), Mild Cognitive Impairment (MCI), and Alzheimer's Disease (AD) respectively. We will construct a classifier,

$$f : X \rightarrow Y; x \mapsto y \tag{1}$$

that predicts a label y in response to an input image x with minimum error rate. The training process of the classifier would be an iterative process to find the set of parameters $w$, that minimizes the classifier's loss

$$L(w, X) = \frac{1}{n} \sum_{i=1}^{n} l(f(x_i, w), \widehat{c_i}) \tag{2}$$

where $x_i$ is $i^{th}$ image of $X$, $f(x_i, w)$ is the classifier function that predicts the class $c_i$ of $x_i$ given $w$, $\widehat{c_i}$ is the ground-truth class for $i^{th}$ image $x_i$ and $l(c_i, \widehat{c_i})$ is the penalty function for predicting $c_i$ instead of $\widehat{c_i}$. We set $l$ to the loss of cross–entropy,

$$l = -\sum_{i} \widehat{c_i} \, log \, c_i \tag{3}$$

### 3.2 Data Selection

For our proposed model, we have used 1726 MRI scans (347 AD, 537 CN, 806 MCI) of 479 patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Specifically We used ADNI1:Annual 2 Yr 1.5T dataset for our model. The subjects were in the age range 55–92. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Up-to-date information related ADNI database can be found at www.adni-info.org.

### 3.3 Data Preprocessing

We downloaded the raw Neuroimaging Informatics Technology Initiative (NiFTI) file format MRI scans from the ADNI website (http://adni.loni.usc.edu/). The structural MRI scans were acquired from 1.5T scanners. These MRI scans were already reviewed for quality and Gradient inhomogeneity correction (gradwarp), B1 non-uniformity correction, and N3 processing (to reduce residual intensity non-uniformity) were applied. Since the raw scans are not skull-stripped and have unnecessary information, we perform cortical reconstruction with Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). We use the function recon-all -autorecon1 which performs 5 out of 31 transformation processes done by Freesurfer. The five transformation processes are - Motion Correction and Conform, NonUniform intensity normalization (NU), Talairach transform computation, Intensity Normalization 1 and Skull Stripping. After these preprocessing steps we get a skull-stripped MRI scan with dimension

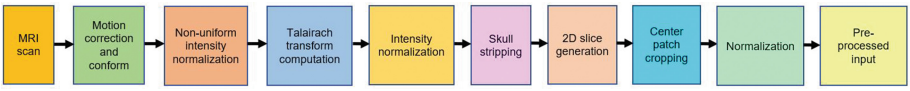



**Fig. 2.** 3D Brain MRI Preprocessing module.

256 * 256 * 256. Some slices from sample skull-stripped MRI scan of CN, MCI, and AD patients are shown in Fig. 3. We discard several slices at the beginning and at the end as they do not have any useful information. After that, we crop a 224 * 224 center patch from each slice to reduce the background image region outside the brain tissue and perform image normalization.

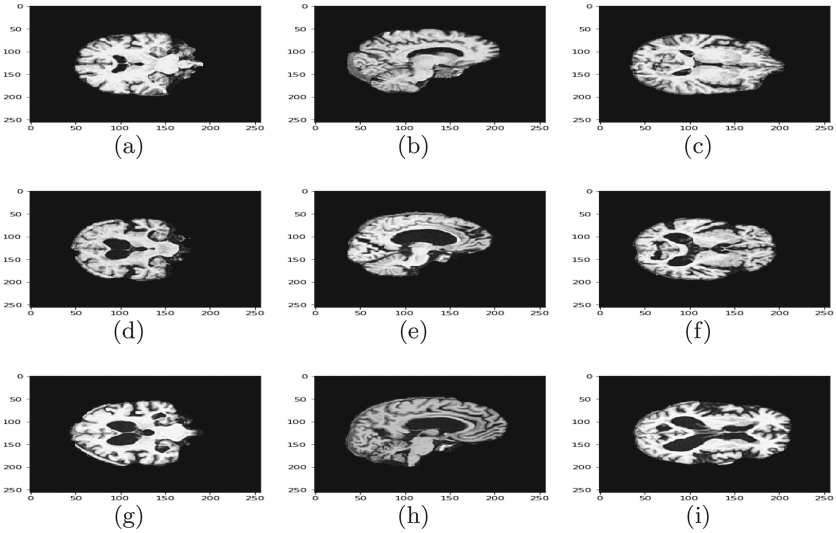



**Fig. 3.** Skull-stripped MRI slices presenting different AD stages. (a)–(c) CN; (d)–(f) MCI; (g)–(i) AD.

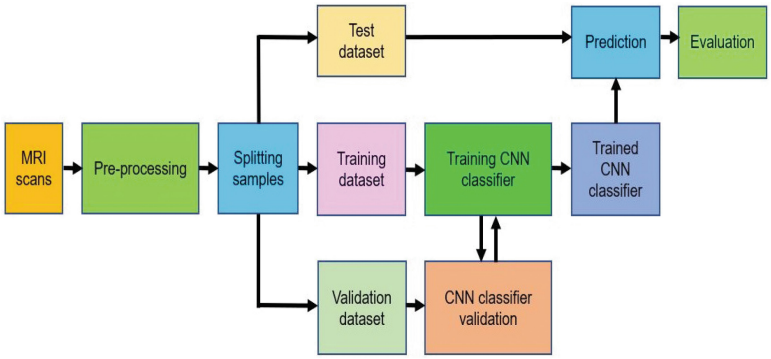



**Fig. 4.** Block diagram of the proposed Alzheimer's Disease diagnosis framework.

### 3.4 Data Augmentation

Data augmentation helps to increase the size of the dataset. For our work, we developed an augmentation scheme involving generating multiple slices from each

MRI scan. Slices are taken from different image plane: Axial or horizontal plane, Coronal or frontal plane, and Sagittal or median plane. Moreover, we applied Horizontal Flipping to increase the amount of training samples.

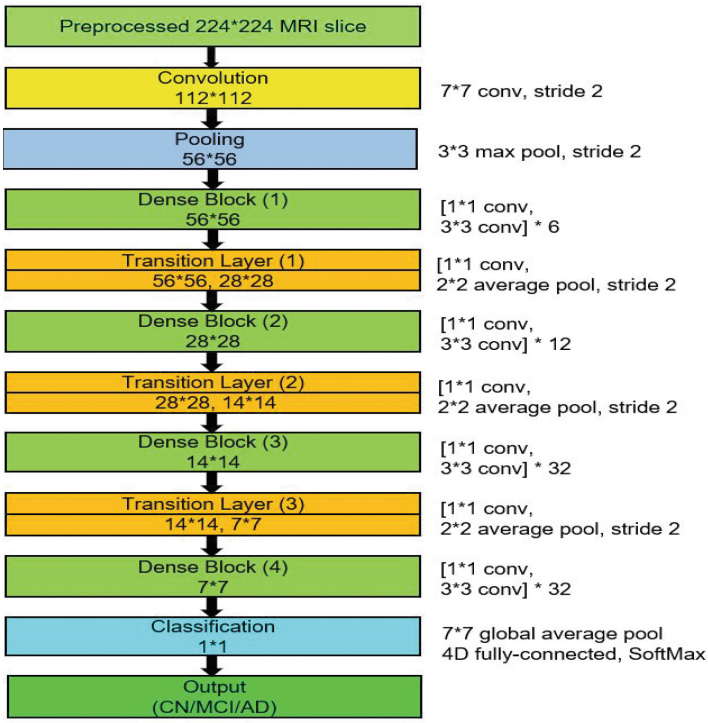



**Fig. 5.** Deep CNN architecture used for the proposed Alzheimer's Disease diagnosis framework.

### 3.5 Network Architecture

Figure 4 shows our proposed model for Alzheimer's Disease diagnosis. The first stage of the pipeline is the preprocessing module illustrated in Fig. 2 and described above. The second stage of the classifier is a deep convolutional neural network as shown in Fig. 5. The CNN model is a 2D network and follows a modified architectural pattern of DenseNet-121 [7]. The CNN classifier has several layers performing the convolution, batch normalization, rectified linear unit, and pooling operation. The layers follow a particular connection pattern known as dense connectivity [7]. We keep these layers very narrow (e.g., 12 filters per layer) and connect each layer to every other layer. Similar to [7], we will refer to the layers as dense layer and combination of the layers as dense block. Since all the dense layers are connected to each other, the $i^{th}$ layer receives the feature-maps $(h_0, h_1, h_2, ..., h_{i-1})$, from all previous layers $(0, 1, 2, ..., i-1)$. The network has a

global feature map set, where each layer adds a small set of feature-maps. Each layer can access the gradients from the loss function and the original input in training time. As a result, the flow of information improves, and gradient flow becomes stronger in the network. Final classification is performed by the softmax layer with three different output classes: CN, MCI, and AD. We optimized the CNN classifier using the Adam algorithm [14].

## 4 Experiments and Results

For our work, we used 80% data from the ADNI1 dataset as training set, and 20% as test dataset. From the training dataset, a random selection of 10% images is used as validation dataset. The experiments were performed using PyTorch framework. Transfer learning [9] was applied to pre-train the CNN classifier using Imagenet database [20]. The parameters used for training process are: learning rate: 0.0001, weight decay: 0.1 after every 7 epochs, and batch size: 16.

To improve the performance of CNN for AD diagnosis from 3D brain MRI, we studied the impact of several factors such as - network pre-training, image preprocessing, choosing random slice from the MRI as network input, and choosing specific slice from three different image plane (axial, sagittal, and coronal). Initially, we trained the network with raw MRI scans. For this approach, training

**Table 1.** Impact of different factors on proposed CNN

| Methods | AD vs CN | | |
|---|---|---|---|
| | Accuracy | Sensitivity | Specificity |
| Without Pre-training | 75.98 | 78.45 | 71.43 |
| Random slice | 75.98 | 79.51 | 68.42 |
| Axial slice | 87.15 | 86.44 | 88.52 |
| Sagittal slice | 89.94 | 87.10 | 96.36 |
| Coronal slice | 94.97 | 94.33 | 95.89 |

**Table 2.** Impact of different CNN architecture on proposed diagnosis framework

| Methods | AD vs CN | | |
|---|---|---|---|
| | Accuracy | Sensitivity | Specificity |
| ResNet-18 | 86.03 | 85.12 | 87.93 |
| ResNet-50 | 82.68 | 85.09 | 78.46 |
| ResNet-101 | 83.79 | 88.18 | 76.81 |
| ResNet-152 | 82.68 | 79.67 | 89.28 |
| DenseNet-169 | 83.24 | 84.35 | 81.25 |
| DenseNet-201 | 83.80 | 88.03 | 75.81 |
| Proposed method | 94.97 | 94.33 | 95.89 |

**Table 3.** Comparison with the State-of-the-Art. '–' indicates that result was not reported by the authors.

| Methods | AD vs CN | | | AD vs MCI | | | MCI vs CN | | |
|---|---|---|---|---|---|---|---|---|---|
| | Accuracy | Sensitivity | Specificity | Accuracy | Sensitivity | Specificity | Accuracy | Sensitivity | Specificity |
| Sergey et al. [15] | 80.00 | – | – | – | – | – | – | – | – |
| Beheshti et al. [2] | 93.01 | 89.13 | 96.80 | – | – | – | – | – | – |
| JLLR+DeepESRNET [24] | 91.02 | 92.72 | 89.94 | – | – | – | 73.02 | 77.60 | 68.22 |
| MOLR+DeepESRNET [24] | 90.28 | 92.65 | 89.05 | – | – | – | 74.20 | 78.74 | 66.30 |
| B. Shi et al. [23] | 91.95 | 89.49 | 93.82 | – | – | – | 83.72 | 84.74 | 82.72 |
| Liu et al. [17] | 92.0 | 90.9 | 93.0 | – | – | – | 85.3 | 82.3 | 88.2 |
| Aderghal et al. [1] | 91.41 | 89.06 | 93.75 | 69.53 | 67.19 | 71.88 | 65.62 | 66.25 | 65.00 |
| Proposed method | 94.97 | 94.33 | 95.89 | 91.98 | 90.47 | 95.38 | 74.70 | 70.96 | 78.20 |

accuracy was more than 95%, but validation accuracy was around 68% which indicates the network lacks generalization. Pre-processed MRI data helped to solve this issue and improved performance of the CNN. Table 1 demonstrates the results of other experiments. From the results, we can see that choosing random slice from the MRI hampers the performance of the CNN classifier even with pre-trained network and pre-processed data. Moreover, the experimental results demonstrate that choosing slices from coronal view have a huge positive impact on the CNN classifier for AD diagnosis. Table 2 shows the effect of different CNN architecture on the performance of the proposed AD diagnosis framework. Here, it is evident that the proposed CNN classifier, shown in Fig. 5 outperforms the other baseline models. Our model is pre-trained with the Imagenet database [20] and we perform the training with the pre-processed coronal slices. These results also demonstrate that the performance of a CNN classifier vastly depends on the architecture and depth of the network. To validate the effectiveness of our model, we compare it with several state-of-the-art methods. The comparison result is shown in Table 3. Following previous approaches, we use accuracy, sensitivity and specificity for performance comparison. The result shows that our model outperforms other competing methods for AD/CN classification, AD/MCI classification and demonstrates comparable performance for MCI/CN classification. The proposed model follows a modified architectural pattern of DenseNet-121 and it outperforms DenseNet-169 and DenseNet-201. The later two models are much deeper and complex than DenseNet-121 and need lot more data for preventing over-fitting and better classification performance.

## 5 Conclusion

In this paper, we proposed a novel automated Alzheimer's Disease diagnosis framework and demonstrated ways to improve the performance of a CNN classifier. The experimental result shows that a pre-trained network with preprocessed slices from coronal view is a reliable technique for MCI and AD diagnosis. The performance of the proposed model shows that it can compete with other state-of-the-art methods for AD diagnosis using 3D brain MRI data. In future,

we plan to extend our work to computer-aided diagnosis in other biomedical fields.

**Acknowledgement.** This study was supported by Brains and Behavior (B&B) Fellowship program from Neuroscience Institute of Georgia State University.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH–12–2–0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

## References

1. Aderghal, K., Benois-Pineau, J., Afdel, K.: Classification of SMRI for Alzheimer's disease diagnosis with CNN: single Siamese networks with 2d+? approach and fusion on ADNI. In: Proceedings of the 2017 ACM on International Conference on Multimedia Retrieval, pp. 494–498. ACM (2017)
2. Beheshti, I., Demirel, H., Matsuda, H., Initiative, A.D.N., et al.: Classification of Alzheimer's disease and prediction of mild cognitive impairment-to-Alzheimer's conversion from structural magnetic resource imaging using feature ranking and a genetic algorithm. Comput. Biol. Med. **83**, 109–119 (2017)
3. Brosch, T., Tam, R., For the Alzheimer's Disease Neuroimaging Initiative: Manifold learning of brain MRIs by deep learning. In: Mori, K., Sakuma, I., Sato, Y., Barillot, C., Navab, N. (eds.) MICCAI 2013. LNCS, vol. 8150, pp. 633–640. Springer, Heidelberg (2013). https://doi.org/10.1007/978-3-642-40763-5_78
4. Cárdenas-Peña, D., Collazos-Huertas, D., Castellanos-Dominguez, G.: Centered kernel alignment enhancing neural network pretraining for MRI-based dementia diagnosis. Comput. Math. Methods Med. **2016**, 10 pages (2016)
5. Gupta, A., Ayhan, M., Maida, A.: Natural image bases to represent neuroimaging data. In: International Conference on Machine Learning, pp. 987–994 (2013)
6. Hosseini-Asl, E., Keynton, R., El-Baz, A.: Alzheimer's disease diagnostics by adaptation of 3d convolutional network. In: 2016 IEEE International Conference on Image Processing (ICIP), pp. 126–130. IEEE (2016)

7. Huang, G., Liu, Z., van der Maaten, L., Weinberger, K.Q.: Densely connected convolutional networks. In: Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition (2017)
8. Islam, J., Zhang, Y.: Brain MRI analysis for Alzheimer's disease diagnosis using an ensemble system of deep convolutional neural networks. Brain Inform. **5**(2), 2 (2018)
9. Islam, J., Zhang, Y.: Visual sentiment analysis for social images using transfer learning approach. In: 2016 IEEE International Conferences on Big Data and Cloud Computing (BDCloud), Social Computing and Networking (SocialCom), Sustainable Computing and Communications (SustainCom) (BDCloud-SocialCom-SustainCom), pp. 124–130. IEEE (2016)
10. Islam, J., Zhang, Y.: An ensemble of deep convolutional neural networks for Alzheimer's disease detection and classification. arXiv preprint arXiv:1712.01675 (2017)
11. Islam, J., Zhang, Y.: A novel deep learning based multi-class classification method for Alzheimer's Disease detection using brain MRI data. In: Zeng, Y., et al. (eds.) BI 2017. LNCS, vol. 10654, pp. 213–222. Springer, Cham (2017). https://doi.org/10.1007/978-3-319-70772-3_20
12. Islam, J., Zhang, Y.: Early diagnosis of Alzheimer's disease: a neuroimaging study with deep learning architectures. In: Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition Workshops, pp. 1881–1883 (2018)
13. Jack, C.R., et al.: The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods. J. Magn. Reson. Imaging **27**(4), 685–691 (2008)
14. Kingma, D.P., Ba, J.: Adam: a method for stochastic optimization. arXiv preprint arXiv:1412.6980 (2014)
15. Korolev, S., Safiullin, A., Belyaev, M., Dodonova, Y.: Residual and plain convolutional neural networks for 3d brain MRI classification. In: 2017 IEEE 14th International Symposium on Biomedical Imaging (ISBI 2017), pp. 835–838. IEEE (2017)
16. Liu, F., Shen, C.: Learning deep convolutional features for MRI based Alzheimer's disease classification. arXiv preprint arXiv:1404.3366 (2014)
17. Liu, M., Zhang, D., Shen, D., Alzheimer's Disease Neuroimaging Initiative: Hierarchical fusion of features and classifier decisions for Alzheimer's disease diagnosis. Hum. Brain Mapp. **35**(4), 1305–1319 (2014)
18. Marcus, D.S., Wang, T.H., Parker, J., Csernansky, J.G., Morris, J.C., Buckner, R.L.: Open access series of imaging studies (OASIS): cross-sectional MRI data in young, middle aged, nondemented, and demented older adults. J. Cogn. Neurosci. **19**(9), 1498–1507 (2007)
19. Payan, A., Montana, G.: Predicting Alzheimer's disease: a neuroimaging study with 3d convolutional neural networks. arXiv preprint arXiv:1502.02506 (2015)
20. Russakovsky, O., et al.: ImageNet large scale visual recognition challenge. Int. J. Comput. Vis. (IJCV) **115**(3), 211–252 (2015)
21. Sarraf, S., Anderson, J., Tofighi, G.: DeepAD: Alzheimer's disease classification via deep convolutional neural networks using MRI and fMRI. bioRxiv, p. 070441 (2016)
22. Sarraf, S., Tofighi, G.: Classification of Alzheimer's disease using fMRI data and deep learning convolutional neural networks. arXiv preprint arXiv:1603.08631 (2016)
23. Shi, B., et al.: Nonlinear feature transformation and deep fusion for Alzheimer's disease staging analysis. Pattern Recognit. **63**, 487–498 (2017)

24. Suk, H.I., Lee, S.W., Shen, D.: Deep ensemble learning of sparse regression models for brain disease diagnosis. Med. Image Anal. **37**, 101–113 (2017)
25. Suk, H.I., Lee, S.W., Shen, D., Alzheimer's Disease Neuroimaging Initiative: Hierarchical feature representation and multimodal fusion with deep learning for ad/MCI diagnosis. NeuroImage **101**, 569–582 (2014)
26. Suk, H.-I., Shen, D., Alzheimer's Disease Neuroimaging Initiative: Deep learning in diagnosis of brain disorders. In: Lee, S.-W., Bülthoff, H.H., Müller, K.-R. (eds.) Recent Progress in Brain and Cognitive Engineering. TAHP, vol. 5, pp. 203–213. Springer, Dordrecht (2015). https://doi.org/10.1007/978-94-017-7239-6_14