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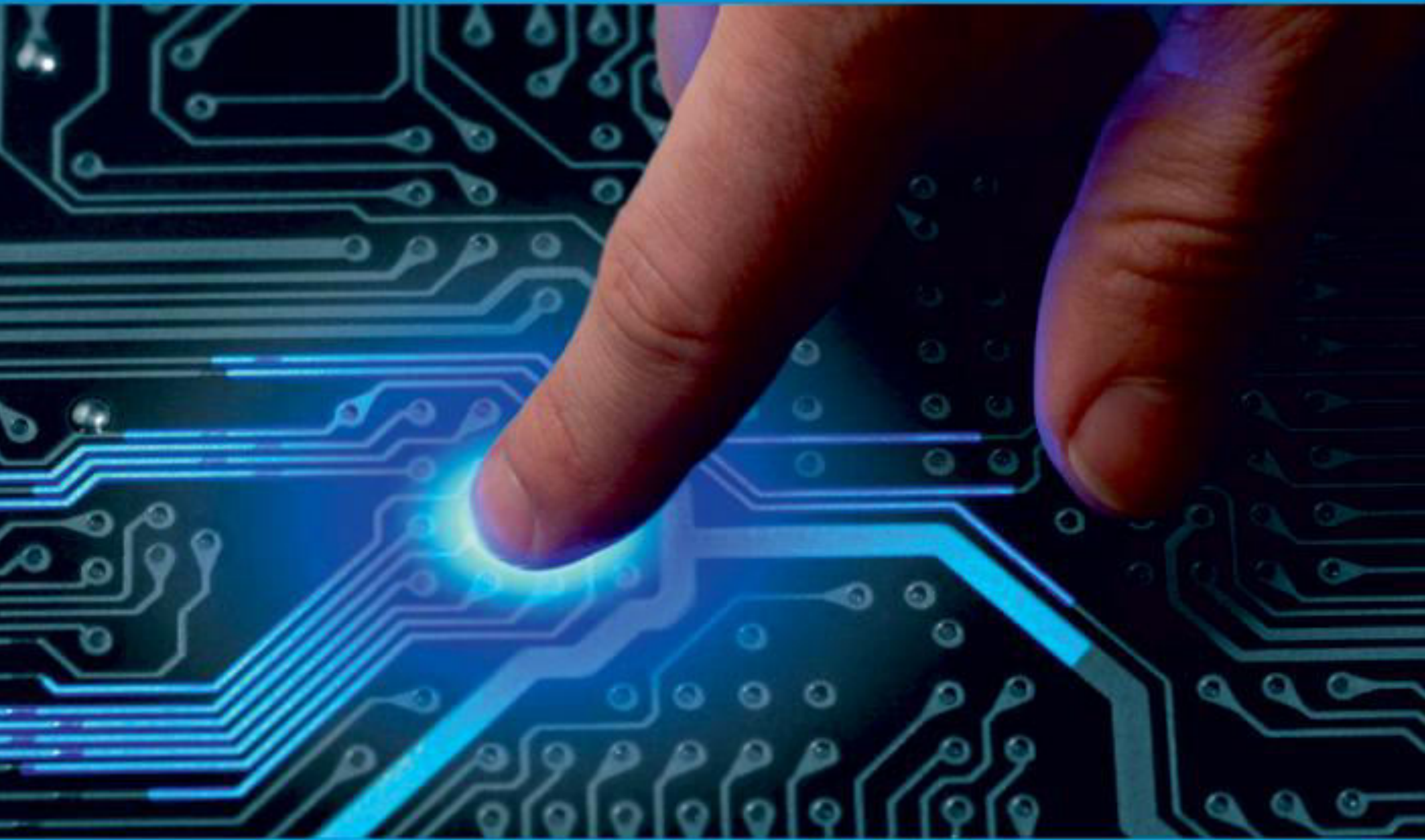

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Diagnosis of Neuro Degenerative diseases Using Convolution Neural Networks

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ABSTRACT: Deep learning has demonstrated excellent performance in finding complicated structures in the difficult high-dimensional data field, particularly in the field of computer vision, above classical machine learning. Recently, much consideration has been given to the application of extensive learning for early detection and automated categorization of Alzheimer disease (AD), as rapid advancement in neuroimaging technologies has created broad multimodal neuroimagery data. A thorough examination of articles was conducted using profound learning and neuroimaging data for the diagnostic classification of AD. A search for deep learning publications published between January 2013 to Juli 2018 in PubMed and Google Scholar was used to identify AD. These documents were analysed, appraised, categorised, and the conclusions were summarised by algorithm and neuroimaging type. Out of 16 research that met criteria of full inclusion, 4 employed a combination from profound learning and traditionals, and 12 used exclusively profound learning methods. The combination of classical machine classification learning and stacked autoencoder (SAE) for feature selection produated accuracy up to 98.8% for the AD classification and 83.7% for the prodromal stage of AD to AD conversion prediction. Deep learning techniques, such as the CNN or the Recent Neural Network (RNN), using neuroimaging data without pre-processing for feature selection have resulted in accurate AD classification of up to 96.0 percent and MCI conversion forecast of up to 84.2 percent. When multimodal neuroimaging and fluid biomarkers were coupled the best classification performance was achieved. Deep learning algorithms continue to improve performance and seem to deliver promise in the use of multimodal neuroimaging data to diagnose AD. Deep learning research still continues to evolve and performance is enhanced by incorporating additional hybrid data, like web data, enhanced transparency and explainable ways that provide knowledge of specific characteristics and mechanisms associated to disease.

KEYWORDS: artificial intelligence, machine learning, deep learning, classification, Alzheimer's disease, neuroimaging, magnetic resonance imaging, positron emission tomography.

I. INTRODUCTION

The most frequent form of dementia, Alzheimer's disease (AD), is a significant health concern in the 21st century. An estimated 5.5 million people aged 65 or older live with DA, and DA is America's sixth most important cause of mortality. In 2018, USD 277 billion in the world's costs for AD management, including medical, social welfare and pay losses for patient families had a major influence on global economy and the US health care system was stressed. (Association of Alzheimer, 2018). AD is an irreversible, progressive, cognitive-functional condition with no validated treatment-modifying disease (1). Thus, much has been done to develop early detection tools, particularly at pre-symptomatic phases, to delay or prevent disease progression [2] In particular, improved methods of neuroimaging (MRI) and positron emission tomography (PET), for the identification of structural and molecular AD biomarkers have been developed and applied to [3]. Rapid progress in the technology of neuroimaging made it difficult for massive, high-dimensional multimodal neuroimaging data to be integrated. The interest in computer-aided learning techniques to integrative analysis has therefore increased fast. We have used and hold promise to early AD detection and predict AD progression, known methodologies for pattern analysis such as linear discriminant analysis, linear programme boost method (LPBM), logistic regression, vector supporting machine removal (SVM), and supporting machine recurrent feature elimination (SVM-RFE) [4].

Applying such algorithms must be predefined by pre-defining the proper architectural design or preliminary stages . Classification studies utilising machine learning usually need four steps: extraction of features, feature selection, reduction in dimensions and selection of feature-based classification algorithms. These processes involve expert expertise and several optimisation steps, which may take time. The reproductivity of these approaches was a problem. For example, in the process of selection of the features AD related to different types of neuroimaging are chosen to derive more informative combinational actions, which can include average subcortical amounts, densities of grey

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matter, cortical thickness, the brain glucose metabolism and accumulation of cerebral amyloid-β in regions of interests, such as hippocampus.

In order to address these obstacles, deep learning in the field of large-scale, high-dimensional medical imaging, a new branch of machine-learning research that leverages raw neuroimaging information to produce functionality through "on-the-fly" learning (Plis et al., 2014). Deep learning methods such as CNN have been proved to outperform current methods of machine learning (LeCun et al., 2015).

We examined publications in systematic ways that employ deep learners and neuroimaging data to detect AD early and to forecast the course of AD. A search for deep learning publications published between January 2013 to Juli 2018 in PubMed and Google Scholar was used to identify AD. The studies were examined, classified according to algorithms and types of neuroimaging, and summarised the findings. Furthermore, we highlight problems and consequences for using profound learning to AD research.

II. DEEP LEARNING METHODS

Deep Learning is a sub-set of machine learning ,which means that the learning process is hierarchical. In different domains, including computer vision and natural language processing, both of them showing advances in performance have been used in depth learning approaches for classification or prediction. Due to the considerable revision of methods of deep learning over the past years, we focus here on the key concepts of deep learning underlying Artificial Neural Networks (ANN). We also describe architectural layouts of deep learning which have been used for the classification of AD and forecasting tasks. The ANN is a network of interconnected processing systems, which were modelled on the concept of perceptron (Rosenblatt, 1957;1958), artificial neuron group and the neocognitron group of artificial neurones (Mcculloch and Pitts, 1943) and are developed in the form. The seminal publications examined efficient error functions and gradient computation approaches, driven by the shown limitation of the single perceptive layer that only linearly separable patterns can learn (Minsky and Papert, 1969). In order to reduce the error function, a back-propagation process using gradient descents has been created and used

2.1 Modern Deep Deep Networks

When a gradient descent method is applied to the reverse of the output layer to calculate the weights of each layer, a disappearing gradient problem develops when the layer is layered, where the differential is set to 0 before the optimal value is found. The value maximum, as shown in Figure 2a, is 0.25, closing at 0 when it continues to be multiplied when the sigmoid is differentiated. It is known as an evaporative problem, a serious hindrance to the deep neural network. Extensive research has addressed the disappearing gradient difficulty .One of the achievements is to replace the Sigmoid function with other functions such as Hyperbolic Tangent, ReLu and Softplus The Sigmoid function. The hyperbolic tangent feature (tanh) widens the derivative value range of the sigmoid. The ReLu function, the most frequently used activation function, substitutes 0, if the value is less than 0, for the value higher than 0. When the value is 1 then the weights can be adjusted without vanishing via the stacked concealed layers till the first layer. This simplistic method allows numerous layers to be constructed and deep learning to be developed. When ReLu becomes zero, the softplus function replaces ReLu with a progressive descent approach.

While a gradient descent method is used to accurately compute weights, a high calculation time is normally required because each update must differentiate all the data. Thus, additional gradient descent methods were created in addition to the activation function to tackle problems in speed and accuracy. For example, a subset that has been extracted randome from the total data is used for faster and more frequent updates (Bottou, 2010) and extended to Momentum SGD Stochastic Gradient Descent (SGD). Today, an adaptive moment estimation is one of the most used approach of gradiente descent (Adam).

2.2 Deep Learning Architectures

In the history of deep learning (Schmidhuber, 2015) overfitting also played a crucial role and efforts were made to resolve it on an architectural level. One of the first models to tackle the overfit problem was the Restricted Boltzmann (RBM) (Hinton and Salakhutdinov, 2006). A deeper structure called Deep Boltzmann Machine (DBM) was constructed when the RBM's were stored (Salakhutdinov and Larochelle, 2010). The DBN is a supervised technique of learning that connects unattended functions by extracting data from each layer stacked (Hinton et al., 2006). DBN has been shown to perform higher than other models and has gained popularity for deeper learning. While DBN solves the problem of overfit with the RBM weight initialization, CNN effectively reduces the number of model parameters by incorporating coalescence and pooling layers which minimise complexity. CNN is commonly employed in the field of

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visual recognition because of its efficiency when given adequate data. The RBM, DBM, DBN, CNN, Auto-Encoder (AE), sparse AE structures, and stacked AE respectively are presented in Figure 3. Auto-Encode (AE) is an unchecked learning approach, which uses the back propagation and SGD to make the output value near the input value (Hinton and Zemel, 1994). AE deals with dimensional reduction, but because to the fading gradient problem it is difficult to train. Sparse AE addresses this problem by allowing only a few hidden units .Sparse AE stacks, such as DBN. Stacked AE stacks.

The deep learning approaches employed to date in the categorization of Alzheimer's disease diagnosis are DNN, RBM, diabetes, AE, Sparse AE, and Stacked AE. Each strategy has been created to define AD patients as the prodromal stage of AD, with cognitive normal (CN) or mild cognitive impairment (MCI). The conversion of MCI to AD with multi-modeal neuroimaging data is predicted using each technique. In this study, the 'hybrid' approach is defined when deep learning is employed simultaneously with classical methods for machine learning, i.e. SVM as a classifier.

III. RESULTS

From the 16 papers included in this review, Table 2 provides the top results of diagnostic classification and/or prediction of MCI to AD conversion. We compared only binary classification results. Accuracy is a measure used consistently in the sixteen publications. However, it is only one metric of the performance characteristics of an algorithm. The group composition, sample sizes, and number of scans analysed are also noted together because accuracy is sensitive to unbalanced distributions. Table S1 shows the full results sorted according to the performance accuracy as well as the number of subjects, the deep learning approach, and the neuroimaging type used in each paper.

3.1 Deep learning for feature selection from neuroimaging data

Multimodal neuroimaging data have been used to identify structural and molecular/functional biomarkers for AD. It has been shown that volumes or cortical thicknesses in pre-selected AD-specific regions, such as the hippocampus and entorhinal cortex, could be used as features to enhance the classification accuracy in machine learning. Deep learning approaches have been used to select features from neuroimaging data.

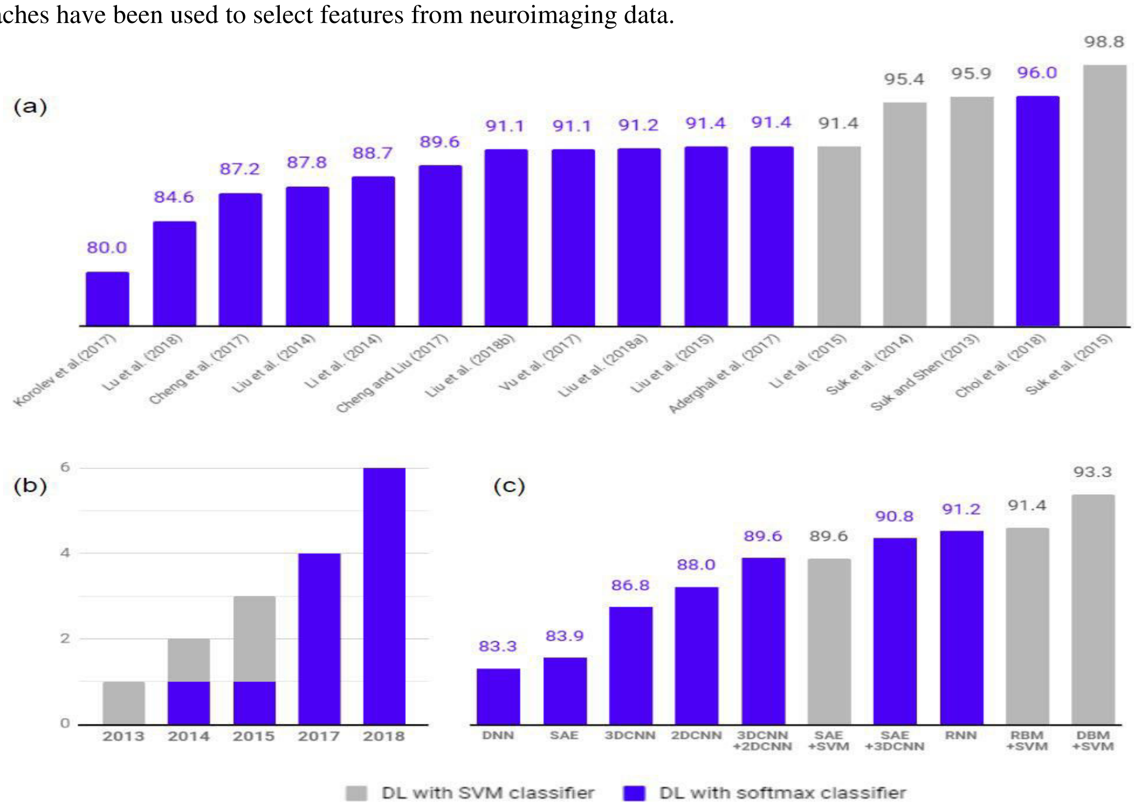

Figure 1.Comparison of diagnostic classification accuracy of pure deep learning and hybrid approach. 4 studies (gray) have used hybrid methods that combine deep learning for feature selection from neuroimaging data and traditional machine learning, such as the SVM as a classifier. 12 studies (blue) have used deep learning method with softmax classifier for diagnostic classification and/or prediction of MCI to AD conversion.

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As shown in Figure 1, 4 studies have used hybrid methods that combine deep learning for feature selection from neuroimaging data and traditional machine learning, such as the SVM as a classifier. Suk and Shen (2013) used a stacked auto-encoder (SAE) to construct an augmented feature vector by concatenating the original features with outputs of the top hidden layer of the representative SAEs. Then, they used a multi-kernel SVM for classification to show 95.9% accuracy for AD/CN classification and 75.8% prediction accuracy of MCI to AD conversion. These methods successfully tuned the input data for the SVM classifier. However, SAE as a classifier (Suk et al., 2015) yielded 89.9% accuracy for AD/CN classification and 60.2% accuracy for prediction of MCI to AD conversion. Later Suk et al. (2015) extended the work to develop a two-step learning scheme: greedy layer-wise pre-training and fine-tuning in deep learning. The same authors further extended their work to use the DBM to find latent hierarchical feature representations by combining heterogeneous modalities during the feature representation learning (Suk et al., 2014). They obtained 95.35% accuracy for AD/CN classification and 74.58% prediction accuracy of MCI to AD conversion. In addition, the authors initialized SAE parameters with target-unrelated samples and tuned the optimal parameters with target-related samples to have 98.8% accuracy for AD/CN classification and 83.7% accuracy for prediction of MCI to AD conversion (Suk et al., 2015). Li et al. (2015) used the RBM with a dropout technique to reduce overfitting in deep learning and SVM as a classifier, which produced 91.4% accuracy for AD/CN classification and 57.4% prediction accuracy of MCI to AD conversion.

3.2 Deep learning for diagnostic classification and prognostic prediction

To select optimal features from multimodal neuroimaging data for diagnostic classification, we usually need several pre-processing steps, such as neuroimaging registration and feature extraction, which greatly affect the classification performance. However, deep learning approaches have been applied to AD diagnostic classification using original neuroimaging data without any feature selection proceduresR Alugubelli. (2016) et.al..

As shown in Figure 1, 12 studies have used only deep learning for diagnostic classification and/or prediction of MCI to AD conversion. Liu et al. (2014) used stacked sparse auto-encoders (SAEs) and a softmax regression layer and showed 87.8% accuracy for AD/CN classification. Liu et al. (2015) used SAE and a softmax logistic regressor as well as a zero-mask strategy for data fusion to extract complementary information from multimodal neuroimaging data (Ngiam et al., 2011), where one of the modalities is randomly hidden by replacing the input values with zero to converge different types of image data for SAE. Here, the deep learning algorithm improved accuracy for AD/CN classification by 91.4%. Recently, Lu et al. (2018) used SAE for pre-training and DNN in the last step, which achieved an AD/CN classification accuracy of 84.6% and an MCI conversion prediction accuracy of 82.93%. CNN, which has shown remarkable performance in the field of image recognition, has also been used for the diagnostic classification of AD with multimodal neuroimaging data. Cheng et al. (2017) used image patches to transform the local images into high-level features from the original MRI images for the 3D-CNN and yielded 87.2% accuracy for AD/CN classification. They improved the accuracy to 89.6% by running two 3D-CNNs on neuroimage patches extracted from MRI and PET separately and by combining their results to run 2D CNN (Cheng and Liu, 2017). Korolev et al. (2017) applied two different 3D CNN approaches (plain (VoxCNN) and residual neural networks (ResNet)) and reported 80% accuracy for AD/CN classification, which was the first study that the manual feature extraction step was unnecessary. Aderghal et al. (2017) captured 2D slices from the hippocampal region in the axial, sagittal, and coronal directions and applied 2D CNN to show 85.9% accuracy for AD/CN classification. Liu et al. (2018b) selected discriminative patches from MR images based on AD-related anatomical landmarks identified by a data-driven learning approach and ran 3D CNN on them. This approach used three independent data sets (ADNI-1 as training, ADNI-2 and MIRIAD as testing) to yield relatively high accuracies of 91.09% and 92.75% for AD/CN classification from ADNI-2 and MIRIAD, respectively, and an MCI conversion prediction accuracy of 76.9% from ADNI-2. Li et al. (2014) trained 3D CNN models on subjects with both MRI and PET scans to encode the nonlinear relationship between MRI and PET images and then used the trained network to estimate the PET patterns for subjects with only MRI data. This study obtained an AD/CN classification accuracy of 92.87% and an MCI conversion prediction accuracy of 72.44%. Vu et al. (2017) applied SAE and 3D CNN to subjects with MRI and FDG PET scans to yield an AD/CN classification accuracy of 91.1%. Liu et al. (2018a) decomposed 3D PET images into a sequence of 2D slices and used a combination of 2D CNN and RNNs to learn the intra-slice and inter-slice features for classification, respectively. The approach yielded AD/CN classification accuracy of 91.2%. If the data is imbalanced, the chance of misdiagnosis increases and sensitivity decreases. For example, in Suk et al. (2014) there were 76 cMCI and 128 ncMCI subjects and the obtained sensitivity of 48.04% was low. Similarly, Liu et al. (2018b) included 38 cMCI and 239 ncMCI subjects and had a low sensitivity of 42.11%. Recently Choi and Jin (2018) reported the first use of 3D CNN models to multimodal PET images (FDG PET and [18F]florbetapir PET) and obtained 96.0% accuracy for AD/CN classification and 84.2% accuracy for the prediction of MCI to AD conversion.

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3.3 Performance comparison by types of neuroimaging techniques

In order to improve the performance for AD/CN classification and for the prediction of MCI to AD conversion, multimodal neuroimaging data such as MRI and PET have commonly been used in deep learning: MRI for brain structural atrophy, amyloid PET for brain amyloid-β accumulation, and FDG-PET for brain glucose metabolism. MRI scans were used in 13 studies, FDG-PET scans in 10, both MRI and FDG-PET scans in 12, and both amyloid PET and FDG-PET scans in 1. The performance in AD/CN classification and/or prediction of MCI to AD conversion yielded better results in PET data compared to MRI.

IV. CONCLUSION

Deep learning algorithms and applications continue to advance and produce the best results in closed scenarios, for example picture recognition (Marcus, 2018). It works especially well if there is a valid inference, i.e. the training and test conditions are similar. This is particularly true with neuroimages while studying AD (Litjens et al., 2017). One limitation of deep learning is that if the complexity is too large for the transparency and reproducibility of the network it is difficult to modify potential bias. The problem can be handled by accumulating large-scale data on neuroimages and analysing connections between deep learning and characteristics. The problem of reproducability can be mitigated by divulging the parameters used to get the results and averages of sufficient experiments.

Deep learning cannot solve all problems. Profound knowledge, which derives attrivings directly from input data, is difficult to integrate data formats such as neuroimaging and genetic data, without pre-processing. Due to the automated weight adjustment for input data inside a closed network, it causes confusion and ambiguousness to add further input data to the closed network. However, a hybrid strategy places more information in the machine and neuroimages into profound learning components before combining the two findings.

Progress in deep learning will be made through the overcoming of these difficulties and solutions. More and more data will have a greater impact on research through deep learning. 2D CNN is expanded to 3D CNN particularly in the AD study, where multimodal neuroimages are dealt with. Generating synthetic medical images for data increase may also apply to Generative Adversarial networks (GAN) . In addition, strengthened learning (Sutton and Barto 2018) can also display application in the field of medicine, a form of knowledge which adjusts to changes in data while deciding itself on the basis of the environment.

Deep learning research on development continues to develop to improve performance and transparency. Multi-mode neuroimaging data and computer resources are growing quickly and research into the diagnostic classification of AD using profound learning is shifted to a model based entirely on in-depth learning algorithms and not on hybrid methodologies.

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