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3D Supervoxel based features for early detection of AD: A microscopic view to the brain MRI

Shiwangi Mishra[1,2] · Iman Beheshti[3] · M. Tanveer[4] · Pritee Khanna[1]

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Abstract

Introduction: Alzheimer's disease (AD) is a chronic form of the neurodegenerative disease marked by atrophy in different brain regions. A region-wise analysis is essential for performing AD detection, as each brain region has different functionalities depending on its location. This work aims to investigate supervoxel based volumetric features in place of traditional voxel-based features from the vital brain regions. **Methods:** In this work, the whole brain structural magnetic resonance imaging (MRI) is segmented into 116 regions using atlas-based segmentation. Important atrophic regions are used for further analysis based on a region ranking procedure from these segmented regions. The focus of this study is to perform supervoxel based partitioning for attaining features prominent for AD detection. Volumetric features are extracted from supervoxels belonging to the selected regions. An optimal feature set is obtained by using the support vector machine recursive elimination (SVM-RFE) method, and classification is performed using SVM. **Results:** ADNI dataset is used for experimentation. Results are obtained by iteratively fusing the features extracted from vital brain regions. The highest classification accuracy of 90.11%, the sensitivity of 86.11%, and the specificity of 93.4% are obtained by fusing features extracted from hippocampus and amygdala regions. **Discussion:** The highest classification accuracy reported in this work for AD detection is obtained by fusing features of the four most important regions, i.e., hippocampus and amygdala, in both left and right hemispheres. These regions are also known to affect the consolidation of memory and decision-making in medical science. Experimental results evaluated on the standard dataset depict that the proposed method performs better than the traditional as well as state-of-the-art methods.

Keywords Alzheimer's disease · AD detection · Brain MRI · Brain region selection · Hippocampus · Amygdala · VBM · Supervoxel · Volumetric features

✉ Pritee Khanna
pkhanna@iiitdmj.ac.in

1 PDPM Indian Institute of Information Technology, Design and Manufacturing, Jabalpur, India

2 Jabalpur Engineering College, Jabalpur, India

3 University of Manitoba, Winnipeg, MB, Canada

4 Department of Mathematics, Indian Institute of Technology Indore, Simrol, India

1 Introduction

Alzheimer's disease (AD) is a debilitating, incurable, and chronic neurodegenerative disorder characterized by progressive deterioration of neurons responsible for cognitive functionalities such as behaviour, memory, learning, and inability to perform day-to-day activities, which eventually leads to death of the victim [9]. Based on the data received from National Centre for Health Statistics, a report by Alzheimer's Association (a non-profit organization for Alzheimer's Disease and Related Disorders) mentioned in 2019 that the death rate from AD is increased by 145% between 2000 and 2017 in the USA [3]. The same report estimates 290 billion USD healthcare costs due to AD, and related diseases. AD is officially listed as the sixth-leading cause of the death in the USA. As given in [21], more than 4 million people are suffering from AD in India. Even after years of research, there is no cure for AD and it cannot be stopped once the onset begins. The only way to reduce the effect of AD is to start early medication, which is only possible with an early stage AD detection [11]. Recent studies reveal that brain changes in AD subjects might start 20 years or more before actual symptoms appear. Thus, early detection of AD becomes highly critical [31].

Whole-brain MRI is segmented into three primary tissues, namely, gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Regional atrophy is a significant biomarker in the diagnosis of AD. Each brain region is responsible for different functioning of the body. Any damage or difference in the volume of these regions results in the loss of brain functionalities. Analysis of brain structural magnetic resonance images (MRI) helps in identifying these biological and imaging biomarkers to detect the onset of AD [36]. Figure 1 shows scans of the human brain in each view for a healthy and AD brain. Variation in intensity can be seen in AD and healthy controls (HCs) due to atrophy and shrinkage of GM. In comparison to HCs, patients having AD show a high level of GM volume reductions in several regions of GM, including hippocampus, insula, amygdala, thalamus, cingulate gyrus, parietal lobule, middle occipital gyrus, caudate gyrus, parahippocampus gyrus, temporal gyrus, and frontal gyrus [37]. Even a slight variation in these distinctive biomarkers can indicate a possible onset of AD in the patient. These minor variations in the biological markers can be detected from brain MRIs through machine learning and object detection algorithms [43].

The objective of this study is to detect AD by harnessing regional atrophy. It is evident that various studies involve the manual selection of predefined brain regions, which is prone to error for performing disease detection. The contribution of this work is investigating supervoxel based features on automatically selected critical brain regions for AD detection. The automated region selection performed in this work is based on statistical testing on the segmented 116 regions. The present study focuses on performing supervoxel based analysis on the selected vital brain regions for AD detection. Supervoxels are clusters of similar pixels helpful in computing robust local statistics. These methods provide higher accuracy along with reduced computational and memory costs for processing high-dimensional 3D data.

The work is organized as follows. Literature review on AD detection is given in Section 2. Dataset used in this work and the proposed methodology are explained in Section 3. Section 4 incorporates experiments and results. The work is concluded in Section 5.

2 Related works

Brain image analysis plays a crucial role in the healthcare domain for the detection of brain related disorders. It facilitate medical practitioners in diagnosing neurodegenerative

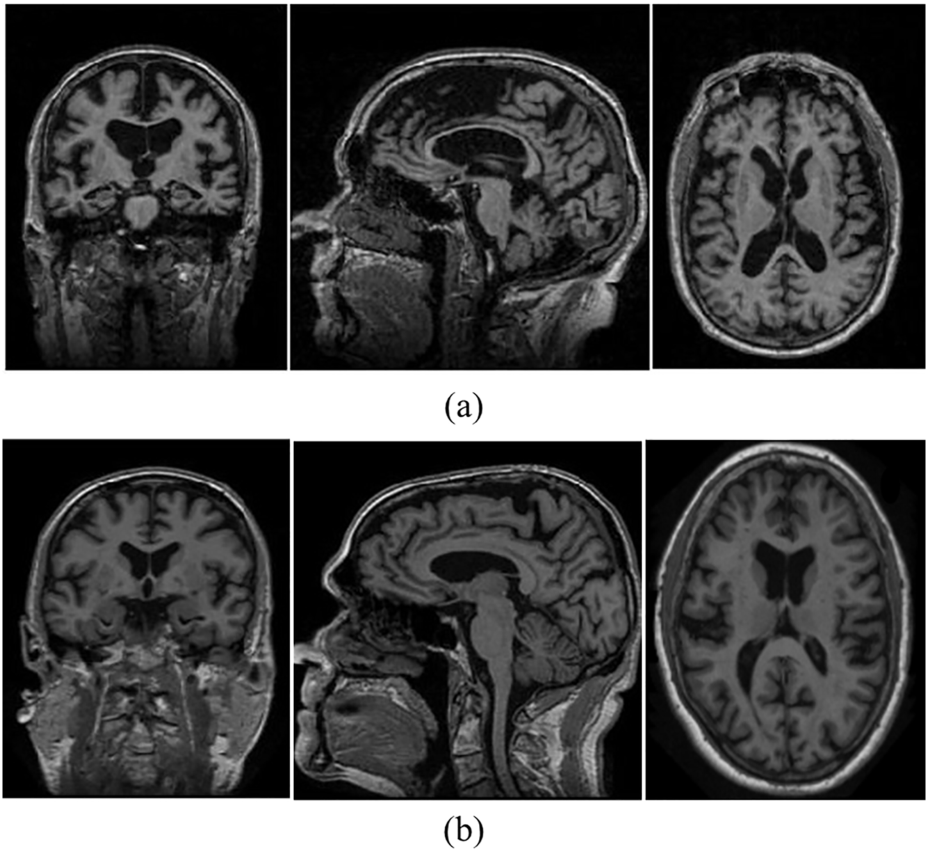

Fig. 1 Brain MRIs from ADNI 1 database showing coronal, sagittal, and axial views (left to right): (a) Alzheimer's disease and (b) healthy controls

disorders by utilizing non-invasive methodologies [6]. Among various imaging modalities, MRI is found to be very useful for analyzing the presence of AD due to its non-invasive nature and good soft-tissue contrast, which helps in the detection of variations in biomarkers [33].

Different feature extraction methods are applied on whole MRI or segmented regions of 2D/3D MRI for AD detection [7, 16]. It is also observed that the fusion of these features can improve AD diagnosis [46]. 3D image analysis is widely used for Alzheimer's diagnosis because it helps in analyzing whole MRI and also captures structural patterns [7]. Texture based analysis is used for finding disease patterns in MRI data. Some research groups used wavelet based analysis in combination with other feature reduction methods. El-Dahshan, Hosny, and Salem [10] applied discrete wavelet transform (DWT) followed by principal component analysis (PCA) for feature extraction. k-nearest neighbor (k-NN) and Artificial neural network (ANN) are used here as classifiers. The highest accuracy of 88.42% is observed with k-NN classifier on normal and abnormal subjects. Also, 3D wavelet based features are applied to explore 3D structures and specific regions. Zhang et al. [47] performed texture analysis by evaluating multiple features such as GLCM, run length matrix, gradients, and histograms obtained using circular region of interest (ROI) on the hippocampus and entorhinal cortex regions of the brain. Classification accuracies based on texture analysis of the ROIs varied from 64.3% to 96.4% due to different ROI selection, feature extraction, and selection options. A very small dataset of 34 images is used for analysis in this work. Zhang et al. [45] used 3D wavelet features and triplet features. The features are reduced by PCA and classified by kernel support vector machine (SVM) using particle swarm optimization with time varying acceleration coefficients resulted in classification accuracy of 81.5%. The whole brain information is used in these works, while in [15], multiscale wavelet features extracted from GM images and the hippocampus region of the brain are used with SVM classifier. They achieved 85.1% accuracy, sensitivity of 84.57%, and specificity of 85.53% for AD classification using features from the hippocampus region.

Apart from wavelet, GLCM and local binary patterns (LBP) are also evaluated on 3D MRI in multiple works. These feature extraction techniques are mainly applied to the whole brain, or GM, or two or more specific brain regions. Simoes et al. [34] evaluated LBP to analyze 3D texture on the image patches obtained from the whole brain and used an ensemble classifier resulting in AD classification accuracy of 84% with the sensitivity of 81% and specificity of 89%. Jha and Kwon [17] applied curvelet and wavelet transform with PCA on MRI images. Extracted features are classified by using k-NN and ANN. Murcia et al. [27] evaluated GLCM measures from different cortical and subcortical structures in the brain. Voxel features extracted from the whole MRI image are selected through *t*-test resulted in 81.3% classification accuracy, sensitivity of 77.5%, and 84.31% for AD. At the same time, voxel features extracted from the hippocampus region only resulted in 75.1% accuracy. Luk et al. [25] performed texture analysis using 3D voxel-based GLCM on three orthogonal planes for extracting eight different measures and combined it with hippocampus volume for better results. For HC and AD classification, this method achieved 83.1% and 92% sensitivity and specificity, respectively.

Some works are focused on multiple slices of 3D MRI for texture feature analysis but lack region-wise analysis. Nanni et al. [32] used VBM and texture features extracted from 3D brain slices of MRI with SVM classifier for AD detection. They achieved the highest accuracy of 87.6%, with the sensitivity of 84.1% and specificity of 90.3% for AD classification. Vaithinathan and Parthiban [41] performed 2D texture analysis on 3D MRI imaging considering three axes axial, sagittal, and coronal. Features like central moments, homogeneity, contrast, inverse different moment, and entropy in segmented ROI acquired using rough ROI (RROI) technique are subjected to multiple feature selection methods and classified using random forest, SVM, and k-NN classifiers. This method reported the highest AD classification accuracy of 87.39%, sensitivity of 85.42%, and specificity of 88.81% with fisher features classified by using random forest and ANN classifier.

Some research groups focused on multivariate data analysis on different regions to increase classification rates. Khedher et al. [18] used PCA based features evaluated on WM and GM regions and classified using SVM with 88.49% accuracy, 85.11% sensitivity, and 91.27% specificity. Ahmed et al. [5] computed circular harmonic functions on the hippocampus and posterior cingulate cortex regions of the brain, which are quantized using the bag of visual words approach. With SVM classifier using RBF kernel, the observed accuracy, sensitivity, and specificity were 83.71%, 77.09%, and 88.2%, respectively. Krashenyi et al. [20] evaluated feature ranking on the segmented 24 regions of the brain and classified features using a fuzzy inference system showing an accuracy of 86.11%, sensitivity of 81.39%, and specificity of 89.06%. Beheshti and Demirel [4] computed the probability distribution function from VBM segmented GM regions for performing feature selection. Classification using SVM resulted in 89.65% accuracy, 87.73% sensitivity, and 91.57% specificity for AD classification. It is worth mentioning that the dataset on which experiments are performed in this work is almost double the size of the dataset used in [4]. Mishra et al. [29] proposed a diagnosis system that uses top regions selected by *t*-test statistics for volumetric feature extraction from VBM generated GM images. The highest AD classification accuracy of these features using SVM classifier is 89.15% with a sensitivity of 85.06% and specificity of 92.53%.

Deep learning based methods are recently explored in AD detection. These methods work on finding patterns from the MRIs, useful for AD detection. Liu et al. [23] performed deep neural network-based learning using Siamese neural networks trained on paired lateral inter-hemispheric regions showing 92.44% sensitivity and 96.15% specificity for ADNI. Also, it showed 43.56% sensitivity and 98.08% specificity for the BIOCARD dataset. Yigit et al. [44] used CNN based models for AD detection and achieved the highest accuracy as 83%, sensitivity as 72%, and specificity as 94% using axial view images. Ferri et al. [12] used a stacked autoencoder (SAE) with a softmax output layer and a pair of internal specialized AEs with an output layer based on the reconstruction error. The reported classification accuracy, sensitivity, and specificity on MRI data are observed as 85%, 89.4%, and 75.9%, respectively.

After voxel based analysis, supervoxel based analysis is explored on the images of various domains in medical science. Toro et al. [39] performed supervoxel based segmentation and calculated histon based features of volumetric images, which are subjected to PCA and classified using SVM. The highest AD classification accuracy obtained using the SVM classifier is 83.66%, with a sensitivity of 87.83% and specificity of 78.85%. However, this work lacks region analysis, which is vital to understand imaging biomarkers for disease detection. Also, deep learning-based methods find patterns from whole MR, but more accurate results may be achieved by performing region-specific analysis.

This work aims to perform supervoxel based analysis for different brain regions. Supervoxels group a number of pixels identified on the basis of similar properties in contrast to voxel based methods. Volumetric features evaluated from supervoxels in comparison to texture features are helpful in extracting statistical information from a natural set of neighborhoods formed through the use of supervoxels. Also, performing region based analysis helps in the identification of critical brain regions that can be used to extract discriminant features helpful in AD detection compared to using whole MRI.

In this work, 3D MRIs are subjected to region segmentation, and supervoxel based volumetric features are harnessed from them. To understand the importance of different brain regions in AD detection, region based segmentation is employed using atlas based segmentation. Important regions depicting AD are identified by region ranking procedure. Supervoxel based features extracted from the top regions are fused to capture structural alterations of these regions in the classification process. In addition, a comparative analysis is performed on using supervoxel based features for AD detection as proposed in this work with the other features including statistical features, GLCM based features, wavelet features, voxel based features, and regional features used for the same purpose.

Table 1 Demographics of ADNI 1 dataset

Diagnosis	No.	Age	Gender (M/F)	MMSE
AD	188	75.36±7.5	99/89	23.2±2.0
HC	229	75.97±5.0	119/110	29.00±1.0

MMSE- mini-mental score examination

3 Material and methods

3.1 Dataset used

Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset [1] is used for experimentation here. ADNI is developed with the goal to explore possible combination of assessments from MRI, PET, and other biological markers with clinical and neuropsychological assessments to estimate the progression of MCI and early AD. These subjects are selected from ADNI dataset using search condition as project = 'ADNI 1' AND Study = 'ADNI Screening' AND slice thickness = '1.2' AND weighing = 'T1'. In this study, 417 T1-weighted 1.5T MRIs consisting of 229 Healthy controls (HC) and 188 AD subjects are used. Table 1 summarizes the demographics of this dataset. It is to be noted that there are no significant differences in age and gender ratio in the two groups (HC and AD). All geometric distortions caused due to gradient non-linearity, bias field, and intensity in-homogeneity are removed by using image corrections such as GradWarp and N3.

3.2 The proposed methodology

The proposed methodology consists of five major steps: (a) pre-processing of brain MRI, (b) region segmentation and selection, (c) supervoxel partitioning and volumetric features extraction, (d) feature selection, and (e) classification and cross-validation. The results obtained by the fusion of features extracted from the selected regions are compared with the results mentioned by state-of-the-art works. This comparison reveals the impact of region atrophy on AD disease identification. Pipeline of the proposed AD detection framework is illustrated in Fig. 2.

3.2.1 Pre-processing

Brain MRIs are subjected to a pre-processing routine to normalize all images into a standard space. Image realignment, spatial normalization, and segmentation are performed by using statistical parameter mapping (SPM) and VBM 8 methods [2]. These normalized images are registered with standard Montreal Neurological Imaging (MNI) templates using linear affine transformation and a non-linear deformation using high dimensional diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) normalization [28]. Brain MRIs are segmented to WM, GM, and CSF regions. GM loss is associated with ongoing pathological and clinical progression of disease and is sensitive marker of AD in comparison to other regions. The segmented GM images are used for analysis. These GM images are spatially smoothed using 8-mm full width half maximum (FWHM) Gaussian

[1] https://ida.loni.usc.edu/

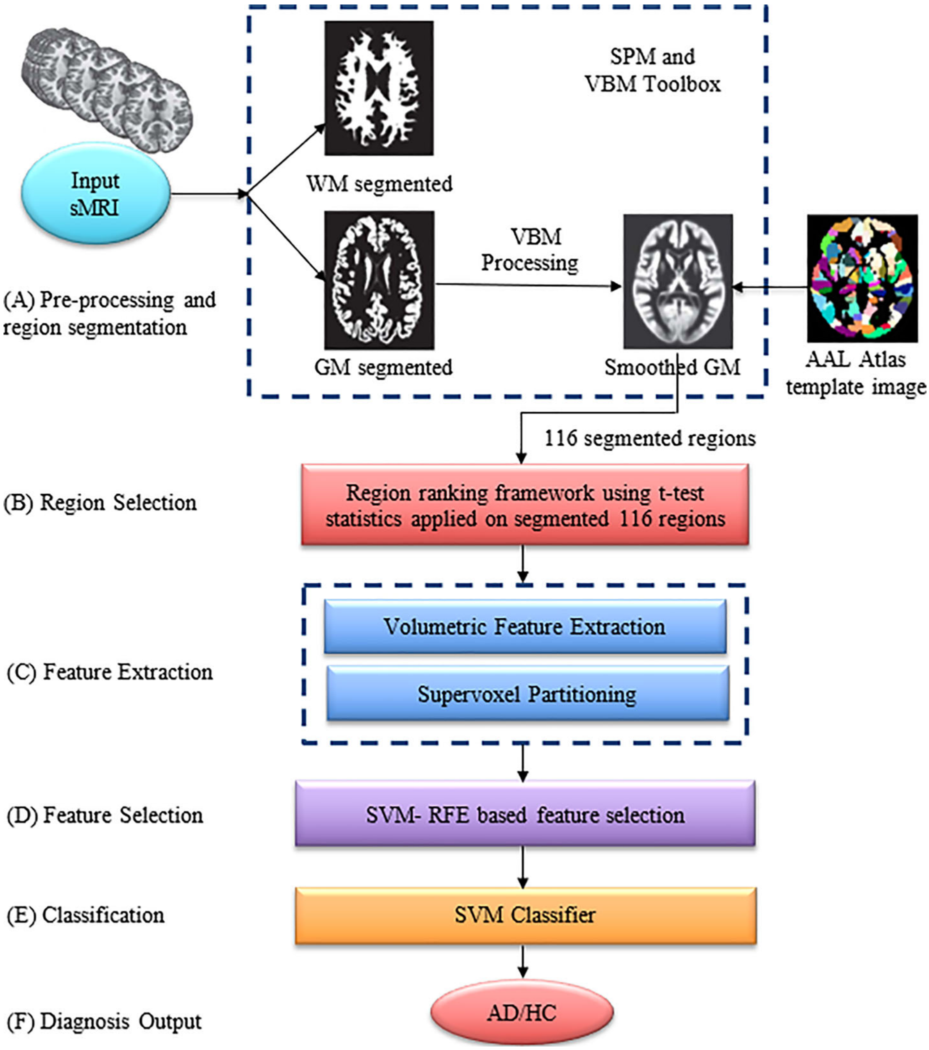

Fig. 2 Proposed supervoxel based framework for AD Detection

kernel. The smoothing operation results in the normally distributed data closer to Gaussian field model, which reduces inter subject variability. Also, it increases the sensitivity and reduces variance across subjects. This results in an increasing validity of parametric tests to detect structural variabilities as required. Pre-processed GM images are used for further analysis as discussed in the sections given below.

3.2.2 Region segmentation and selection

Brain MRI can be segmented into different regions by performing manual segmentation by expert neurologists or by using atlas-based segmentation. Atlas-based segmentation is performed via MRI registration with atlas image. The obtained labels are propagated to the target image for obtaining different regions [40]. Further segmentation of GM image helps in analyzing the role of various GM regions for AD detection. WFU PickAtlas3 tool is used to segment GM images into different regions using a standard automated anatomical labeling (AAL) atlas [2] [26]. PickAtlas uses a template suggested by MNI for performing normalization and selects Talairach daemon to get coordinate position-based data [22]. The output of this step is 116 ROIs for a single GM image. These brain regions have different functionalities depending on their location.

Region Selection is an important step in differentiating HC and AD subjects based on anatomy of the brain. The 116 segmented regions are ranked to find the most informative regions from which features can be extracted for further evaluation of HC and AD subjects. A statistical analysis based method for ranking of atlas-based segmented brain MRI regions used here is based on evaluating t-test statistics of different regions [29]. The region volume parameter for each region is evaluated using SPM and used for performing region ranking procedure based on t-test analysis. The resulting t-test value is used to evaluate p-value for each region. Regions having p-value less than the significance level of .001 are ranked based on the t-test evaluation. The obtained ranking values are used to identify the most discriminating regions for further analysis.

3.2.3 Feature extraction

Feature extraction plays an important role in the process of AD detection. It helps in dimensionality reduction of high dimensional MRI and reflects properties of each anatomical region. For performing feature extraction on the 3D MRI, conventional methods use voxels as a feature, i.e., directly using MRI voxels. Region-based analysis is also performed by dividing the whole MRI into different regions. In this work, supervoxel based volumetric feature extraction is performed on different regions of MRI. During experimental analysis, statistical/volumetric features [29], GLCM, and wavelet features are also extracted for comparison with supervoxel based features in the context of AD detection.

Supervoxel Partitioning Superpixel is a set of adjacent pixels in a slice with similar intensity or/and texture (in 2D), while Supervoxel is a set of superpixels with similar intensity in the 3D volume [1, 38]. It can be easily evaluated by combining slices of superpixels to create a supervoxel. An intersection between a supervoxel S_i and slice j is a superpixel S_i^j. A supervoxel is defined as:

$$S_i = S_i^j, j = \{1, 2, ..., \|S_i\|\}, i = 1, 2, ..., S \tag{1}$$

where S is the number of the supervoxels in an MRI volume, $\|S_i\|$ is lifespan of S_i. The j^{th} superpixel of S_i is S_i^j, which consists of a set of pixels in one slice. Here, supervoxels are obtained by using a simple linear iterative clustering (SLIC) method [1]. In most works, it is used for performing region segmentation and classification tasks [35, 38].

The MRI is segmented to supervoxels with similar properties. This segmentation is performed on the smoothed GM density volumes obtained by the VBM plus DARTEL analysis. The dimensionality of the supervoxels is very high to be directly used for classification. It can be reduced with the help of feature extraction technique. These segmented regions are further subjected to volumetric feature extraction. Each segmented region of the MRI

[2]https://www.nitrc.org/projects/wfu_pickatlas/

depicts different number of supervoxels based on the dimension of the particular region. Features extracted from these regions are concatenated to form a single feature vector.

Volumetric Features The obtained supervoxels are subjected to volumetric feature extraction as more information is extracted for performing classification through volumetric features. Various volumetric features used here are standard deviation (sd), skewness (sk), kurtosis (ku), energy (en), and Shannon entropy (shen) [29, 45]. Let S_s (x, y, z) is the pixel value at location (x, y, z) for a supervoxel s, $\bar{m}_s$ is the mean of all pixel intensities of supervoxel s, and N_s is the number of pixels present in the supervoxel s. Various volumetric features for supervoxel s are evaluated as follows:

$$sd_s = \sqrt{\frac{1}{N_s}\sum_x\sum_y\sum_z (S_s(x,y,z) - \bar{m}_s)^2} \tag{2}$$

$$sk_s = \frac{\frac{1}{N_s}\sum_x\sum_y\sum_z (S_s(x,y,z) - \bar{m}_s)^3}{sd_s^3} \tag{3}$$

$$ku_s = \frac{\frac{1}{N_s}\sum_x\sum_y\sum_z (S_s(x,y,z) - \bar{m}_s)^4}{sd_s^4} \tag{4}$$

$$en_s = \sum_x\sum_y\sum_z S_s^2(x,y,z) \tag{5}$$

$$shen_s = -\sum_x\sum_y\sum_z S_s^2(x,y,z)\log\left(1 + S_s^2(x,y,z)\right) \tag{6}$$

3.2.4 Feature selection

Feature selection is an important task which reduces the cardinality of the feature set based on the predefined criteria to select number of attributes based on their usefulness to complete the given purpose. SVM-RFE is one of the popular wrapper approach for feature selection proposed by Guyon et al. [13]. SVM-RFE computes ranking weight vector and uses these weight vectors for ranking features. The algorithm is designed as follows. Initially, the dataset is used to train SVM classifier [42]. Then, based on this classification, ranking weights are allotted to each feature. Features with smaller weights are iteratively removed, resulting in a sorted list of all features based on their significance. Using subset of selected ranked features to train the SVM classifier and using SVM classification accuracy as a criterion, optimal feature set is obtained.

3.2.5 Classification and cross validation

After obtaining optimal set of features as output of the feature selection method, classification task is done by using a supervised learning technique, SVM. For completing this task, LIBSVM [3] is used. The settings used for performing two class classification are default with linear kernel. Performance parameters for classification as given in the literature are used here in the context of the classification of HC and AD subjects. Considering true positive (TP) as the number of AD subjects correctly classified as AD, true negative (TN) as

[3] https://www.csie.ntu.edu.tw/~cjlin/libsvm/

the number of HC subjects correctly classified as HC, False negative (FN) as the number of AD subjects incorrectly classified as HC, and false positive (FP) as the number of HC subjects incorrectly classified as AD, these parameters are defined below.

$$Accuracy(ACC) = \frac{(TP + TN)}{(TP + FP + FN + TN)} \tag{7}$$

$$Sensitivity(SEN) = \frac{TP}{(TP + FN)} \tag{8}$$

$$Specificity(SPE) = \frac{TN}{(TN + FP)} \tag{9}$$

These performance parameters are evaluated through 10-fold cross-validation to ensure reliable results and prevent over-fitting [19]. The training set consists of 373 subjects, and the test set contains 41 subjects selected randomly for 10-fold cross-validation.

4 Experimentation and results

The experiments are performed using the volumetric features obtained from supervoxel of different GM regions obtained through VBM followed by atlas-based segmentation. SPM version 12 is used for performing VBM. WFU PickAtlas (v3.0.5b) is employed for performing region based segmentation. All experiments are performed on a 64-bit system with 2.30 GHz Intel®Xeon processor and 128 GB RAM. Classification experiments are performed in MATLAB®.

Four experiments are performed to understand the importance of supervoxels for identification of AD: (i) Supervoxel based features in comparison with other 3D image features extracted from GM region for AD detection, (ii) Supervoxel based features in comparison with features extracted by using other partitioning methods on GM region for AD detection, (iii) Fusion of supervoxel features extracted from top rank GM regions, and finally (iv) The obtained results using fusion of supervoxel features extracted from top rank GM regions are compared with the recent works in literature. Results obtained from all experiments are summarized and discussed below.

4.1 Supervoxel based features in comparison with other 3D image features extracted from GM region for AD detection

Performance of supervoxel based features discussed in Section 3.2.3 is compared with other 3D texture features namely, statistical, GLCM, and wavelet based features in the context of AD detection from GM region and the performance is summarized in Table 2. Statistical features (standard deviation, skewness, kurtosis, energy, entropy) are evaluated on 116 regions

Table 2 Results using supervoxel based features as compared to other 3D image features

Features	ACC	SEN	SPEC
Statistical features	76.82%	76.46%	77.11%
GLCM features	81.3%	77.50%	84.7%
Wavelet features	79.75%	85.18%	75.3%
Supervoxel features	**83.33%**	**84.21%**	**82.6%**

The highlighted values are depicting highest accuracy among other methods shown in the table

and fused feature is used to perform classification, which resulted in 76.82% classification accuracy, 74.46% sensitivity and 77.11% specificity. Haralick et al. [14] proposed feature extraction using GLCM as a method of quantifying the spatial relation of neighboring pixels in an image. The detail formulae and its interpretation is discussed in [14]. Texture analysis on the MRI is performed with Haralick texture features. GLCM features fused over 116 regions showed 81.3% classification accuracy, 77.5% sensitivity, and specificity of 84.7%. Texture analysis using 3D-DWT is performed on brain regions obtained through atlas-based segmentation. Hence, volumetric features of all sub-bands' coefficients of 3D-DWT are obtained as feature vector [24]. A three-level 3D-DWT with Daubechies basis function is applied on each 3D brain MRI. Daubechies are compact orthogonal wavelets, that are compact in both temporal and spectral domains. Details of 3D-DWT performed on brain regions used in this work are given in [30]. Experiment conducted by extracting wavelet features from 116 regions and concatenating those features to perform AD classification resulted in classification accuracy of 79.75% with sensitivity of 85.18% and 75.3%. In comparison to these features, the proposed supervoxel based segmentation and volumetric features showed better AD classification accuracy of 83.33% with sensitivity of 84.21% and 82.6%.

4.2 Supervoxel based features in comparison with features extracted by using other partitioning methods on GM region for AD detection

In this section, the results are compared based on the use of different partitioning/ segmentation methods before volumetric features extraction. Features are obtained by considering i). Voxel as features from GM region, ii). Volumetric features from 116 regions, and iii). Volumetric features from supervoxels based features. The volumetric features discussed in Section 3.2.3 are evaluated for all these methods and linear SVM is used for AD classification. The results are summarized in Table 3. It shows that supervoxel based method obtained the highest accuracy of 83.33% for AD detection with sensitivity of 84.21% and specificity of 82.6% in comparison to voxels as features from GM regions showing accuracy of 76.8% with sensitivity of 75.2% and specificity of 78.5%, and region based volumetric features showing accuracy of 76.82% with sensitivity of 76.46% and specificity of 77.11%.

4.3 Fusion of supervoxel features extracted from top rank GM regions

The feature fusion is performed to enhance the accuracy of AD detection by using features of the most discriminating regions. In order to find important GM regions for AD classification, region ranking algorithm is performed on the supervoxel features of each of the 116 brain segmented region. Table 4 shows the top 10 regions ranked using region ranking algorithm. Supervoxel based volumetric features are evaluated on these ten regions for further analysisand classification is performed using SVM. Results for fusion of supervoxel based volumetric features obtained from the selected top discriminating regions are summarized in Table 5. Using supervoxel features for each region, it is observed that the highest accuracy

Table 3 Results using voxel features, region based features, and supervoxel based features of GM regions

Features	ACC	SEN	SPEC
Voxel as feature (GM)	76.8%	75.2%	78.5%
Region based segmentation+volumetric features	76.82%	76.46%	77.11%
Supervoxel based segmentation+volumetric features	**83.33%**	8**4.21%**	**82.6%**

The highlighted values are depicting highest accuracy among other methods shown in the table

Table 4 Top 10 regions identified by the region ranking algorithm and supervoxel based features

Rank	Brain region
1	Hippocampus_L
2	Hippocampus_R
3	Amygdala_L
4	Amydgala_R
5	Parahippocampal_L
6	Temporal_Inf_L
7	Parahippocampal_R
8	Temporal_Mid_R
9	Temporal_Inf_R
10	Temporal_Mid_L

is obtained by hippocampus region followed by amygdala, parahippocampal, and temporal lobe. Classification accuracy obtained by the use of features from the hippocampus region is 85.52% with sensitivity of 84.50% and specifictiy of 86.36%. Results are obtained by iteratively fusing the features extracted from top regions. The highest classification accuracy of 90.11%, sensitivity of 86.11% and specificity of 93.4% is obtained with the fusion of features extracted from hippocampus and amygdala region. Both these regions are located close to each other and are responsible for memory related functioning. Further in the analysis, it is observed that by adding features of other regions in the ranking list result in the decrease of classification accuracy. This observation is in line with the findings of medical theory as hippocampus and amygdala are considered important regions for AD detection. Hippocampus is the most important region for consolidation of information which affects short-and long-term memory, while amygdala plays a primary role in the decision-making, emotional reactions, and consolidation of memory [8].

4.4 Performance comparison with the existing methods

The results obtained with the proposed framework for AD detection are compared with the performance of existing methods for AD detection involving statistical features, voxel based features, texture based features. The performance is also compared with state-of-the-art deep learning based methods for AD detection. The results are summarized in Table 6. As compared to these approaches, the proposed automated system performs supervoxel

Table 5 Results for fusion of supervoxel based volumetric features obtained from selected top discriminating regions

Features	ACC	SEN	SPEC
Hippocampus L features (Top 1 region)	85.52%	84.5%	86.36%
Hippocampus (L+R) features (Top 2 regions)	86.06%	81.37%	89.92%
Hippocampus (L+R) features+amygdala (L) (Top 3 regions)	87.7%	82.92%	91.62%
Hippocampus (L+R) features+amygdala (L+R) (Top 4 regions)	**90.11%**	**86.11%**	**93.4%**
Hippocampus (L+R) features+amygdala (L+R)+ parahippocampus L (Top 5 regions)	88.19%	84.01%	91.64%

The highlighted values are depicting highest accuracy among other methods shown in the table

Table 6 Supervoxel based framework as compared to the existing methods

Approaches and Authors	ACC	SEN	SPEC
LBP-TOP (2014) [34]	84%	81%	89%
HCF+SVM (2014) [5]	83.71%	77.09%	88.2%
PCA+PLS+SVM (2015) [18]	88.49%	85.11%	91.27%
PDF+SVM (2015) [4]	89.65%	87.73%	91.57%
Mean+Std+FI (2016) [20]	86.11%	81.39%	89.06%
Wavelet frame+SVM (2016) [15]	85.1%	84.57%	85.53%
3D GLCM (2017) [27]	81.3%	77.5%	84.31%
Volumetric features+SVM (2018) [29]	89.15%	85.06%	92.53%
VGLCM-TOP+Hippocampal volume (2018) [25]	–	83.1%	92%
Supervoxel based histon+PCA+SVM (2018) [39]	83.66%	87.83%	78.85%
Fisher+RF (2019) [41]	87.39%	85.42%	88.81%
Texture descriptors + SVM (2019) [32]	87.6%	84.1%	90.3%
Siamese neural networks (2019) [23]	–	92.44%	96.15%
CNN based models (2020) [44]	83%	72%	94%
Stacked encoder (SAE) + softmax output layer (2021) [12]	85%	89.4%	75.9%
Proposed Method	**90.11%**	**86.11%**	**93.4%**

The highlighted values are depicting highest accuracy among other methods shown in the table

based segmentation on GM region followed by extraction of volumetric features. The highest accuracy is obtained by performing feature fusion on the identified vital atrophy regions. The features extracted from these selected regions are subjected to the feature selection using SVM-RFE and classified through SVM. With the highest accuracy of 90.11%, sensitivity of 86.11%, specificity of 93.4%, the results obtained in this work are better as compared to the results showcased by the existing methods.

5 Conclusions

This work proposes a system for AD detection from brain MRIs using supervoxel based analysis and region ranking procedure. It is seen in the analysis that supervoxel based features have shown better results in comparison to voxel as features. Grouping of similar pixels in supervoxels gives better results by covering detailed information. Instead of working with high dimensional 3D MRI images, it is proposed to begin with anatomize brain MRI having 116 GM regions and later select the most informative regions. Brain regions vital for AD detection are selected from the ranked list for further analysis. Features obtained from vital brain regions are fused and subjected to feature selection. Finally, fused features extracted from the top four regions, i.e., hippocampus and amygdala (left and right), are classified using SVM on the Standard ADNI dataset (188 AD/229 Normal). Variation in intensity can be seen in AD and HC subjects, and this difference in structures is due to the atrophy and shrinkage of GM. Classification for AD detection using features from these regions resulted in the highest accuracy. This observation is in line with the findings of medical theory, as the hippocampus and amygdala are considered important regions for AD detection. Hippocampus and amygdala are located close to each other in the human brain and are responsible for memory related functioning. As stated in medical theory, the hippocampus is the most crucial region for the consolidation of information which affects short-and long-term memory, while the amygdala plays a primary role in the decision-making, emotional reactions, and consolidation of memory [8]. In addition, a comparative analysis is performed on using supervoxel based features for AD detection as proposed in this work with other features like statistical features, gray level co-occurrence matrix (GLCM) based features, and wavelet features used for the same purpose. Also, supervoxel based features are compared with features extracted by using other partitioning/segmentation methods such as voxel as features and regional features. The experimental results also show that the obtained results are better as compared to some state-of-the-art deep learning-based methods. As future work, the supervoxel-based strategy is planned to analyze in the context of other neurological diseases such as PD and epilepsy. Also, future directions lie in automated diagnosis and multi-class classification of progression stages of AD patients based on MRI and PET scans. For this, deep learning based robust feature representation for AD/MCI classification is required to be explored in light of the observations obtained from this study.

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