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# Deep and Statistical-Based Methods for Alzheimer's Disease Detection: A Survey

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**Abstract**
Detection of Alzheimer's disease (AD) is one of the most potent and daunting activities in the processing of medical imagery. The survey of recent AD detection techniques in the last 10 years is described in this paper. The AD detection process involves various steps, namely preprocessing, feature extraction, feature selection, dimensionality reduction, segmentation and classification. In this study, we reviewed the latest findings and possible patterns as well as their main contributions. Different types of AD detection techniques are also discussed. Based on the applied algorithms and methods, and the evaluated databases (e.g., ADNI and OASIS), the performances of the most relevant AD detection techniques are compared and discussed.

**Category:** Bioinformatics

**Keywords:** Alzheimer's disease; Statistical methods; Deep learning methods; Segmentation methods

## I. INTRODUCTION

Medical imaging refers to different technologies and techniques that aim to have a comprehensive view of the human body in order to diagnose, prevent, screen and treat medical conditions more efficiently. X-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI), ultrasound, positron emission tomography (PET), and radioactive pharmaceuticals are among the most often utilized medical imaging modalities. In the literature,

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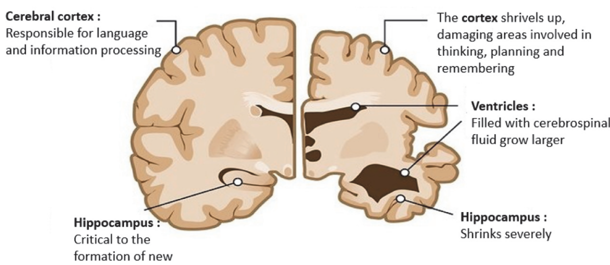


**Fig. 1.** Difference between a healthy brain and a brain with AD.

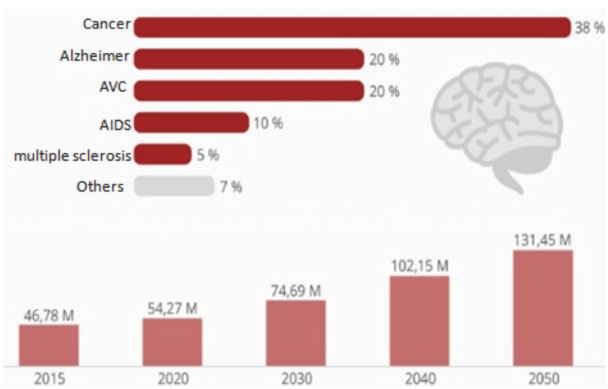


**Fig. 2.** Estimated number of people with AD in the world.

we were able to find many studies on Alzheimer's disease (AD) detection using certain technologies.

The most common cause of dementia is AD, provoking major social and health problems. It is one of the most dangerous neurodegenerative disorders that cause a short-term loss of memory, behavioral disturbances, cognitive actions, and language comprehension issues.

AD typically affects individuals over 65 years of age and whose occurrence rate increases with age exponentially. Therefore, except for the most fundamental daily activities (e.g., washing, eating, dressing), people continuously need caregivers in the late stages, which inevitably leads to death. Fig. 1 shows the difference between a healthy brain and a brain with AD. With the aging of the population, this disease will become more prevalent in the coming years: If in 2020, the number of people with AD in the world exceeded 54 million, more than 131 million people could be affected by 2050, according to the data obtained from the Alzheimer Disease International Association (Fig. 2).

There is no successful cure for AD so far, but early diagnosis is important for finding a safe treatment and slowing down the progression of symptoms. Thus, the automated diagnostic tools have gained a lot of attention in recent years. A recent analysis of the various methods for AD detection is discussed in this paper.

The rest of the paper is structured as follows: We present a summary of the current methods of AD detection in Section II. Section III provides a distinction between the available databases. We discuss the usefulness of the examined methods and techniques in Section IV. Conclusions and future trends end the paper.

## II. MEDICAL IMAGING TECHNOLOGIES

Medical imaging field has grown exponentially in the last years and has been successfully used to develop automated methods for clinical decisions and disease diagnosis. Subsequently, it has received wide acceptance by the medical community. In the following, we present the most used medical imaging technologies for Alzheimer's disease detection namely MRI and PET.

### *A. MRI*

MRI is an effective, non-invasive brain imaging tool that offers higher quality information on the volume and the shape of the brain. It offers superior differentiation of the soft tissue, excellent spatial resolution, and perfect contrast. The principle of MRI operation is based on a physical phenomenon that exploits the magnetic properties of atoms (these atoms have the particularity of emitting radio waves when exposed to a magnetic field, making them detectable). Furthermore, the diagnostic use of MRI has been substantially enhanced as a result of automatic and accurate labeling of MRI images, which plays an important role in the detection of AD.

### *B. PET*

PET is also a non-invasive imaging technique that allows molecular processes to be visualized and quantified, affording responsive and early illness detection. This technique provides disease identification of molecular processes before clinical symptom manifestation. PET is based on the principle of scintigraphy which consists in injecting a radioactive tracer intravenously, representing the information in the form of an image showing in color the areas of high concentration of the tracer. PET imaging enhances the perception of possible AD causes, molecular event timeline, and early AD detection.

## III. AD DETECTION METHODS

According to the literature, there are several strategies for identifying AD, which are categorized into three groups: statistical methods, deep learning methods, and segmentation methods. We detailed these three types in this study by highlighting recent and successful strategies proposed in the literature. Fig. 3 displays the taxonomy of methods of detecting AD.

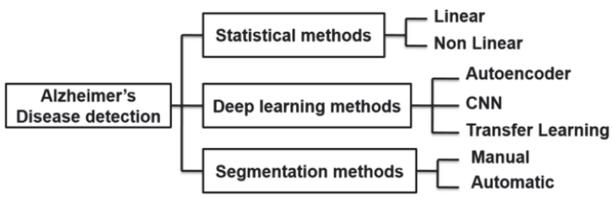


**Fig. 3.** Taxonomy of methods of detecting AD.

### *A. AD Detection using Statistical-based Methods*

We highlight the latest statistical methods for AD detection. Such methods often use a dimensionality reduction mechanism after the feature extraction step, or simply for feature selection. Using one or more classifiers, classification is then implemented by taking the obtained features as input. These methods can be categorized according to the space in which the classification was performed, into linear and non-linear methods.

In [1], the principal component analysis (PCA) was utilized to pick the important features from a process that focuses on the multidimensional classification of the features of longitudinal brain atrophy. It is a way of describing models in data and utilizing them in a way that demonstrates their similarities as well as differences. This approach enables the feature space dimension to be reduced and become further effective. The K-means, support vector machine (SVM), and fuzzy clustering methods (FCM) are the basis of the classification process. In the analysis of 2D and 3D MRI images for classification, the local binary pattern (LBP) approach was used in [2] for texture analysis. They improved the LBP method using a sign and magnitude value to utilize extraction of features from three brain areas (named advanced local binary pattern, ALBP). The input function for dealing with ALBP was composed of the concatenation of its binary values. After that, they used PCA and factor analysis for selection of features. Next, as a classification tool, they used SVM. The negative point in this analysis was that the extraction of high-dimensional features contributed to high computing processing. So, concentrating on extracting features of a large MRI dataset using parallel computing methods may be easier. In terms of feature extraction, the authors of [3] used the discrete wavelet transform (DWT) technique. Then, for feature selection, PCA was applied. Next, for classification, linear discriminant analysis (LDA) was used. The accuracy rate of this method was 77.78%.

Similarly, the authors of [4] employed the DWT for the extraction of the feature and the PCA for the reduction of the feature. Then, they used the Normalized Mutual Knowledge Feature Selection (NMIFS) method for the selection of features. A similar approach was suggested in [5]. A system composed of three phases was proposed. Initial extraction of features utilizing a dual-tree complex wavelet transform (DTCWT), reduction of feature dimensionality using PCA and finally, the feed-forward artificial neural network (FNN) was used for classification. The results of this approach (accuracy 90.06%) were considered to be successful. It was noticed that with the use of another preprocessing tool, the efficiency can be further improved. Furthermore, the authors of [6] have used the PCA for feature selection in order to reduce the dimensionality of data. Three classifiers were used for classification SVM, import vector machine (IVM), and regularized extreme learning machine (RELM). The accuracy rate was considered relatively low for the last three classifiers.

A computer-aided diagnostic system consisting mainly of three parts was proposed in [7]. First, the automatic segmentation of brain tissue has been applied for each image. Second, partial least squares (PLS) and PCA were used for extraction of features. Lastly, with the SVM, image classification was applied. The PCA-based method in [8] was paired with supervised methods of learning. This combination helped address the limited sample size issue. In this research, PCA was first used with two linear feature selection techniques—LDA and Fisher discriminant ratio (FDR)—to obtain the final characteristics that will then feed the two subsequent classifiers—neural networks (NN) and SVM.

The authors of [9] suggested a novel method for the diagnosis of AD using voxel-based morphometry (VBM) detected features by the classifier self-adaptive resource allocation network (SRAN). Furthermore, PCA has been carried out on the morphometric features acquired mainly from the VBM analysis for feature reduction. As for the SRAN classifier input, these reduced characteristics were used. Another analysis of using an SVM classifier on the PCA's reduced features was also performed. Also, in [10], by using the PCA, the authors applied an automated AD classification method. Then, to identify the level of AD in the input MRI, the reduced dimensional information is transmitted to an artificial neural network (ANN). The classification rate of this method reached 89.22%. The latter can be improved by using more data in the learning phase or focusing on another region of the brain affected by AD.

For AD identification, non-linear statistical-based techniques have also been used. For instance, the authors of [11] introduced an approach based on the combination of the extracted characteristics with the Mini-Mental State Examination (MMSE) scores, applying a two-sample t-test to pick a subset of features.

In [12], another method using similar characteristics was suggested, which consists of four stages: (1) a brain network was constructed from the functional magnetic resonance imaging (fMRI) data, using a minimum spanning tree, (2) frequent subnetworks were operated via the graph substructure pattern mining (gSpan), (3) to discover the

**Table 1.** Statistical methods

| Study | Technique | Classifier | Dataset | Accuracy (%) |
|---|---|---|---|---|
| [1] | PCA | K-mean / FCM SVM | ADNI | 83.3 / 90 |
| [2] | LBP+PCA | SVM | ADNI | 96.28 |
| [3] | DWT, PCA | LDA | ADNI | 77.78 |
| [4] | DWT+PCA | SVM | ADNI | 95 |
| [5] | DTCWT, PCA | FNN | OASIS | 90.06 |
| [6] | PCA | SVM / IVM / RELM | ADNI | 75.33 / 60.20 / 76.61 |
| [7] | PLS | SVM | ADNI | 88.49 |
| [8] | PSA | SVM / NN | ADNI | 96.7 / 89.52 |
| [9] | VBM | SRAN | OASIS | 91.18 |
| [10] | PCA | ANN | OASIS | 89.22 |
| [11] | PCA, LDA | SVM | ADNI | 93.85 |
| [12] | Kernel PCA | SVM | ADNI | 91.3 |
| [14] | Kernel PCA | SVM | ADNI | 84 |

important discriminative subnetworks, they used the sub-network selection algorithm, and (4) to extract features from the reconstructed networks, graph kernel PCA was applied. The SVM was finally used for classification. Deficiency of generality due to the small data used (68 participants) affected the results of the classification. Also, the authors of [13] used the SVM for AD detection. On the other hand, the authors of [14] introduced a kernel PCA as a form of feature selection which was incorporated to the extraction of the feature of 3D texture descriptor, CLBPSM-TOP (complete local binary pattern from three orthogonal planes). Then, they used an SVM for the classification. Table 1 recaps the statistical methods listed above and their accuracies [1-14].

## B. AD Detection using Deep Learning-based Methods

In the field of medical imaging, many methods based on deep neural networks have significantly improved precision and outperformed traditional methods, one of which is the detection of COVID-19 [15].

We distinguished various types of deep learning strategies to detect AD. Each strategy is aimed to accurately employ the deep architecture of the deep models, and eventually make a good classification. The choice of the strategy was dependent on many factors such as the database size, availability of labeled images, number of layers, and the learning technique that will be employed. In the following, we present the main deep learning strategies for AD detection.

### *1) Autoencoder based Methods*

One of the vast families of deep learning techniques is an auto-encoder. It consists of two symmetrical deep networks, which typically have shallow layers illustrating the network's encoding section, and second layers representing the decoding section. Here, using the auto-encoder network, we concentrate on AD detection methods.

For instance, in [16] the authors suggested a deep learning method based on sparse auto-encoder (SAE) for the detection of AD. This auto-encoder enabled the features to be selected in an unsupervised way by reducing reconstruction errors (cost-function optimization is the basis of the training process). It consisted of an encoder followed by a decoder. Two auto-encoders were trained and then a softmax layer was built to classify the vector characteristics.

Other autoencoder-based methods can also be found using linear activation features and weights, as in [17], using a k-sparse auto-encoder (KSA) for classification. The downside to this approach was the overfitting of multiple parameters that can occur when small data sets were employed. Furthermore, the authors of [18] used the architecture of deep convolutional auto-encoder (CAE), a method that can decompose a very large dataset automatically and nonlinearly (using convolutional layers, this architecture can extract data-based features straight from 3D maps).

The authors of [19] used the texture details and other related features to achieve a multi-class classification. Then, deep learning was implemented on the basis of two separate models. In particular, subcortical region-specific feature extraction, feature selection and a deep stacked auto-encoder were subsequently performed successively. In order to improve classification accuracy, computing fractal dimension cooccurrence matrix (FDCM) from texture has been utilized. The two models achieved 56.6% and 58.0% cross-validation accuracy. Using other texture characteristics, these rates can be increased. Another approach was proposed in [20] that used the brain network and clinical text knowledge. By computing the functional connectivity of brain regions utilizing resting-state functional MRI data, the brain network was built. A stacked auto-encoder network was applied in order to differentiate among normal aging and early stage of AD. The precision of the classification reached 86.47%. By utilizing a larger data set, this outcome can be improved. In [21], the proposed strategy was presented in two steps. An ensemble of auto encoder-based feature extraction modules was utilized in the first step to produce image features from a 3D input image, and a convolutional neural network (CNN) was employed in the second step to diagnose AD. The accuracy of the results obtained was 95%.

#### *2) CNN based Methods*

In recent years, CNN has been highly used in AD detection methods owing to its ability to automatically learn features and also to use them on a large dataset. Therefore, different approaches have been suggested in the literature for that purpose. For example, the authors of [22] used a CNN for feature extraction then they employed the random forest (RF), SVM and K-nearest neighbor (KNN) for classification of images.

In [23], an analytical approach based on multi-modal MRI was suggested that was suitable also for fMRI or diffusion tensor imaging (DTI) data. Connectivity network images were extracted by using DTI and FMRI conjointly. It was then used as an input of a CNN for classification. The obtained accuracy of classification was 92.06%. This rate can be improved by trying 3D convolution instead of 2D convolution. Yue et al. [24] utilized for the extraction of features a deep convolutional neural network (DCNN). Initially, the structural MRIs were pre-processed inside a strict pipeline. Next, instead of parceling regions of interest, they resliced each volume and put the resliced images directly into a DCNN. Also, the authors of [25] used the graph convolutional neural network (GCNN) classier. It was based on structural connectivity inputs in the form of Laplacians graphs. This network composed of 11 layers (nine convolutional layers and two fully connected layers) allowing the classification of individuals of AD.

Besides classifying AD patients utilizing a structural brain MRI, the authors of [26] introduced a deep 3D CNN model. Although this technique used two databases, the classification accuracy reached 73.4% (ADNI) and 69.6% (OASIS). These values can be improved by optimizing the shape of the network. Also, the authors of [27] suggested a new AD recognition CNN system where 3D CNN and 3D convolutional long-term memory (3D CLSTM) were used. To learn informative features, they used initially a six-layer 3D CNN, next 3D CLSTM was exploited to extract higher-level channel-wise information.

On the other hand, in [28], 2D slices obtained from the decomposed 3D PET images were learned by recurrent neural networks (RNN) and 2D-CNN conjointly. The hierarchical 2D-CNNs were then constructed to capture the intra-slice features whereas RNN's gated recurrent unit (GRU) was applied to extract the inter-slice features for final classification. The authors of [29] used a 3D-CNN capable of learning generic characteristics capturing biomarkers of AD. The 3D-CNN was based on a 3D CAE pre-trained to identify anatomical form variations in MRI scans. Then, the 3D-CNN fully connected layers were fine tuned for task-specific classification. Backstrom et al. [30] also utilized a 3D-CNN compound of five convolutional layers for feature extraction, and three fully connected layers and softmax for performance of classification. In addition, in [31], a classification method based on a combination of multimodal convolutional networks was used to learn the different features. Initially, 3D-CNN is used to extract high-level features hierarchically. Next, multi-scale 3D CAEs are designed to learn different features. Then, such convolutional networks combine the features learned with the fully connected layers and softmax layers for image classification.

Besides, a deep 3D-CNN (HadNet) has been proposed in [32], which compounds five types of processing layers (data layer, convolutional layer, 3D max-pooling, global average pooling, and dense layer). The HadNet architecture was categorized in three blocks: STEM that down samples the MR-image data; MAIN that used starting blocks to get the most hidden features; and HEAD where classification of the output was applied. In [33], a CNN model was used to classify slice data that has been randomly partitioned and slice data with independent participants. Then, MRI participants were diagnosed using a slice voting approach. The proposed method's accuracy was 93.10%.

#### *3) Transfer Learning*

We can discover transfer learning-based approaches in the literature that seek to manipulate the problem of AD detection accurately. The saved information was gained while dealing with a vast problem and applying it to another problem which was taken into account in this form of model. In these approaches, one of the old CNN architectures "LeNet-5" [34] detects AD. The LeNet model relied on the architecture of CNN, consisting of three convolutional layers, two subsampling layers, and a fully connected layer. In [35], the authors used another CNN architecture named AlexNet pretrained on the ImageNet dataset, containing five convolutional layers and three fully connected layers. Also, the method proposed in [36] was based on the model AlexNet-SVM, which consists of four procedures.

Another approach based on transfer learning using a mathematical model was proposed in [37]. This model contained three steps: pre-processing; choosing most informative MRI slices; and classification utilizing transfer learning (applying the VGG-16 architecture). The accuracy was 95.73%. Using the fine-tuning approach (training the model's pre-trained convolutional layers), this can be improved. Also, in [38], for the detection of AD, before using the VGG-16 architecture for feature extraction, the authors applied the preprocessing to convert images 3D to 2D. Then, decision tree, SVM, K-means clustering and linear discriminate were used for classification.

In addition, the authors of [39] applied a 2D convolutional network "DemNet," founded on VGGNet, for the detection of AD, which took the slices in input. Thirteen convolutional layers and three fully connected layer were built into this network. The convolutional layers were split into five batches through a max pooling layer. After that, it produces three outputs corresponding to the classification ratings. The VGG-19 architecture was also used in [40] to diagnose AD. Besides, in [41], other than VGG-16, the authors used another architecture called Inception-V4. The breakthrough of the Inceptions was in the realization that by modifying how convolutional layers were connected, nonlinear functions can be studied. Therefore, the fully connected layer was then rejected in preference of a global average pooling (GAP) which averaged the maps of features. Then, it was connected for classification with a softmax layer.

The approach in [42] was focused also on deep learning. The method treated the 3D input volumes and then applied the SPM eight for every volume to bring out the gray matter. Each volume was translated to 166 slices of 2D. Afterwards, these slices were moved onto two architectures (GoogLeNet and ResNet). The GoogLeNet was composed of 22 layers and concentrated on accurate augmentation of modules in depth of the network. It is known for its inception module as well. Several filters extract multi-scale information that was combined prior to transfer to the next layer. Otherwise, the residual learning theory was the foundation of ResNet. This model enabled the depth to increase dramatically and reduced the complexity of calculation. This was due to the implementation of identity connections through various convolutional layers, which transmitted directly the input to the output with its transformed information $f(x)$.

In [43], there were three phases of the method proposed: initially, converting a whole-brain MRI to a 2D cortical thickness sheet, then, extracting brain slices from MRI volume data, and lastly classifying with CNN, ResNet architecture, and Inception architecture. Another method of detection was proposed in [44]. In order to add more functionality, the ResNet extracts the feature vectors from MRI scans. Then, these vectors were concatenated with their respective values of age and sex. Finally, these extended features were fed into an SVM classifier. Table 2 recaps the deep learning methods listed above and their accuracies [16-44].

Besides, ResNet-18 was the CNN architecture used in [45]. The temporal convolutional network (TCN) and several types of RNN were used as sequence-based models. This model achieved a precision of 91.78% in [46]. The identification of AD was proposed using a novel DSC (depthwise separable convolution) network-based method. The CNN was initially employed to detect AD, with a classification accuracy of 78.02%. Then, a strategy that combined DSC and CNN was proposed. In addition, transfer learning was used to increase model performance in this method. Two trained models (AlexNet and GoogLeNet) showed a classification accuracy of 91.40% and 93.02%, respectively. Also, to improve classification accuracy, an ensemble model was applied in [47], where Xception and MobileNet, two pre-trained models, were combined. The results reveal that using the separable convolution layer of both Xception and MobileNet, the ensemble model improved classification accuracy (91.3%).

**Table 2.** Deep learning methods for AD detection

| Study | Technique | Dataset | Accuracy (%) |
|---|---|---|---|
| [16] | SAE | OASIS | 91.6 |
| [17] | KSA | ADNI | 74.605 |
| [18] | CAE | ADNI | 80 |
| [19] | SAE | ADNI | 56.6 (model1) / 58 (model2) |
| [20] | SAE | ADNI | 86.47 |
| [24] | DCNN | ADNI | 96.9 |
| [25] | GCNN | ADNI | 89 |
| [26] | 3DCNN | ADNI / OASIS | 73.4 / 69.6 |
| [27] | 3D CNN+3D CLSTM | ADNI | 94.19 |
| [28] | CNN+RNN | ADNI | 95.28 |
| [30] | 3D ConvNet | ADNI | 98.74 |
| [31] | Multimodal CNN | ADNI | 88.31 |
| [32] | 3D CNN | ADNI | 88.31 |
| [34] | LeNet-5 | ADNI | 96.85 |
| [35] | Alexnet | ADNI | 67.62 |
| [36] | Alexnet-SVM | ADNI | 96.39 |
| [37] | VGG-16 | ADNI | 95.73 |
| [38] | VGG-16 | ADNI | 73.46 |
| [39] | DemNet | ADNI | 91.85 |
| [40] | VGG-19 | ADNI | 99.36 |
| [41] | VGG-16 / Inception V4 | ADNI | 92.3 / 96.2 |
| [42] | GoogLeNet / ResNet | ADNI | 99.18 / 99.08 |
| [43] | Inception / ResNet | ADNI | 81 / 72 |
| [44] | ResNet | ADNI / OASIS | 78.64 / 86.81 |

## C. AD Detection-based Segmentation

There are several automatic segmentation methods that aim to localize the hippocampus region to accurately diagnose AD. For example, the authors of [48] proposed a method for hippocampus segmentation. This method involved several stages. The extraction of the skull from the brain was the first step, then a selection of the region of interest was done using OpenCV. Also, they used K means to isolate the white matter and the gray matter. All the pixels were scanned in order to separate all related regions into a label, thus separating regions of the same image by boundary. The idea to coherently select the hippocampus region was to choose among the labelled regions, their maximum two areas which represented the target region. On the other hand, the Atlas model containing two volumes of images were used by Dill et al. [49], based on a structural brain MRI and a binary image with the corresponding hippocampus map. Twenty-five atlases were used: Twenty-four were chosen to show a combination of features associated to three parameters while the last atlas was MNI152 with 21 hippocampal subcortical structures. Besides, in [50], the authors proposed a model containing four steps: The first step presented the preprocessing utilizing the non-rigid registration implemented in the Advanced Normalization Tools (ANTs). The displacement fields were calculated through this non-rigid registration.

Furthermore, the ANTs also calculated a coefficient that indicated the similarity between the training and target images in terms of image features and brain morphometrics. In the third step, using a surface triangulation module, every labelled image was converted to training point set representation. In the fourth step, the training point sets and their corresponding coefficients were added. On the other hand, authors of [51] presented an approach for segmenting hippocampus automatically utilizing a fully-convolutional network (FCN) with a conditional random field (CRF) layer. This approach allowed more accurate segmentation of the edge with integrating details about the edge into the loss function.

In [52], the authors proposed a dual functional 3D-CNN that incorporated 3D hippocampus segmentation into the classification of brain pathological states. To segment the hippocampus, they utilized variant V-Net. Finally, by connecting a 3D-CNN, the classification was conducted. The downside of this method was that the dataset was small; therefore, the features that the samples have learned was limited. Moreover, a hybrid convolutional and RNN has been proposed in [53]. This method was composed of three steps. For each hippocampus, a binary mask was created by segmentation. Then, the 3D image batch was divided into two patches, namely the external-hippo and internal-hippo. Next, RNN was applied to learn the decomposed patches obtained after applying 3D DenseNet. The aim was to get high-level correlation features which will feed a classifier through the fully connected layer.

To gain more contextual knowledge for hippocampus segmentation, the authors of [54] used a deep network, DCCNet (dual dense context-aware network). A combination of two modules, a multi-resolution feature fusion module (multi-resolution feature fusion module, MRFFM) and a multi-scale input module (multi-scale input module, MSIM), highlighted the contextual detail. By collecting the location data and detailed characteristics from various viewpoints, the MSIM was efficient in segmenting target items and backgrounds. The MRFFM was used to combine features between the encoder and the decoder from different resolution layers via cross-connections. It used high-resolution encoder features to direct segmentation of the hippocampus edge in the decoder process. The method in [55] was centered on segmenting the corpus callosum and ventricle regions utilizing the multi-level thresholding techniques such as artificial bee colony (ABC) and ant colony optimization (ACO). Using different measures of ground truth (GT) pictures, these methods have been quantitatively and qualitatively tested. Then, the CNN was introduced in order to extract the characteristics of the segmented image for the classification. The method in [56] used a 3D structural brain MRI images to isolate the MRI images of white and gray matter, extract 2D slices and pick main slices from them for extraction of features. In order to calculate the first-order statistical features, feature extraction is applied on top of these slices and the prominent feature vectors produced by PCA were selected. In the classification process, these features were taken as input by various classifiers to predict the AD classes.

An automatic hippocampus segmentation process based on the assembly of convolutional multiview networks was proposed by Chen et al. [57]. Initially, to perform 2D segmentation on the slices extracted from nine different views, they used U-SegNet (a modified U-Net) architecture, creating nine 3D probability maps for each hippocampus. Then, the Ensemble-Net was trained to combine probability maps to generate the final segmentation. In addition, to manipulate the task of 3D hippocampus segmentation, the authors of [58] proposed a new two-stage process, which incorporated a localization step and a segmentation step. There were two steps in the localization phase: extraction of the slices of interest (slices containing the hippocampus) using Bi LeNets and generation of candidate regions (using U-Nets). The segmentation process consisted of two phases: First the selected regions are combined (using modified U-Nets), and second, a decision is made for to multi-view. A hippocampus segmentation strategy based on iterative local linear mapping (ILLM) is proposed in [59], with a representative and local structure-preserved feature embedding mechanism. The proposed framework consists of three phases: (1) the LLM used for preliminary segmentation forecasting; (2) the object of the semi-supervised deep autoencoder is to map the samples from the MR patch to the embedded feature manifold in a nonlinear manner; and (3) ILLM is used to achieve accurate segmentation. In addition, Cui and Liu [60] proposed a hippocampus analysis method focused on the fusion of densely connected convolutional networks (3D DenseNet) and the analysis of shape. This method combines four stages: segmentation of hippocampus and extraction of a patch, 3D DenseNet models constructed, shape analysis based on an MLP (multi-layer perceptron), and classification. On the other hand, the authors of [61] proposed the improved deep learning algorithm (IDLA) and statistically important text information for early detection of AD. For the measurement of connectivity in brain regions, the brain function was identified with resting-state functional data. Between normal aging and disorder development, an autoencoder network is used. The proposed method integrated efficiently biased neural network features and authorized for accurate detection of AD.

In [62], the authors suggested using the ROI-based contourlet sub-band energy (ROICSE) feature to achieve AD classification. After preprocessing, the structural MRI image was segmented into 90 distinct ROIs via a brain mask. Next, the contourlet transform was performed on these ROIs to obtain their sub-bands, and then sub-band energy feature vectors of multiple brain ROIs were concatenated to generate the ROICSE feature. Then, to classify the subjects, the SVM was applied. Moreover, for detection AD, in [63] the hippocampus was segmented bilaterally by multi-atlas. Intensity-based features, shape-based features, and texture-based features were among the characteristics recovered. The segmentation was then accomplished using local label learning. In [64], the authors suggested a new approach that only uses features that show significant variations across the classes. An ANOVA test was used to do this. They only used structural hippocampal asymmetrical features based on the directional response of 3D log-Gabor filters. These features were subsequently incorporated to train the SVM model. The authors of [65], on the other hand, utilized an icobrain dm, an automated technology that allows for the segmentation of brain areas that are significant for the diagnosis of dementia (cerebral lobe, hippocampus). As a result, they are focusing on the precision, reliability, and diagnostic effectiveness of these volumetric measures for assessing the brain volume of specific dementia patients.

Other techniques seek to quantify the hippocampal volume in order to achieve an accurate segmentation of its area. For instance, the authors of [66] used 3-channel 2D patches, obtaining the volume by multiplying the volume of the voxel and the number of hippocampal estimates.

Manual segmentation methods that proposed at localizing the hippocampus can also be found, as in [67]. They used manual segmentation of the hippocampus in which 32×32 patches (of each coronal view, axial view and sagittal view) were formed and then combined in one sample. The three view patches were then inserted in CNN.

**Table 3.** Segmentation methods for AD detection

| Study | Technique | Dataset | Performance |
|---|---|---|---|
| [50] | Coherent Point Drift | OASIS | RMSE = 0.6827 |
| [51] | FCN+CRF-RNN | ADNI | Acc = 87.31% |
| [52] | Dual functional 3D CNN | ADNI | Acc = 84% |
| [53] | CNN+RNN | ADNI | Acc = 91% |
| [54] | DCCNet | ADNI | Acc = 95.71% |
| [56] | First-order statistical features | OASIS | Acc = 90.09% |
| [57] | U-SegNet | ADNI | 89% Dice ratio |
| [58] | Bi-LeNet+U-Net | ADNI | DSC = 92.69 |
| [59] | ILLM | ADNI | DSC = 0.8852 ± 0.0203 |
| [60] | 3D DenseNet | ADNI | Acc = 95.29% |
| [61] | IDLA | ADNI | Acc = 94.6% |
| [66] | Volume measurement | ADNI | Average errors: (4.3173 ± 3.5436) and (4.1562 ± 3.5262) |
| [67] | Manual segmentation | ADNI | Acc = 90.05% |
| [68] | Volumetric changes | Regional Ethics Committee | Stratum pyramidal of subiculum ($p < 0.05$) |
| [69] | Combination of cerebral image features | ADNI | AUC = 0.8906 |
| [70] | harmonized protocol (manual) | ADNI | Volume (left/right hippocampus): 1.990 / 2.070 |

DSC: dice similarity coefficients.

Also, in [68] the proposed method was based on the evaluation of seven T-MRIs for the detection of volumetric changes in the structure of the hippocampus. Using a procedure that classified layers into two classes in neuronal bodies, manual segmentation of subregions within the hippocampus was performed. Five subregions in the hippocampus region are then segmented. The approach suggested by Jongkreangkrai et al. [69] was based on a combination of the volume of the amygdala, hippocampus, and thickness of the entorhinal cortex. Initially, with FreeSurfer tools, T1-weighted MR brain images were analyzed to extract features in both brain hemispheres. Then, the relative volumes of the hippocampus and amygdala were measured. Next, the characteristics were used for classification as input into the SVM. As a serious drawback of this research, the relatively limited number of subjects used in the training phase can be considered. In [70], various protocols were used to assess hippocampus volume using manual segmentation. To this end, they have introduced a harmonized protocol which makes it possible to reduce the heterogeneity of anatomical landmarks. This protocol has been tested on each tracing unit to segmentation accuracy and volumetric differences between patients and controls. The aforementioned hippocampus segmentation-based techniques and their performance are summarized in Table 3 [50-54, 56-61, 66-70].

## IV. DATA COMPARISON

A brief comparison between two main datasets, for the AD detection task, used in the literature depending on two criteria was provided to give further idea into our research [71, 72] (Table 4).

**Alzheimer's Disease Neuroimaging Initiative (ADNI):** It is a multicenter longitudinal study utilized for the early detection and monitoring to establish clinical genetic imaging. Cognitive and functional clinical examination tests were carried out for 819 subjects (for 12 months, they were monitored).

**Open Access Series of Imaging Studies (OASIS):** It's a collection of MRI data sets that were available for study and examination. The initial data set consisted of a cross-sectional collection of 416 subjects. Three or four individual T1-weighted MRI scans acquired in single imaging sessions were integrated for each individual subject.

## V. DISCUSSION

The reported results in the previous tables showed very different performances on the same databases. This difference was highly dependent on the feature extraction stage as well as the classification algorithm and the applied protocol. These performances were further enhanced through the preprocessing stages that can be employed as an initial treatment. However, other researchers eliminated this preprocessing step to reduce the computing complexity and to prove the efficiency of their methods in the presence of some imperfections in the images.

The three main categories proposed in this survey showed that the deep learning techniques prove more robust against the image variations and gave higher detection performances than the classical methods using statistical models.

This performance was explained by the high discriminative power of the deep features that were mostly extracted using pretrained models. These models were initialized after long training on very large databases such as ImageNet database. The diversity of these databases played an important role to build a robust model that can still be efficient in the presence of very high challenging classification problems such as AD detection, where distinguishing between the two main classes (AD or normal) is a very hard task. One of the best strategies to accurately employ the deep learning models is transfer learning. This strategy aims to fine-tune the pre-trained models to the problem of AD detection while freezing the initial parameters. The last fully connected layer, however, is changed to classify the images into AD or normal case. As an example, [38] achieved an accuracy of 99.36% using VGG-19 fine-tuned with ADNI database. OASIS database was another challenging database that contained fewer numbers of images. In [15], the accuracy was 91.6% using another deep learning strategy called auto-encoder. This is a different way to use the deep features with two different stages encoder and decoder. Good performances have been achieved.

Recently, the generative models have been used to handle the problem of the lack of grand labeled datasets. These models aimed to generate new images using the images of small datasets. This strategy enhanced the discriminative power of the deep models, and thus improved the classification performance.

**Table 4.** AD datasets comparison

| Dataset | Number of subjects | Technology |
|---|---|---|
| ADNI [71] | n = 819 (229 CN, 229 CN, 192 AD) | MRI acquisition |
| Oasis [72] | n = 416 (aged 18 to 96) | T1-weighted MRI scans |

## VI. CONCLUSION

We presented in this paper a detailed survey which highlighted the main approaches and methods proposed in the last decade to handle the problem of AD detection. We proposed a taxonomy that divides these methods into three main categories according to the applied strategy and the type of the extracted features as well as the classification method. From this comprehensive review, we can notice that the deep learning methods outperform previous methods based on statistical models and dimensionality reduction. This performance was achieved due to the suitable architecture of the deep models, especially the pre-trained ones, to extract meaningful and high discriminative features from MRI images. Future challenges raised by the studied methods aim to initialize the deep models through training on large AD datasets, and fine-tune them using similar AD images. Moreover, generative models using the GANs was one of the future solutions due to their high accuracy achieved with other image classification applications.

## CONFLICT-OF-INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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