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Review

A Short Survey on Computer-Aided Diagnosis of Alzheimer's Disease: Unsupervised Learning, Transfer Learning, and Other Machine Learning Methods

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Abstract: Alzheimer's Disease (AD) is a neurodegenerative disorder, which is irreversible and incurable. Early diagnosis plays a significant role in controlling the progression of AD and improving the patient's quality of life. Computer-aided diagnosis (CAD) methods have shown great potential to assist doctors in analyzing medical data, such as magnetic resonance images, positron emission tomography, and mini-mental state examination. Contributed by the advanced deep learning models, predictions of CAD methods for AD are becoming more and more accurate, which can provide a reference and verification for manual screening. In this paper, a short survey on the application of recent CAD methods in AD detection is presented. The advantages and drawbacks of these methods are discussed in detail, especially the methods based on convolutional neural networks, and the future research directions are summarized subsequently. With this survey, we hope to promote the development of CAD for early detection of AD.

Keywords: Alzheimer's disease; computer-aided diagnosis; magnetic resonance image; positron emission tomography; convolutional neural network

1. Introduction

Alzheimer's Disease (AD) is a progressive disorder of the neural system in humans, which accounts for about 80% of all dementia [1]. The main symptoms of AD are gradual memory decline, regression of cognitive function, language disorders, and changes in emotional personality [2]. The severity of these symptoms gradually intensifies as the disease progresses, and patients in the late stages of AD may even completely lose their self-care ability, fail to recognize family members, and ultimately die.

Currently, the exact cause of AD has not been elucidated, but studies suggest that various factors may be associated with the disease, such as genetic factors, abnormal protein deposition, and neurotransmitter imbalances. According to the progression of AD, it can be divided into three stages: mild, moderate, and severe, with a time-span of up to 10 years or more. Although current treatments cannot completely cure AD, early diagnosis is of great significance for delaying the progression of the disease and improving the quality of life of patients [3,4].

The diagnosis of AD primarily relies on neuropsychological assessments, blood tests, spinal fluid tests, and imaging examinations. Among these, Magnetic Resonance Imaging (MRI) is the most commonly used method for brain imaging in clinical settings. MRI images can be used to observe structural changes in the patient's brain and detect changes in brain volume in AD patients, such as atrophy of the hippocampus and temporal lobe cortex, ventricular enlargement, and white matter microlesions. However, manually analyzing high-dimensional brain MRI images is not only time-consuming but also requires specialized knowledge and extensive experience [5,6]. Moreover, manual analysis is highly subjective, and different doctors may provide different diagnostic results for the same set of images, leading to inconsistencies in the results.

Computer-aided diagnosis (CAD) is a method that uses computer algorithms and technology to assist doctors in disease diagnosis. With the development of artificial intelligence and particularly significant progress in computer vision and deep learning over the past decade, CAD applications in the medical field have become increasingly widespread and play an important role in the diagnosis of AD [7]. CAD leverages large amounts of case data and deep learning models to automatically analyze and judge the brain MRI images of suspected patients, for example, quantitatively analyzing the degree of atrophy in the hippocampus and brain volume on MRI [8]. This helps doctors make more accurate, reliable, and consistent diagnoses, reduces subjectivity, and improves the sensitivity and specificity of diagnosis.

The remainder of this review is organized as follows. Information for famous public AD datasets is discussed in section 2. Section 3 presents a comprehensive review of existing CAD methods for AD detection, including models by transfer learning, models trained from scratch, unsupervised models, and other related models. In section 4, the conclusions are summarized, and future research directions are given.

2. Public Datasets for AD

Public AD datasets are vital to train and validate deep models for early AD detection. In this section, three well-known datasets are discussed, including Alzheimer's Disease Neuroimaging Initiative, Open Access Series of Imaging Studies, and Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing.

- **Alzheimer's Disease Neuroimaging Initiative (ADNI)**: This initiative offers a comprehensive dataset comprising MRI and PET images, genetic data, and various biomarkers for AD. The dataset is designed to help researchers develop and validate advanced diagnostic tools and methodologies. Access is granted upon application approval through the ADNI website.
- **Open Access Series of Imaging Studies (OASIS)**: Focused on both normal aging and clinical populations, OASIS datasets include longitudinal MRI data across a broad age range. These datasets are freely available to the scientific community and can be accessed online without extensive application procedures.
- **Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL)**: This study provides data on imaging, lifestyle, biomarkers, and the progression of AD, as well as healthy controls. Access to the data requires registration and approval.

2. CAD Methods for AD Classification

Generally, CAD methods for AD classification are based on either supervised learning or unsupervised learning. For supervised learning, the data samples are annotated and labeled, so the training is aimed at minimizing the error between the predictions of the deep model and the ground truth labels. On the other side, for unsupervised learning, ground truth labels are not available, so deep models are trained with proxy tasks, such as reconstruction, colorization, and contrastive learning. In this section, we will discuss these methods in detail.

2.1. *CAD Methods for AD Using Transfer Learning*

Transfer learning is the most popular approach for applying deep models in downstream tasks. With pre-trained weights, deep models can converge faster on medical datasets. Raza, et al. [9] leveraged the AlexNet to detect AD from normal control (NC). They used the ADNI and OASIS for training and testing. The accuracies were 98.74% and 95.93% for ADNI and OASIS, respectively. Puente-Castro, et al. [10] used a pre-trained ResNet as the backbone for representation learning. The representations were combined with the age and sex information of the subjects. Finally, an SVM was trained for multi-class classification. The accuracies were 86.81% and 78.64% for OASIS and ADNI, respectively. Ashraf, et al. [11] employed 13 different CNN models for AD detection using transfer learning, including AlexNet, DenseNet, ResNet, VGG, and SqueezeNet. They found that DenseNet outperformed other models with an accuracy of 99.05% on the MRIs from ADNI. Cilia, et al. [3] leveraged the handwriting data of the subjects to classify AD. They employed four models for feature learning, including ResNet-50, VGG-19, InceptionV3, and InceptionResNetV2. Data augmentation techniques were used to generate synthetic handwriting images for training. The deep features were combined with handcrafted features to train four traditional classifiers, including SVM, random forest, multi-layer perceptron, and k nearest neighbors. The best accuracy was 81.03%. Helaly, et al. [8] used a pre-trained VGG-19 as the backbone for AD classification. The pre-trained VGG-19 was fine-tuned on the 2D brain MRIs and achieved an accuracy of 97%. Loddo, et al. [12] utilized three pre-trained CNNs for AD detection in brain MRIs, including ResNet-101, AlexNet, and InceptionResNetV2. The three pre-trained models were fine-tuned on the MRIs, and their predictions were obtained by averaging across the three models. Their method was experimented on three datasets: OASIS, ADNI, and the Kaggle dataset, yielding an accuracy of over 98% for binary classification and multi-class classification.

A summary of the abovementioned methods is given in Table 1.

Table 1. CAD methods for AD classification using transfer learning.

Author	Model	Dataset	Result
Raza, et al. [9]	AlexNet	MRIs from ADNI and OASIS	The accuracies were 98.74% and 95.93% for ADNI and OASIS, respectively.
Puente-Castro, et al. [10]	ResNet and SVM	MRIs from ADNI and OASIS	The accuracies were 86.81% and 78.64% for OASIS and ADNI, respectively.
Ashraf, et al. [11]	AlexNet, DenseNet, ResNet, VGG, and SqueezeNet	MRIs from ADNI	The best accuracy was 99.05% by transferring DenseNet.
Cilia, et al. [3]	ResNet-50, VGG-19, InceptionV3, InceptionResNetV2, SVM, random forest, multi-layer perceptron, and k nearest neighbors	Private handwriting images	The best accuracy was 81.03%.
Helaly, et al. [8]	VGG-19	MRIs from ADNI	The model achieved an accuracy of 97%.
Loddo, et al. [12]	ResNet-101, AlexNet, and InceptionResNetV2	MRIs from OASIS, ADNI, and the Kaggle dataset	Their method yielded an accuracy of over 98% for binary classification and multi-class classification.

Note: CAD: Computer-Aided Diagnosis; AD: Alzheimer's Disease; MRI: Magnetic Resonance Imaging; ADNI: Alzheimer's Disease Neuroimaging Initiative; OASIS: Open Access Series of Imaging Studies.

2.2. CAD Methods for AD Trained from Scratch

Medical images vary significantly from natural images, so pre-trained weights cannot always work because of this gap between the source domain and the target domain. In addition, if the structure of the backbone model is modified or a new deep model is constructed, there are no pre-trained weights available. Therefore, training from scratch is preferred, which allows high flexibility in architecture design and customization for AD classification. Islam and Zhang [13] developed a CNN based on Inception-V4 for AD classification. The configurations of the original Inception-V4 were modified to fit the resolution of the MRI slices. In experiments, the Open Access Series of Imaging Studies (OASIS) dataset was employed for evaluation. Their model achieved an accuracy of 73.75%, which was not satisfactory. Bi, et al. [14] employed a CNN and a recurrent neural network (RNN) for feature extraction from the brain network generated from MRIs. An extreme learning machine (ELM) was trained to identify AD from mild cognitive impairment (MCI). They leveraged the brain MRIs from the AD neuroimaging initiative (ADNI) for evaluation. Traditional handcrafted features with the SVM classifier were implemented for comparison. The area under the curve (AUC) was chosen as the performance metric, and the best value was 84.7% for the classification of AD, MCI, and normal control (NC). Feng, et al. [15] designed a 3D-CNN to generate latent features from brain MRIs and PETs and developed a bi-directional long short-term memory (LSTM) structure for AD classification. Their model achieved an accuracy of 94.82% in recognizing AD versus NC. Hussain, et al. [16] suggested building a 12-layer CNN to classify AD in brain MRIs. In their experiments, pre-trained CNNs were leveraged using transfer learning for comparison, including MobilenetV2, VGG, InceptionV3, and Xception. Their 12-layer CNN outperformed the four models. Wang, et al. [4] used functional MRI time series data to detect AD. A CNN was trained to generate spatial representations, and an LSTM was implemented to get temporal information. Their model was evaluated on the ADNI dataset, and the accuracy was 71.76% for the classification of AD, MCI, and NC. Kundaram and Pathak [17] designed a deep CNN using 3 convolutional layers, 3 max-pooling layers, and 2 fully-connected layers. The network was trained on the brain MRIs and produced an accuracy of 87.72% for validation. Zhu, et al. [18] designed a Patch-Net to generate local representations from the brain MRIs. Then, an attention-based pooling block was developed for feature fusion. Fully-connected layers served for final predictions. The model was experimented on ADNI and AIBL datasets, and the best accuracy was 92.4% in distinguishing AD and NC. Alorf and Khan [19] developed two different networks for AD classification using brain MRIs from the ADNI dataset. The first model was a stacked sparse autoencoder with softmax activation for classification. The second one was built upon a graph neural network, which exploits the connectivity of different brain regions. Their models were evaluated using the ADNI dataset, and the graph network outperformed with an accuracy of 84.03%. El-Sappagh, et al. [20] employed brain MRIs and time series data to detect AD and MCI and predict the conversion time. An LSTM and a feedforward neural network were combined and trained for classification and prediction. Results from the ADNI dataset revealed that their model produced an accuracy of 93.87%. Houria, et al. [21] used MRIs and diffusion tensor images (DTIs) to detect AD and MCI. They first developed a 2D-CNN structure to generate features from different images, and fused them. An SVM was trained as the classification model. The performance of the model was evaluated on the ADNI dataset, and satisfactory results were obtained.

A summary of the abovementioned methods is given in Table 2.

Table 2. CAD Methods for AD Classification Trained from Scratch.

Author	Model	Dataset	Result
Islam and Zhang [13]	CNN based on Inception-V4	MRIs from OASIS	The best accuracy was 73.75%.
Bi, et al. [14]	CNN, RNN, and ELM	MRIs from ADNI	The AUC for the 3-type classification was 84.7%.
Feng, et al. [15]	3D-CNN and LSTM	MRIs and PETs from ADNI	For AD and NC classification, the accuracy was 94.82%.
Hussain, et al. [16]	12-layer CNN	MRIs from OASIS	Their model achieved an accuracy of 97.75% for binary classification.
Wang, et al. [4]	CNN and LSTM	MRIs from ADNI	The accuracy was 71.76% for the classification of AD, MCI, and NC.
Kundaram and Pathak [17]	CNN	MRIs from ADNI	The model produced an accuracy of 87.72% for validation.
Zhu, et al. [18]	CNN with an attention mechanism	MRIs from ADNI and AIBL	The best accuracy was 92.4% in distinguishing AD and NC.
Alorf and Khan [19]	Stacked sparse autoencoder and graph neural network	MRIs from ADNI	The graph network achieved an accuracy of 84.03%.
El-Sappagh, et al. [20]	LSTM and feedforward neural network	MRIs and time series data from ADNI	Their model produced an accuracy of 93.87%.
Houria, et al. [21]	2D-CNN and SVM	MRIs from ADNI	The accuracy for CN and MCI classification was 97.00%.

2.3. CAD Methods for AD Using Unsupervised Learning

Unsupervised learning can learn patterns from data without label information, which is often used in medical applications because it is difficult to get labels without expertise. Ju, et al. [22] generated brain networks from the MRIs in the ADNI dataset and constructed an autoencoder for representation learning. The pre-training of the autoencoder was based on unsupervised learning, and the labels were used with a softmax output layer during fine-tuning. The autoencoder yielded an accuracy of 86.47% on the correlation coefficient data. Bi, et al. [23] utilized a PCANet to generate representations from the brain MRIs and used the k-means algorithm for classification. In the PCANet, convolutional layers and PCA operations were constructed. Therefore, the entire model can be trained by unsupervised learning. The average accuracy was 92.5% on the MRIs from the ADNI dataset. Jin, et al. [24] used a variational autoencoder as the encoder of the generative adversarial network for data augmentation. The reconstructed brain MRI and the original one were used to generate the residual image, which was fed into a multi-layer perceptron for AD classification. Cabreza, et al. [25] developed a generative adversarial network for detecting AD in brain MRIs. Their model was trained by unsupervised learning, and an anomaly score was proposed to classify the AD and NC samples. MRIs from OASIS were used for training and testing, and the accuracy of their method was 74.44%. Shi, et al. [26] proposed a generative adversarial network for segmentation of regions of interest for tau decomposition and AD classification in tau PET images. In the training of the model, multiple losses were used to achieve better generalization performance. The final AUC for binary classification was 92.9%. Zhang, et al. [27] developed a generative adversarial network with pyramid attention blocks to obtain more training PETs. The metabolic features in PETs were combined with MRIs for classifier training. For AD, MCI, and NC classification, the accuracy was 89.9%.

A summary of the abovementioned methods is given in Table 3.

Table 3. CAD methods for AD using unsupervised learning.

Author	Model	Dataset	Result
Ju, et al. [22]	Autoencoder	MRIs from ADNI	Based on the correlation coefficient data, the accuracy was 86.47%.
Bi, et al. [23]	PCANet and k-means	MRIs from ADNI	The average accuracy was 92.5%.
Jin, et al. [24]	Variational autoencoder, generative adversarial network, and multi-layer perceptron	MRIs from ADNI	The accuracy was 94%.
Cabreza, et al. [25]	Generative adversarial network	MRIs from OASIS	The overall accuracy was only 74.44%.
Shi, et al. [26]	Generative adversarial network with multiple losses	Tau PETs from ADNI	The final AUC for binary classification was 92.9%.
Zhang, et al. [27]	Generative adversarial network with pyramid attention blocks	MRIs and PETs from ADNI	For AD, MCI, and NC classification, the accuracy was 89.9%.

2.4. Other CAD Methods for AD

There are some AD detection methods based on traditional machine learning algorithms and networks other than CNNs or recurrent neural networks. For instance, Almubark, et al. [28] employed principal component analysis (PCA) with machine learning classifiers to detect AD from neuropsychological and cognitive data, including SVM, random forest, gradient boosting, and AdaBoost models. Uysal and Ozturk [29] attempted to diagnose AD based on hippocampal atrophy conditions. They segmented the brain MRIs to obtain the volume information of the hippocampal, which was fused with age and gender information. The SVM, Logistic regression, Gaussian naïve Bayes classifier, decision tree, random forest, and k-nearest neighbors were trained for identification of AD. The highest accuracy was 98% for AD and NC classification. Alvi, et al. [2] employed a gated-recurrent unit, a variant of the recurrent neural network to detect MCI using electroencephalography data. The electroencephalography data were pre-processed and segmented before feature extraction. Subsequently, a gated-recurrent unit was trained to identify MCI and NC. The experiment results showed that their method achieved an accuracy of 96.91%. Ilias and Askounis [30] proposed that transformer-based language models can be employed to detect AD in transcript data. The results were obtained on the ADReSS challenge dataset, and the model achieved an accuracy of 86.25% for multi-class classification. Meanwhile, they also analyzed the transcript and found out the words related to AD. Khan and Zubair [31] tried to detect AD using cognitive and demographic data from the ADNI dataset. Six different traditional machine learning classifiers were trained and compared in their experiments, and the best accuracy was 93.90%.

A summary of the abovementioned methods is given in Table 4.

Table 4. Other CAD methods for AD.

Author	Model	Dataset	Result
Almubark, et al. [28]	PCA with SVM, random forest, gradient boosting, and AdaBoost	Neuropsychological and cognitive data	The best accuracy was 91.08%.
Uysal and Ozturk [29]	SVM, Logistic regression, Gaussian naïve Bayes classifier, decision tree, random forest, and k nearest neighbors	MRIs from ADNI	The highest accuracy was 98% for AD and NC classification.
Alvi, et al. [2]	Gated-recurrent unit	Private electroencephalography data	The experiment results showed that their method achieved an accuracy of 96.91%.
Ilias and Askounis [30]	Transformer	ADReSS challenge dataset	The model achieved an accuracy of 86.25% for multi-class classification.
Khan and Zubair [31]	SVM, extreme Gradient Boosting, Logistic regression, naïve Bayes classifier, decision tree, and random forest	Cognitive and demographic data from ADNI dataset	The best accuracy was 93.90%.

3. Conclusion

This paper presents a comprehensive survey of CAD methods for AD detection. The review highlights the critical role of early diagnosis in managing AD progression and improving patient quality of life. In recent years, CAD methods utilizing advanced deep learning models have shown promising results in analyzing medical data such as MRI, PET, and cognitive assessments to aid in accurate diagnosis.

The CAD methods can be categorized into supervised learning, unsupervised learning, and other techniques. This study describes the application of pre-trained deep models like AlexNet, ResNet, and VGG in transfer learning, the development of custom CNN and RNN architectures for training from scratch. Unsupervised learning approaches, including autoencoders, generative adversarial networks, and PCA networks, are also explored for AD detection. Additionally, the use of traditional machine learning, transformer models, and other networks beyond CNNs in AD classification is discussed. The comparison of the three main methods is presented in Table 5.

Table 5. Comparison of three main methods.

Method	Advantages	Limitations
Transfer Learning	- Requires less training data - Faster convergence - Leverages pre-trained models to enhance feature extraction	- Potential for overfitting on small datasets - Dependent on the relevance of pre-trained model
Training from Scratch	- Customized to specific tasks - Full control over architecture	- Requires large datasets - Long training times
Unsupervised Learning	- No need for labeled data - Can discover unexpected patterns	- Less accurate than supervised methods - Complex interpretation of results

Despite the advancements in CAD methods, several challenges remain, including the need for larger and more diverse datasets, the incorporation of multimodal data, and improvements in model generalization. Future research directions should emphasize the importance of continued research to develop more accurate and robust CAD systems, leveraging advanced deep learning techniques and integrating multimodal data, to assist doctors in the early detection and diagnosis of AD. The application of CAD methods in clinical practice is yet to be achieved currently. This is because the CAD systems need to be subjected to rigorous regulatory approval processes, which can be lengthy and costly, especially for tools that use machine learning. Issues such as patient data privacy, consent for using patient data in training models, and the potential for bias in algorithmic decisions must be carefully managed. Moreover, clinicians may be skeptical of CAD systems, especially if they do not understand how decisions are made by the algorithms.

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Conflicts of Interest

The authors declare no conflict of interest.

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