Alzheimer’s Disease Diagnosis Based on Cortical and Subcortical Features

Yubraj Gupta,1,2 Kun Ho Lee,3,2 Kyu Yeong Choi,2 Jang Jae Lee,2 Byeong Chae Kim,4,2 and Goo-Rak Kwon1,2

1School of Information Communication Engineering, Chosun University, 309 Pilmun-Daero, Dong-Gu, Gwangju 61452, Republic of Korea
2National Research Center for Dementia, Chosun University, 309 Pilmun-Daero, Dong-Gu, Gwangju 61452, Republic of Korea
3Department of Biomedical Science, College of Natural Sciences, Chosun University, 309 Pilmun-Daero, Dong-Gu, Gwangju 61452, Republic of Korea
4Department of Neurology, Chonnam National University Medical School, Gwangju 61469, Republic of Korea

Correspondence should be addressed to Goo-Rak Kwon; grkwon@chosun.ac.kr

Received 19 July 2018; Revised 8 September 2018; Accepted 13 February 2019; Published 3 March 2019

Guest Editor: Qiu-Hua Lin

Copyright © 2019 Yubraj Gupta et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Alzheimer’s disease (AD) is a common neurodegenerative disease with an often seen prodromal mild cognitive impairment (MCI) phase, where memory loss is the main complaint progressively worsening with behavior issues and poor self-care. However, not all patients clinically diagnosed with MCI progress to the AD. Currently, several high-dimensional classification techniques have been developed to automatically distinguish among AD, MCI, and healthy control (HC) patients based on T1-weighted MRI. However, these method features are based on wavelets, contourlets, gray-level co-occurrence matrix, etc., rather than using clinical features which helps doctors to understand the pathological mechanism of the AD. In this study, a new approach is proposed using cortical thickness and subcortical volume for distinguishing binary and tertiary classification of the National Research Center for Dementia dataset (NRCD), which consists of 326 subjects. Five classification experiments are performed: binary classification, i.e., AD vs HC, HC vs mAD (MCI due to the AD), and mAD vs aAD (asymptomatic AD), and tertiary classification, i.e., AD vs HC vs mAD and AD vs HC vs aAD using cortical and subcortical features. Datasets were divided in a 70/30 ratio, and later, 70% were used for training and the remaining 30% were used to get an unbiased estimation performance of the suggested methods. For dimensionality reduction purpose, principal component analysis (PCA) was used. After that, the output of PCA was passed to various types of classifiers, namely, softmax, support vector machine (SVM), \( k \)-nearest neighbors, and naïve Bayes (NB) to check the performance of the model. Experiments on the NRCD dataset demonstrated that the softmax classifier is best suited for the AD vs HC classification with an F1 score of 99.06, whereas for other groups, the SVM classifier is best suited for the HC vs mAD, mAD vs aAD, and AD vs HC vs mAD classifications with the F1 scores being 99.51, 97.5, and 99.99, respectively. In addition, for the AD vs HC vs aAD classification, NB performed well with an F1 score of 95.88. In addition, to check our proposed model efficiency, we have also used the OASIS dataset for comparing with 9 state-of-the-art methods.

1. Introduction

Alzheimer’s disease (AD) is the most usual neurodegenerative dementia and a rapidly growing health problem, which is the main reason for causing dementia in the elderly population [1]. A conclusive analysis can only be made postmortem and requires histopathological confirmation of neurofibrillary tangles and amyloid plaques. Early and correct diagnosis of AD is not only difficult but also vital from the perspective of future treatments.

Although there is currently no treatment for AD, there are several promising pharmacologic compounds in advanced stages of development, and it is expected that a treatment will be soon available. One of the factors that have been speculated to be the cause of lack of success in developing disease-modifying treatments thus far is the
inability to correctly differentiate patients at the mild cognitive impairment (MCI) stage who will progress on to develop AD from those that have MCI symptoms that are due to other causes. A potentially promising treatment for AD may not be beneficial when administered to those whose MCI symptoms are not due to AD, causing an apparently promising treatment to be considered a failure. Another reason for distinguishing those patients with prodromal AD at the MCI stage is that interventions early in the course of the disease may help delay the onset and/or mitigate the risk of full-blown AD [2], whereas interventions later in the course of the disease may limit the disease but would not be able to reverse the pathology-induced neuronal loss after it has already occurred. Hence, diagnosis of presymptomatic AD in the MCI stage is a highly important task, which will become even more crucial and urgent when curative treatment becomes available. Such diagnosis can also be valuable for those whose MCI is due to causes other than AD, as these causes may be easier to determine and manage. Hence, neuroimaging improves the positive predictive value of the diagnosis and involves measurements by structural MRI to test medial temporal lobe atrophy (MTL) and positron emission tomography using fluorodeoxyglucose (FDG) or amyloid markers. MTL structures are fundamental for the creation of new memories and are centrally related to the growth of AD [3]. Specifically, MTA atrophy and allied episodic memory impairment are trademark features of AD. Cortical thickness analysis establishes as another widely accepted approach to measure gray matter atrophy in the AD, and cortical thinning has been found in MCI and AD. Despite evidence for subcortical amyloid and neurofibrillary tangle formation in AD [15], MRI research has drawn its attention to AD-related subcortical structure changes only recently. Advanced segmentation techniques now permit the quantification of subcortical volumes and provide the basis for subcortical shape analysis. Measurement of structural changes based on brain MRI scans has previously been used to classify AD patients versus cognitively normal (CN) subjects and to predict the risk of progression from MCI to the AD. Jha et al. [16] proposed a method for diagnosis of the AD using complex dual-tree wavelet principal coefficients transform (DTCWT). They have used two datasets, OASIS and ADNI, for the validation of their results. An extreme learning machine was used as a classifier, and an accuracy of 90.26%, sensitivity of 90.27%, and specificity of 90.27% were achieved for the 2D ADNI dataset, and an accuracy of 95.75%, a sensitivity of 96.59%, and a specificity of 93.03% were achieved for the OASIS dataset. Chyzhyk et al. [17] uses a lattice independent component analysis (LICA) technique for the feature section stage with combine kernel transformation of the data. Their approach improved the generalization of the dendritic computing classifiers. Then, they apply their proposed model on the OASIS dataset for classification of AD patients with normal subjects, and their model achieve 74.77% accuracy, 96% sensitivity, and 52.5% specificity. Khajehnejad et al. [18] uses the manifold-based semisupervised learning method for early diagnosis of the AD. They have used the OASIS dataset for experiment, and their proposed method yield accuracy of 93.86%, sensitivity of 94.65%, and specificity of 93.22%. Jha and Kwon [19] proposed an AD detection method using sparse autoencoder, scale conjugate gradient, and softmax output layer with fine-tuning. They have used the OASIS dataset and achieved an accuracy of 91.6%, 98.09% of sensitivity, and 84.09% of specificity. Islam and Zhan [20] proposed an ensemble of a deep convolutional neural network for early detection of AD. Here, they have used DenseNet-121, DenseNet-161, and DenseNet-169 deep learning models for classification of the OASIS dataset, and later, they have used their proposed ensemble model, which was fused with deep learning for classification of the same dataset. Their proposed method yields 93.18% of accuracy, 94% of precision, 93% of sensitivity, and 92% of F1 score. Farhan et al. [21] proposed a model, which uses two extracted features of the brain: first features are the volume of GM, WM, and CSF and second features are the (lh/rd) area of the hippocampus. In addition, later, they have used four different classifiers (SVM, MLP, j48, and ensemble of classifiers) to evaluate the classification accuracy. An ensemble of classifiers has got the high accuracy compared to other classifiers with 93.75% accuracy for combined features. Lama et al. [22] proposed a binary and a tertiary classification between AD, HC, mAD (MCI due to AD), and aAD (asymptomatic AD) using structural MRI. By using the atrophy measure from sMRI scans, the intensity and stage of the neurodegeneration can be determined. These studies include morphometric approaches, such as the region of interest (ROI) and volume of interest (VOI) of gray matter voxels for the automatic segmentation of sMRI images, and the sMRI volume measurement of the hippocampus and the medial progressive lobe [8]. Various machine-learning methods have been used to differentiate binary and tertiary classification between AD, HC, mAD, and aAD. As suggested in [9, 10], only using amyloid imaging biomarker may be less sensitive in tracing AD progression, mainly in the symptomatic stage, recent consensus statements have underlined the importance of a biomarker of neurodegeneration, which is a critical component of AD pathophysiology in the prodromal and early dementia stages, and also from [11], atrophy on sMRI reflects on cumulative loss and shrinkage of the neuropil [12–14]. These indicate that a volumetric measure of cortical thickness and subcortical volume is one essential biomarker for early detection of the AD. Cortical thickness analysis establishes as another widely accepted approach to measure gray matter atrophy in the AD, and cortical thinning has been found in MCI and AD. Despite evidence for subcortical amyloid and neurofibrillary tangle formation in AD [15], MRI research has drawn its attention to AD-related subcortical structure changes only recently. Advanced segmentation techniques now permit the
Optimum sensitivity and specificity values were (81%, 95%) for AD vs HC, (70%, 61%) for S-MCI vs P-MCI, and (73%, 85%) for HC vs P-MCI. Zhang et al. [24] proposed a multimodal classification approach by employing a multiple-kernel support vector machine (SVM) based on biomarkers including sMRI, PET, and cerebrospinal fluid (CSF) to distinguish AD (or MCI) and normal control (NC) subjects. For the binary classification (AD vs NC and MCI vs NC) results, their suggested model had high accuracy for AD classification, whereas for MCI classification, satisfactory accuracy was obtained. More recently, Cho et al. [25] conducted an experiment on 72 MCIc and 131 MCInc subjects using the incremental learning technique based on spatial frequency, which shows the representation of cortical thickness data. In addition, their proposed method yielded better results than the ten benchmark techniques for MCIc vs. MCInc classification as reported in [23], and a sensitivity of 63% and a specificity of 76% were obtained. Wolz et al. [26] used four different automated feature extraction techniques (namely, hippocampal volume, TBM, cortical thickness, and manifold-based learning) to analyze structural MRI data of 834 ADNI AD, MCI, and healthy control (CTL) subjects. The extracted features were used to compare the performance of two classifiers, namely, LDA and SVM, for AD classification and MCI prediction. The best accuracy for AD versus CTL classification was obtained by combining all extracted features and utilizing a LDA classifier, that is, an accuracy of 89% (sensitivity and specificity of 93% and 85%, respectively). Similarly, using combined features and the LDA classifier resulted in the highest accuracy of 68% (sensitivity and specificity of 67% and 69%, respectively) for classification of MCI-converter and MCI-stable subjects. When different feature types were studied individually, the TBM features yielded the best result.

Compared to earlier work, this study aims at establishing the enhancement in accuracy and constancy that can be attained by combining more than one MR-based feature. Here, we are going to investigate a combined feature of cortical thickness and subcortical volume in the AD and aAD with stable cognitive abilities compared to HC as well as in mAD which converted to AD. NRCD data were used to test the potential combination of diverse MR-based features for improving classification accuracy. For evaluation, all 326 NRCD dataset images provided by the dementia center of Chosun University hospital were used and NeuroI [27] which was developed at NRCD was also used. Specifically, the binary classifications AD vs HC, HC vs mAD, and mAD vs aAD and the tertiary classifications AD vs HC vs mAD and AD vs HC vs aAD were used. To this end, four representative classifiers are presented and compared, using an efficient feature selection approach, including SVM, k-nearest neighbors (KNN), naive Bayes (NB), and softmax classifiers, for the multiclass classification of various stages of the AD progression.

2. Materials and Methods

2.1. Subjects. The data utilized in this research were obtained from the National Research Center for Dementia (NRCD). All the patients for whom preprocessed images were available were selected. The dataset contained 326 subjects: 81 AD subjects (39 males, 42 females; age ± SD = 71.86 ± 7.09 years, range = 56–83 years; education level = 7.34 ± 4.88, range = 0–18), 171 cognitively normal health control (HC) subjects (83 males, 88 females; age ± SD = 71.66 ± 5.43, range = 60–85; education level = 9.16 ± 5.54, range = 0–22), 39 patients with mAD (MCI who had converted to AD) (25 males, 14 females; age ± SD = 73.23 ± 7.09, range = 49–87; education level = 8.20 ± 5.19, range = 0–18), 35 patients with aAD (MCI who had not converted) (15 males, 20 females; age ± SD = 72.74 ± 4.82, range = 61–83; education level = 7.88 ± 6.30, range = 0–18).

Table 1 shows the demographics of the 326 study subjects. Statistical significant differences in demographics and clinical variables between the study groups were measured using Student’s unpaired t-test. In this study, the significance level was set to 0.05, which is a standard alpha value. There were more females in all groups except for the mAD group. The education level was highly dissimilar in the pairwise comparisons between all other study groups. Compared to the patients in all other groups, AD patients had significantly a lower education level.

To obtain unbiased estimations of the performance, the set of contestants was randomly split into two parts in a 70/30 ratio for training and testing. The algorithm was trained on a training code, and the measures of the group performance were evaluated in terms of accuracy, sensitivity, specificity, precision, and F1 score using an independent test set.

2.2. MRI Acquisition. Standard 3T T1-weighted images were obtained using the volumetric 3D MPRAGE protocol with resolution 1 mm × 1 mm × 1 mm (voxel size). These were N4 bias correction images.

2.3. Feature Selection. Subcortical volumetric and cortical thickness measures have been widely used for classification purposes. From [28], we can say that cortical thickness is a direct index of atrophy and is, therefore, a potentially powerful candidate in the diagnosis of AD. In this experiment, cortical thickness and subcortical volume are extracted using FreeSurfer (v5.3). In total, 110 features were extracted from 3D sMRI T1-weighted image. FreeSurfer is a set of tools for analysis and visualization of cortical (Figure 1) and subcortical (Figure 2) brain imaging data. FreeSurfer was designed around an automated workflow that includes several standard image processing phases which are necessary to achieve a final brain parcellation image within the subject’s space; however, manual image editing is also allowed after each stage to ensure quality control (http://surfer.nmr.mgh.harvard.edu/fswiki). At first, a good quality of T1-weighted sMRI image volume is passed to the FreeSurfer pipeline, and after that, FreeSurfer performs a series of steps, start from motion artifact correction, affine transformation (12 degrees of freedom) to Talairach image space, nonuniform intensity normalization for intensity inhomogeneity correction, and removal of nonbrain tissues.
Table 1: Demographic characteristics of the studied population (from the NRCD database).

| Group | Number of subjects | Age            | Gender | Education |
|-------|--------------------|----------------|--------|-----------|
| AD    | 81                 | 71.86 ± 7.09 [56–83] | M 39   | F 42      | 7.34 ± 4.88 [0–18] |
| mAD   | 39                 | 73.23 ± 7.34 [49–87]  | M 25   | F 14      | 8.20 ± 5.19 [0–18] |
| aAD   | 35                 | 72.74 ± 4.82 [61–83]  | M 15   | F 20      | 7.88 ± 6.30 [0–18] |
| HC    | 171                | 71.66 ± 5.43 [60–85]  | M 83   | F 88      | 9.16 ± 5.54 [0–22] |

Values are specified as mean ± standard deviation [range].

Figure 1: Cortical thickness showing left and right hemisphere of pial and white surface.

The remaining brain image volume is intensity normalized to tie with the Freesurfer atlas image intensity histogram, which is followed by a nonlinear warping of the atlas brain image to subject brain image. A warped Atlas 3D brain image in the subject space is utilized in atlas-based tissue segmentation, for labelling subcortical brain structures, like brain stem, cerebellum, and cerebral cortex. The next step in Freesurfer is to generate topologically correct cortical surface representation per hemisphere, like gray-white matter segmentation [29], and the third segments of 34 ROIs based on anatomic landmarks [30].

Freesurfer also provides the ability to construct a surface-based morphometry (SBM) for representations of the cortex, from which neuroanatomic volume, cortical thickness, and surface area can be derived. Cortical surface lies either at the WM/GM tissue interface or at the GM/CSF tissue interface. Each hemisphere’s cortical surface representation is mapped automatically to a standard spherical coordinate system. Key components of the surface mapping include surface inflation with minimal metric distortion, topology correction, projection to spherical coordinates, and SBM warping to correctly align anatomical homologous points. Mapping to the standard spherical coordinate system defined by Freesurfer atlas brain allows for automated anatomical parcellation of cortex into gyral regions. Surface parcellation is then extended to GM volume, yielding parcellation of GM tissue sheet and regional cortical volumes. The precise matching of a morphologically homologous cortical location for each patient was obtained by plotting the atlas-based cortical surface on a sphere aligning the cortical patterns. Table 2 presents an overview of the features calculated for all 326 available NRCD images. After the preprocessing stage, all the data extracted by Freesurfer were normalized to zero mean and unit variance for each feature, as shown in Figure 3 using standard scalar function of Scikit-learn library. That is, given the data matrix $X$, where rows represent subjects and columns represent features, the normalized matrix with elements $x(i, j)$ is given by

$$
X_{\text{norm},(i,j)} = \frac{x(i,j) - \text{mean}(x_j)}{\text{std}(x_j)}
$$

where $X_j$ is the $j$th column of the matrix $(X)$. Subsequently, principal component analysis (PCA) was performed [31], which is a dimensionality reduction technique whereby the features are mapped onto a lower dimensional space. PCA is a feature selection process generating new features that are linear combinations of the initial features. PCA maps the data in a $d$-dimensional space to a new $k$-dimensional subspace with $k < d$. The new $k$ variables are called principal components (PC), and each principal component has maximum variance eliminating the variance that is already accounted for in all succeeding components. Consequently, the first component has a larger variance than the components that follow. The principal components can be defined by the following equation:

$$
PC_i = a_1b_1 + a_2b_2 + \cdots + a_d b_d,
$$

where $PC_i$ is a principal component in $i$, $x_d$ is an original feature in $d$, and $a_d$ is a numerical coefficient of $x_d$. The number of principal components is always less than or equal to the number of original observations.

The obtained principal components for AD vs HC are shown in Figure 4. The number of components was determined by maintaining the variance greater than 99%. In total, there were 110 features; however, not all features were required for convergence. As can be seen in Figure 4, the first principal component achieved 99% of the variance compared to the other features. Therefore, the values that were obtained first were taken as a principal component for AD vs HC. Likewise, for other binary and tertiary classification, the same procedure was followed.

2.4. Classification Method. Once the sMRI-based features were extracted from the automated toolbox in both cortical and subcortical regions, feature vectors containing mean-centered voxel intensities were created combining all features. The classification approach we design is aimed to combine two sources of features: cortical thickness and...
subcortical volume. These features are used for global decision framework to discriminate AD with other groups. The overall diagram of the approach is presented in Figure 3. Here, our aim is early classification of an AD from other groups by using combined features of cortical thickness and subcortical volume of the same subjects. Our aim is to classify binary and tertiary groups. Moreover, classification is the problem of categorizing to which a new set of observation belongs, based on a training dataset whose group affiliation is already known. Moreover, we know that different classifiers follow a different mathematical function for classification. That is why we have used four best machine-learning classifiers, which are in practice like SVM and its variants, KNN, NB, and softmax classifiers, to know which classifier learns our model accurately to classify the different groups, and we also compared their results. All classification methods give a decision output.

2.5. SVM. This is the most common classification method to analyze sMRI data [23]. SVM [32] is the most commonly used algorithm in AD research for multivariate classification [26]. This method is based on choosing a critical point for the classification task. Support vectors are the elements of the data that are relevant in the splitting into two classes. The

Table 2: Features used in this study.

| Methods                                      | Number of features | Descriptions                                      |
|----------------------------------------------|--------------------|---------------------------------------------------|
| Cortical thickness and subcortical volume    | 110                | Based on group-level statistical analysis measure of subcortical segmentation volume and cortical thickness |

Figure 2: Subcortical brain segmentation.

Figure 3: Workflow of proposed method: (a) 3D input image, (b) skull stripping, (c) white and pial surface, (d) cortical thickness and subcortical volume segmentation features, (e) feature selection (f) cross validation, (g) various classifiers, and (h) diagnosis output.
SVM algorithm determines the parameters of the decision function that maximizes the margin between the training examples and the class boundary, as shown in Figure 5. A number of nonlinear SVM approaches have also been used, such as kernel SVM and multikernel SVM [33].

The main concept of kernel techniques is to map the input data, which are linearly nonseparable into a higher dimensional feature space, where they are more likely to be linearly separable.

2.6. KNN. Cover and Hart proposed KNN in 1968 [34], which is one of the simplest machine-learning algorithms. It is an extension of the simple nearest neighbor technique. KNN classifies an unknown sample depending on the “vote” of the $k$-nearest neighbors rather than the single nearest neighbor.

The main steps of KNN implementation are as follows:

1. **Similarity assessment**: the similarity between the test sample and each sample of the training set is calculated. In general, the resemblance can be measured by, for instance, the Euclidean distance, the Manhattan distance, the Jaccard similarity coefficient, and the correlation coefficient. Among these, the Euclidean distance method is the most widely used. For a given feature sample $\text{test}\{x_{j1}, x_{j2}, \ldots, x_{jn}\}$ and training set feature sample $\text{train}\{x_{j1}, x_{j2}, \ldots, x_{jn}\}$, the Euclidean distance is calculated as follows:

$$d_j = \sqrt{\sum_{i=1}^{n} (\text{test}_{ji} - \text{train}_{ji})^2}, \quad (3)$$

where $n$ is the number of feature vectors, $j$ is the number of training and testing trials, and $d_j$ is the Euclidean distance between the $j$th sample of the training set and a test sample.

2. In the second step, the neighbor’s nearest distances should be determined and sorted in ascending order. There are several methods (like elbow method and thumb rule) which help us to achieve the best $k$ value for KNN. The optimum $k$ value will always vary depending on the dataset, so it should be as big as that its noises will not disturb the prediction highly and as low as that one factor will not dominate another. Then, the selection of the value will directly affect the classification result and should thus be carefully made.

3. In the third step, the “vote and classify” method is applied, whereby the test sample is classified to a class according to the voting result of each category.

2.7. NB. NB is a machine-learning technique that has been utilized for over 50 years in biomedical informatics [35, 36]. These classifiers are a family of simple “probabilistic classifiers” based on Bayes’ theorem with strong independence assumptions between their features. An NB classification model is easy to construct, with no complex iterative parameter approximation, which makes it particularly useful for large datasets. Despite its simplicity, the NB model often performs unexpectedly well and is widely used for classification because it often outperforms several more sophisticated classification approaches. Bayes’ theorem is used to determine the posterior probability $p(c|x)$ from $p(c)$, $p(x)$, and $p(x|c)$. The NB classifier assumes that the effect of the parameter of a predictor ($x$) on a specified class ($c$) is autonomous compared with the other predictor’s parameters. This assumption is called class-conditional independence:

$$p\left(\frac{c}{x}\right) = \frac{p(x|c)p(c)}{p(x)}, \quad (4)$$

where $p(c|x) = p(x_1|c) \cdot p(x_2|c) \cdot \ldots \cdot p(x_n|c) \cdot p(c)$, $p(c|x)$ is the posterior likelihood of the class (target), given the predictor (attribute); $p(c)$ is the prior probability of the class; $p(x|c)$ is the probability of the predictor given the class; and $p(x)$ is the prior probability of the predictor.
2.8. Softmax Classifier. Softmax regression is a generalized form of logistic regression that can be used in multiclass classification problems where the classes are mutually exclusive. The earlier linear regression model [19, 37] produces continuous or unbounded \( y \) values. To proceed from arbitrary values \( y \in \mathbb{R}^c \) to normalized probability values, \( p \in \mathbb{R}^c \) is estimated for a single instance and exponentiation and normalization are used as follows:

\[
p_i = \frac{\exp y_i}{\sum_{c=1}^{C} \exp y_c},
\]

where \( i, c \in \{1, \ldots, C\} \) is the range over the classes, \( p_i \) refers to the probabilities, and \( y_i \) and \( y_c \) refer to the value of a single instance. This is called the softmax function, which takes the vector of arbitrary real-valued scores in \( y \) and transforms it into a vector of values ranging between 0 and 1 that later sum to 1. A model that converts the un-normalized values at the end of a linear regression to normalized probabilities for classification is called softmax classifier. Here, the softmax layer takes the learned representation \( p_i \) and interprets it to the output class. A probability score \( p_i \) is also assigned to the output class. The softmax classifier understands the scores inside the output vector \( y \) as the un-normalized log likelihoods for each specific class and then replaces the hinge losses with a cross-entropy loss that has the form:

\[
L_i = -\log(p_i),
\]

where \( L_i \) is the loss of cross entropy of the network. Exponentiation of these quantities yields the (un-normalized) likelihoods, and their division performs the normalization so that their probabilities sum to 1. In probabilistic terms, the negative log probability of the accurate class is minimized, which can be regarded as performing maximum likelihood estimation (MLE). A fine feature of this observation is that the regularization term \( R(W) \) can now be interpreted as the full loss function as approaching from a Gaussian prior over the weight matrix \( W \), where we are executing the maximum a posteriori (MAP) estimation instead of MLE.

3. Results and Discussion

3.1. Background. In this study, the proposed method is presented using SVM, KNN, NB, and softmax classifiers. The details are shown in Figure 3. The proposed idea is to combine two extracted features, namely, cortical thickness and subcortical volume, from Freesurfer toolbox to differentiate between AD vs other groups. For early prediction, we perform a binary and tertiary classification using the AD, HC, mAD, and aAD datasets to check how well our proposed method has performed on the sMRI 3D image. At the preprocessing stage, normalization was performed for each case. Moreover, the PCA dimensionality reduction technique is utilized to find the optimal number of principal components for each classification, as shown in Figure 4 for AD vs HC. Different numbers of principal components were obtained for different cases. In addition, stratified K-Fold (SKF) cross-validation (CV) was used to confirm the robustness of the classification results. Four different types of classifiers were used to obtain the test sample accuracy, sensitivity, specificity, precision, and F1 score.

3.2. Evaluation. To obtain unbiased estimations of the performance, the set of subjects was randomly separated into two parts in a 70/30 ratio for training and testing. The training set was utilized to determine the optimal hyperparameters of each classifier or method and later, to train the classifier. Subsequently, the testing set was used to evaluate the classification performance. The training and testing datasets were identical for all techniques. On the training set, SKF CV was used to estimate the optimal hyperparameters. Two kernel parameters \( c \) and \( \gamma \) for radial basic function SVM and one kernel value \( c \) for linear SVM were required to be determined according to the Libsvm library. The SVM algorithm performs poorly on the experimental data when the default parameter values are selected. Therefore, the grid search method was utilized to determine the optimal parameters for \( c \) and \( \gamma \) before they were used for training. The pair \((c, \gamma)\) with the highest cross-validation accuracy was
chosen as the best values. In the present study, the search scales for these two values were set as follows: $c = 1$ to 10 and $\gamma = (1e^{-4}, 1e^{-2}, 0.0001)$ for all cases.

In addition, the obtained values of $c$ and $\gamma$ for all cases are shown in Table 3. For each method, the obtained best-suited optimized value was set to the hyperparameters, which were later utilized to train the classifier using the training groups, and the performance of each resulting classifier was then assessed on the testing set. Thereby, unbiased evaluations of the performances of each method were obtained, whereas for KNN classifier, we have used the elbow method to decide the $k$ value. As we know that in the elbow method, if one plots the percentage of variance explained by the cluster against the number of clusters, the first cluster will add much information (explain a lot of variances), but at some point, the marginal gain will drop, giving an angle in the graph. So, the number of clusters is chosen at this point. First, we plot the elbow curve using the Matplotlib library. Moreover, in our case, we provide a range of 1 to 251 for AD vs HC classification problem (which represents the number of subjects for each classification). Therefore, when we plot the graph, the $k$ value from the graph where there is a bend tells us how many clusters are there.

The performance of a binary and multiclass classifier can be understood using confusion matrix, as shown in Table 4. The performance of the system was assessed using the SVM, KNN, NB, and softmax classifiers for each precise test including binary and tertiary classification tasks. The diagonal elements of the matrix show the number of correct predictions made by the classifier. These elements can be further separated into true positive (TP) and true negative (TN), i.e., accuracy. The corresponding contingency chart is shown in Table 5.

$$\text{acc} = \frac{TP + TN}{TP + TN + FP + FN} \quad (7)$$

However, for a dataset with unstable class distribution, calculating only the accuracy may result in a misleading estimation of the performance. Therefore, four additional performance metrics should be calculated, namely, specificity, sensitivity, precision, and F1 score. They are defined as follows:

$$\text{sen} = \frac{TP}{TP + FN} \quad (8)$$

$$\text{spe} = \frac{TN}{TN + FP} \quad (9)$$

$$\text{ppv} = \frac{TP}{TP + FP} \quad (10)$$

$$F1 \text{ score} = \frac{2TP}{2TP + FP + FN} \quad (11)$$

Sensitivity (8) indicates the accuracy of the prediction group, and specificity (9) indicates the accuracy of the prediction of the absence group. Sensitivity measures the success rate for a particular class, i.e., within a class, the percentage of correctly determined subjects (by the classification algorithm) to be in the class. Specificity provides a measure for those not in the class, i.e., it is the percentage of those not in the class that were found not to be in the class. Precision (10) (which is also termed as positive predictive value (PPV)) is the fraction of relevant occurrences among the retrieved occurrences, and F1 score (11) (which is also called F score or F measure) is a quantity related to a test’s accuracy.

To evaluate whether each technique performs significantly better than a random classifier, McNemar’s chi-squared test was used and its significance level was kept to 0.05, which is a benchmark value. McNemar’s test examines the difference between proportions in paired observations. It was used to evaluate the difference between the proportions of accurately classified subjects, i.e., accuracy. The corresponding contingency chart is shown in Table 5.

### 3.3. Classification Results

Both binary and tertiary classification methods were used to measure the classification performance in obtaining cortical and subcortical features.

The obtained results of the classification tests are shown in Tables 6–10 for AD vs HC, HC vs mAD, mAD vs aAD (binary), AD vs HC vs mAD, and AD vs HC vs aAD (tertiary), respectively. The classification report for each case and the performance are shown in Figure 6. All programs were executed in 64-bit Python 3.6 environment on Intel(R) Core(TM) i3-7100 at 3.90 Hz and 8 GB of RAM running Ubuntu 16.04 LTS. The model may be implemented on any computer in which Python 3.6 is compatible.

#### 3.3.1. Binary Classification: AD vs HC, HC vs mAD, and mAD vs aAD

**AD vs HC.** The classification results for AD vs HC are summarized in Table 6 and Figure 6(a). For each case, the dataset was divided into two parts in a 70/30 ratio. All
The classification report for HC vs mAD is summarized in Table 7 and Figure 6(b). In this case, all techniques achieved significantly better $P$ value than chance ($P < 0.05$); however, SVM classified HC vs mAD highly significantly ($P < 0.000001$) with an accuracy of 99.2, sensitivity of 99.02, specificity of 100, precision of 100, and F1 score of 99.51.

$mAD$ vs $aAD$. The classification results for mAD vs aAD are summarized in Table 8 and Figure 6(c). Here, three methods performed significantly better than chance, and their $P$ value was less than the conventional value ($P < 0.05$); however, KNN had a $P$ value greater than the conventional value. SVM had a $P$ value significantly better than the other three methods and classified mAD vs aAD with a high accuracy of 97.77, sensitivity of 100, specificity of 95.25, precision of 96, and F1 score of 97.95.

### 3.3.2. Multiclass Classification

For multiclass classification, accuracy may be a misleading indication of the performance; thus, in this case, the F1 score metric is particularly useful.

$AD$ vs $HC$ vs $mAD$. The classification results for AD vs HC vs mAD are summarized in Table 9, and the plot is shown in Figure 6(d). In this case, SVM classified AD vs HC vs mAD with an accuracy of 99.42, sensitivity of 99.18, specificity of 99.5, precision of 99.99, and F1 score of 99.43. The F1 score indicates a high correct percentage; it can be claimed that SVM classified AD vs HC vs mAD more accurately.

$AD$ vs $HC$ vs $aAD$. The classification results for AD vs HC vs aAD are summarized in Table 10 and are shown in Figure 6(d). It can be seen that NB classified the multiclass case significantly more accurately, with an accuracy of 96.53, sensitivity of 95.88, specificity of 97.64, precision of 95.88, and F1 score of 95.88.

### 3.3.3. Comparing with Others’ State-of-the-Art Methods

As we know the NRCD dataset is not available publicly, that is why we apply our proposed method on the OASIS dataset which can be downloaded from (https://www.oasis-brains.org/). The OASIS database was launched in 2007 as a public-private partnership. OASIS provides brain-imaging dataset, which is freely available for sharing and data study. This dataset consists of a cross-sectional group of 416 patients, which covers the adult lifespan aged from 18 to 96 including individuals with early-phase Alzheimer’s disease (AD). The subjects are right-handed, and they include both men and women. From 416 subjects, 100 included subjects above the age of 60 have been identified with the very mild-to-mild AD and the remaining 316 are diagnosed as normal. All structural sMRI scans used in this experiment were acquired from 1.5T scanners.

At first, we extracted 110 (cortical and subcortical) features from all 416 subjects using the same Freesurfer version which is used for the NRCD dataset. After that, we followed the same procedure that we had applied for the NRCD dataset. As can be seen from Table 11, all methods performed significantly better, and their $P$ value was smaller.
than the conventional 0.05. The assumption was that there were significant dissimilarities between these two parts. Our proposed method achieved a better result with 98.40% of accuracy, 93.75% of sensitivity, 100% of specificity, 100% of precision, and 96.77% of F1 score with softmax classifier. It can also be seen that SVM follows the softmax classifier in terms of performance.

To further demonstrate the usefulness of our proposed method, we compared it with 9 state-of-the-art approaches as shown in Table 12. The result in Table 12 shows that Jack et al. [11] used the kernel-LICA-DC method to classify the AD vs HC and achieved a classification accuracy of 74.25%, a sensitivity of 96%, and a specificity of 52.5%. Jha et al. [19] used (deep learning method) sparse autoencoder technique to classify the problem and achieved a classification accuracy of 91.6%, a sensitivity of 98.09%, and a specificity of 84.09%. In both of these cases, they have achieved decent accuracy but their specificity is very low compared to our proposed method. Likewise, Islam and Zhang [20] used an ensemble of deep convolutional neural networks technique and achieved a classification accuracy of 93.18% and a specificity of 93%. Farhan et al. [21] used an ensemble of a classifier for the classification of AD vs HC and achieved a classification accuracy of 93.75%, a
sensitivity of 100%, and a specificity of 87.5%. Despite using deep learning and ensemble classifier methods, their accuracy, sensitivity, and specificity are low compared to our proposed method. Khajehnejad et al. [18] used the semi-supervised technique for classification and achieved an accuracy of 93.86%, a sensitivity of 94.65%, and a specificity of 93.22%. Jha et al. [16] used the extreme learning machine method for classification of AD vs HC with dual-tree wavelet principal coefficients and achieved an accuracy of 95.27%, a sensitivity of 96.59% and a specificity of 93.03%. And, Lama et al. [22] used cortical features for early detection of AD and RELM for classification and achieved an accuracy of 77.88%, a sensitivity of 68.85%, and a specificity of 83.54%. Despite using new methods for classification, their classification performance is very low compared to our results as shown in Table 12.

As can be seen from Table 12, our proposed method using softmax classifier has outperformed all state-of-the-art methods and achieved an accuracy of 99.34%, a sensitivity of 98.14%, and a specificity of 100%. And, the proposed method had effectively predicted future clinical changes between (mAD vs aAD) patients, as can be seen in Table 8. Our proposed model has achieved 97.99% of accuracy, 100% of sensitivity, 95.23% of specificity, 96% of precision, and F1 score as 97.95% using the RBF-SVM classifier for mAD vs aAD classification. Efficient and reliable outcomes were obtained, which prove the effectiveness of the proposed technique. Comparison of the results showed that the RBF-SVM classifier achieved highly satisfactory performance for three cases (HC vs mAD, mAD vs aAD, and AD vs HC vs mAD), where the NB classifier was suitable for predicting AD vs HC vs aAD. As we can say that, our proposed technique to combine cortical thickness and subcortical volume features of the same subjects for classification of a binary and tertiary group performed very well in our dataset as well as in the OASIS dataset.

In the present study, only cortical thickness and subcortical volume features were considered for the classification process. However, in the future, other different types of features will be used, such as the hippocampus and amygdala for the classification of the AD. Moreover, longitudinal datasets will be used for studying the changes over time between AD, mAD, and aAD. In this study, only NRCD

Table 12: Algorithm performance comparison over OASIS and ADNI MRI data.

| Approach                        | Year | Dataset | Classifier | Modalities | AD vs HC Accuracy | AD vs HC Sensitivity | AD vs HC Specificity |
|---------------------------------|------|---------|------------|------------|-------------------|----------------------|----------------------|
| Cuinnet et al. [23]             | 2011 | ADNI    | SVM        | MRI        | 91.6              | 98.09                | 84.09                |
| Cho et al. [25]                 | 2012 | ADNI    | LDA        | MRI        | NA                | 81%                  | 95%                  |
| Chyzhyk et al. [17]             | 2012 | OASIS   | Kernel-LICA-DC | MRI        | 74.25             | 96%                  | 52.5%                |
| Lama et al. [22]                | 2017 | ADNI    | RELM       | MRI        | 77.88             | 68.85                | 83.54%               |
| Jha and Kwon [19]               | 2017 | OASIS   | Sparse autoencoder | MRI        | 91.6              | 98.09                | 84.09%               |
| Islam and Zhang [20]            | 2017 | OASIS   | Ensemble of deep convolutional neural networks | MRI        | 93.18             | NA                   | 93%                  |
| Farhan et al. [21]              | 2014 | OASIS   | Ensemble of classifier | MRI        | 93.75             | 100%                 | 87.5%                |
| Khajehnejad et al. [18]         | 2017 | OASIS   | Semisupervised classifier | MRI        | 93.86             | 94.65                | 93.22%               |
| Jha et al. [16]                 | 2018 | ADNI    | ELM        | MRI        | 90.26             | 90.27                | 90.20                 |
|                                 | 2018 | OASIS   | Softmax classifier | MRI        | 95.27             | 96.59                | 93.03%               |
| Proposed method                 | 2018 | NRCD    | Softmax classifier | MRI        | 99.34             | 98.14                | 100%                 |
|                                 | 2018 | OASIS   | Softmax classifier | MRI        | 98.40             | 93.75                | 100%                 |

5. Conclusions

A new method for automatic classification of an AD from MCI (asymptomatic or converted to the AD) and a healthy group is proposed using combined features extracted from an automated toolbox, where sMRI scans of NRCD dataset is used as an input image. Here, four different types of classifiers (softmax classifier, SVM, KNN, and naïve Bayes) were used to classify five different types of the classification problem. These experimental results confirm that the proposed method had effectively predicted future clinical changes between (mAD vs aAD) patients, as can be seen in Table 8. Our proposed model has achieved 97.99% of accuracy, 100% of sensitivity, 95.23% of specificity, 96% of precision, and F1 score as 97.95% using the RBF-SVM classifier for mAD vs aAD classification. Efficient and reliable outcomes were obtained, which prove the effectiveness of the proposed technique. Comparison of the results showed that the RBF-SVM classifier achieved highly satisfactory performance for three cases (HC vs mAD, mAD vs aAD, and AD vs HC vs mAD), where the NB classifier was suitable for predicting AD vs HC vs aAD. As we can say that, our proposed technique to combine cortical thickness and subcortical volume features of the same subjects for classification of a binary and tertiary group performed very well in our dataset as well as in the OASIS dataset.

In the present study, only cortical thickness and subcortical volume features were considered for the classification process. However, in the future, other different types of features will be used, such as the hippocampus and amygdala for the classification of the AD. Moreover, longitudinal datasets will be used for studying the changes over time between AD, mAD, and aAD. In this study, only NRCD
dataset was used for research, so in future, we are going to compare our model with differently available datasets for early prediction of the AD.

Data Availability

The National Research Center for Dementia (NRCD) dataset was used to support the findings of this study. At first, we would like to say that NRCD is a private dataset which was generated in Chosun University hospitals, and it originally belongs to Chosun University. We cannot share it or open it online for others due to privacy reasons. Later, to compare with other recent state-of-the-art methods, we have used OASIS dataset which was downloaded from https://www.oasisbrains.org/.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors’ Contributions

Yubraj Gupta and Kun Ho Lee contributed equally to this work.

Acknowledgments

This research was supported by the Brain Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (NRF-2014M3C7A1046041 and NRF-2014M3C7A1046050). Additionally, this work was supported by the National Research Foundation of Korea grant funded by the Korean government (NRF-2017R1A2B4006533).

References

[1] C. P. Ferri, M. Prince, C. Brayne et al., “Global prevalence of dementia: a Delphi consensus study,” The Lancet, vol. 366, no. 9503, pp. 2112–2117, 2005.
[2] P. B. Rosenberg and C. Lyketsos, “Mild cognitive impairment: searching for the prodrome of Alzheimer’s disease,” World Psychiatry, vol. 7, no. 2, pp. 72–78, 2008.
[3] M. S. Albert, “Cognitive and neurobiologic markers of early Alzheimer disease,” Proceedings of the National Academy of Sciences, vol. 93, no. 24, pp. 13547–13551, 1996.
[4] C. Marra, M. Ferraccioli, M. G. Vita, D. Quaranta, and G. Gainotti, “Patterns of cognitive decline and rates of conversion to dementia in patients with degenerative and vascular forms of MCI,” Current Alzheimer Research, vol. 8, no. 1, pp. 24–31, 2011.
[5] K. R. Gray, R. Wolz, R. A. Heckemann, P. Aljabar, A. Hammers, and D. Rueckert, “Multi-region analysis of longitudinal FDG-PET for the classification of Alzheimer’s disease,” NeuroImage, vol. 60, no. 1, pp. 221–229, 2012.
[6] H. Hanyu, T. Sato, K. Hirao, H. Kanetaka, T. Iwamoto, and K. Koizumi, “The progression of cognitive deterioration and regional cerebral blood flow patterns in Alzheimer’s disease: a longitudinal SPECT study,” Journal of the Neurological Sciences, vol. 290, no. 1-2, pp. 96–101, 2010.
[7] Y. J. Chen, G. Deutsch, R. Satya, H. G. Liu, and J. M. Mountz, “A semi-quantitative method for correlating brain disease...
groups with normal controls using SPECT: Alzheimer’s disease versus vascular dementia,” *Computerized Medical Imaging and Graphics*, vol. 37, no. 1, pp. 40–47, 2013.

[8] J. Barnes, J. W. Bartlett, L. A. van de Pol et al., “A meta-analysis of hippocampal atrophy rates in Alzheimer’s disease,” *Neurobiology of Aging*, vol. 30, no. 11, pp. 1711–1723, 2008.

[9] J. R. Petrella, “Neuroimaging and the search for a cure for Alzheimer disease,” *Radiology*, vol. 269, no. 3, pp. 671–691, 2013.

[10] G. B. Frisoni, N. C. Fox, C. R. Jack Jr., P. Scheltens, and P. M. Thompson, “The clinical use of structural MRI in Alzheimer disease,” *Nature Reviews Neurology*, vol. 6, no. 2, pp. 67–77, 2010.

[11] C. R. Jack, D. A. Bennett, K. Blennow et al., “NIA-AA research framework: toward a biological definition of Alzheimer’s disease,” *Alzheimer’s & Dementia*, vol. 14, no. 4, pp. 535–562, 2018.

[12] F. Barkhof, T. M. Polvikoski, E. C. W. van Straaten et al., “The significance of medial temporal lobe atrophy: a postmortem MRI study in the very old,” *Neurology*, vol. 69, no. 15, pp. 1521–1527, 2007.

[13] C. Zarow, H. V. Vinters, W. G. Ellis et al., “Correlates of hippocampal neuron number in Alzheimer’s disease and ischemic vascular dementia,” *Annals of Neurology*, vol. 57, no. 6, pp. 896–903, 2005.

[14] M. Bobinski, M. J. de Leon, J. Wegiel et al., “The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer’s disease,” *Neuroscience*, vol. 95, no. 3, pp. 721–725, 2000.

[15] E. Braak and H. Braak, “Alzheimer’s disease: transiently developing dendritic changes in pyramidal cells of sector CA1 of the Ammon’s horn,” *Acta Neuropathologica*, vol. 93, no. 4, pp. 323–325, 1997.

[16] D. Jha, S. Alam, J. Y. Pyun, K. H. Lee, and G. R. Kwon, “Alzheimer’s disease detection using extreme learning machine, complex dual tree wavelet principal coefficients and linear discriminant analysis,” *Journal of Medical Imaging and Health Informatics*, vol. 8, no. 5, pp. 881–890, 2018.

[17] D. Chyzhyk, M. Graña, A. Savio, and J. Maiora, “Hybrid dendritic computing with kernel-LICA applied to Alzheimer’s disease detection in MRI,” *Neurocomputing*, vol. 75, no. 1, pp. 72–77, 2012.

[18] M. Khajehnejad, F. Saatlu, and H. Mohammadhadezade, “Alzheimer’s disease early diagnosis using manifold-based semi-supervised learning.” *Brain Sciences*, vol. 7, no. 12, p. 109, 2017.

[19] D. Jha, Department of Information and Communication Engineering Chosun University, and G. R. Kwon, “Alzheimer’s disease detection using sparse autoencoder, scale conjugate gradient and softmax output layer with fine tuning.” *International Journal of Machine Learning and Computing*, vol. 7, no. 1, pp. 13–17, 2017.

[20] J. Islam and Y. Zhang, “An ensemble of deep convolutional neural networks for Alzheimer’s disease detection and classification,” 2017, http://arxiv.org/abs/1712.01675.

[21] S. Farhan, M. A. Fahiem, and H. Tauseef, “An ensemble-of-classifiers based approach for early diagnosis of Alzheimer’s disease: classification using structural features of brain images,” *Computational and Mathematical Methods in Medicine*, vol. 2014, Article ID 862307, 11 pages, 2014.

[22] R. K. Lama, J. Gwak, J. S. Park, and S. W. Lee, “Diagnosis of Alzheimer’s disease based on structural MRI images using a regularized extreme learning machine and PCA features,” *Journal of Healthcare Engineering*, vol. 2017, Article ID 5485080, 11 pages, 2017.