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One Step Measurements of hippocampal Pure Volumes from MRI Data Using an Ensemble Model of 3-D Convolutional Neural Network

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Abstract

The hippocampal volume atrophy is known to be linked with neuro-degenerative disorders and it is also one of the most important early biomarkers for Alzheimer's disease detection. The measurements of hippocampal pure volumes from Magnetic Resonance Imaging (MRI) is a crucial task and state-of-the-art methods require a large amount of time. In addition, the structural brain development is investigated using MRI data, where brain morphometry (e.g. cortical thickness, volume, surface area etc.) study is one of the significant parts of the analysis. In this study, we have proposed a patch-based ensemble model of 3-D convolutional neural network (CNN) to measure the hippocampal pure volume from MRI data. The 3-D patches were extracted from the volumetric MRI scans to train the proposed 3-D CNN models. The trained models are used to construct the ensemble 3-D CNN model and the aggregated model predicts the pure volume in one-step in the test phase. Our approach takes only 5 seconds to estimate the volumes from an MRI scan. The average errors for the proposed ensemble 3-D CNN model are 11.7±8.8 (error%±STD) and 12.5±12.8 (error%±STD) for the left and right hippocampi of 65 test MRI scans, respectively. The quantitative study on the predicted volumes over the ground truth volumes shows that the proposed approach can be used as a proxy.

Keywords : Hippocampus | Pure Volume | MRI | 3-D Patch| 3-D CNN| Alzheimer's Disease

I. INTRODUCTION

The shape, size, and structural changes of different brain regions can cause various neurological disorders [1-3]. Hippocampus is one of the most important regions of interest (ROIs) which has been investigated by different research groups [4-6] for several reasons, such as Alzheimer's disease. The neuro-degenerative disorders are a significant research area where researchers are contributing to assist in the diagnosis process. Several biomarkers, such as Amyloid beta (Aβ42), Tau protein (Tau), Phosphorylated Tau (P-Tau) and hippocampal volume are used to diagnose Alzheimer's disease [3,7,8]. The hippocampal volume atrophy is known to be linked with Alzheimer's disease and Epilepsy. Therefore, automatic hippocampal volume measurement is an important task to provide on-site diagnosis.

Although several semi-automatic and automatic methods [4,6,9] have already been proposed to measure the hippocampal volume, however, the manual intervention by expert radiologist remains the gold standard method. Automatic tools, such as FreeSurfer, FIRST and SPM are being used to measure the hippocampal volume. FreeSurfer [6,10,11] is an atlas-based system that uses its reference atlas image to register/segment and estimate the volumes of ROIs of the target Magnetic

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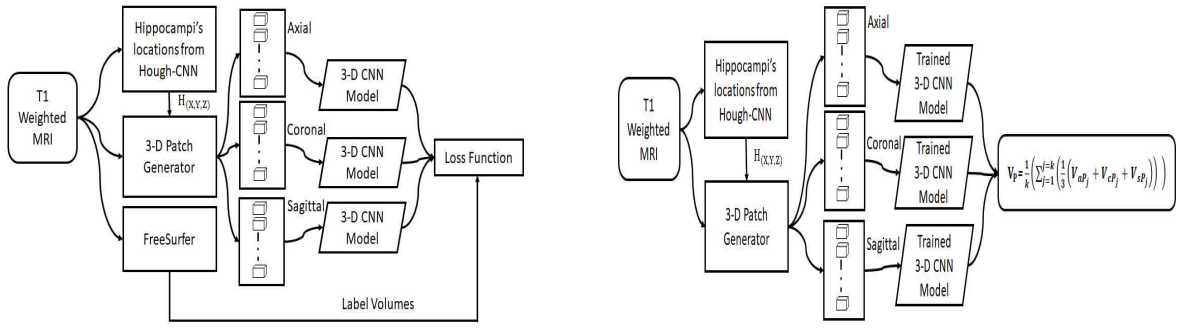

(a) (b)

Fig. 1. Soft segmented pure volume measurement network pipeline for training and testing is shown in above figures. (a) T1-weighted MRI scans were fed into the trained two-stage ensemble Hough-CNN to locate the left and right hippocampi and then to the 3-D patch generator to extract 3-D patches. The preprocessed 3-D axial, coronal and sagittal patches were used to trained the models. The same MRI scans were analyzed using FreeSurfer to measure the volumes. The measured volume was used as the ground truth during the models' training. The axial, coronal and sagittal models were trained separately. For simplicity, one loss function was drawn in the above figure. (b) In the test phase, extracted 3-D patches were fed into the trained ensemble model. The ensemble model predicts the volumes which were further processed and compared with the ground truth volumes.

Resonance Imaging (MRI) data.

FreeSurfer is a software package to analyze and visualize the structural and functional MRI data from cross sectional/longitudinal studies. FreeSurfer offers a full processing stream for both types of data (structural and functional MRI data), which includes skull stripping, B1 bias field correction, gray and white matter segmentation, labeling of regions of cortical and sub-cortical structure, statistical analysis as well as analysis on the cortical surface data and so on. We have used FreeSurfer (version 6.0) to measure ground truth volumes for our proposed model's training, validation and testing. FreeSurfer using recon-all pipeline with additional flags to measure the hippocampal volumes analyzed the Gwangju Alzheimer's and Related Dementia (GARD) cohort data set. This version of FreeSurfer [6,10] has auxiliary facilities to estimate the hippocampal subfields volumes as well.

Deep learning-based approaches are contributing widely in various fields, such as agriculture, medical imaging, traffic detection, automobiles and so on. The convolutional neural network (CNN) [12-13] is mainly used in an image-based study. In medical imaging, 2-D and 3-D image data are analyzed using CNN to detect abnormalities, localize an exact position of any specific ROI, segment the ROIs and measure the volumes and thickness of ROIs as well as classify the abnormal and normal growth of tissue/cell in any specific ROI.

An ensemble model of 3-D convolutional neural network has been proposed to measure the hippocampal volume in one-step in this research work. The proposed model uses a two-stage ensemble Hough-CNN [14] predicted hippocampal voxel location to extract 3-D patches to estimate the left and right hippocampi's volumes from an MRI scan. The 3-D patches centers were selected uniformly, which covered 8x8x8 cubic regions from the two-stage ensemble Hough-CNN localized hippocampal voxel position.

1. Contribution

We proposed a novel technique to estimate the volume from 3-D MRI data in a single step. This proposed method does not generate any mask images, which means that this method directly leads to a straight forward floating numbers of a ROI's volume and discard the unnecessary post processing of the mask image. Dependency on mask generation is common for atlas-based methods as well as other deep learning-based methods. Our method comparatively takes less time (5 seconds only) to infer the volume. The proposed 3-D CNN network is designed with a very few numbers of parameters to reduce the model complexities and training time.

Table 1. The network architectures used to measure the left and right hippocampi's pure volume

[1]Model Name	Network Architecture	Activation Function	Batch Normalization	Optimizer
LH	$I_{32x32}, C^{8}_{3x3x3}, C^{16}_{3x3x3}, P^{m}_{2x2x2}, C^{32}_{3x3x3}, P^{m}_{2x2x2}, C^{128}_{3x3x3}, F^{128}, F^{64}, F^{1}$	ReLU	All Layers	Adam
RH	$I_{32x32}, C^{8}_{3x3x3}, C^{16}_{3x3x3}, P^{m}_{2x2x2}, C^{32}_{3x3x3}, P^{m}_{2x2x2}, C^{128}_{3x3x3}, F^{128}, F^{64}, F^{1}$	ReLU	All Layers	Adam

$I_{sample\ size}$ = Network input, $C^{\#filter}_{kernel\ size}$ = Convolutional layer, $P^{m}_{2} = Max\ Pooling$ with stride 2, $F^{\#filter}$ = Fully connected layer.

II. RELATED WORK

Several research initiatives [1,8,15-18] are being conducted on different regions of brain for various neurological developments and dysfunction. Aging, accidental damage, combat-related post-traumatic stress and mental pressure can cause neurological disabilities, which can lead to different form of dementia, such as Alzheimer's disease and Epilepsy [3]. In addition, various types of neurodevelopment, such as memory development on early age of infant are being analyzed based on different biomarkers [1]. The correlation of these disorders and the neurodevelopment with the hippocampal volume were studied thoroughly by the number of research groups [1,8,15]. On the other hand, the brain regions were segmented and the volumes were measured by other groups of researchers [9,18-19].

The most popularly used method to segment the brain regions from MRI is atlas-based method [6, 10-11,15,20]. The cerebral substructure volumes were measured and the cerebral cortex were segmented in [15]. The structural changes of hippocampal volume, thickness and shape are being analyzed by the neuroscience researchers to find the causes of normal aging and disorders. The imaging properties of brain tissue can alter because of these changes. In addition, these changes also can alter the morphometric properties of the subcortical structures. The concentrated study on hippocampus was carried out by [8,10,16-19] to find the possible causes for neurodegenerative disorder and normal aging. On the other hand, a discriminant method was proposed by aggregating an Adaboost classifier to effectively classify the cognitive states from fMRI data in [21].

Different network architectures and methods [22-25] have been proposed to perform classification, detection, localization, segmentation and super-resolution in medical and non-medical fields using Hough-forest, machine learning and deep learning. Deep learning-based approaches are being investigated to estimate the hippocampal volumes as well as the neurological development. A group of researchers [1] developed a CNN-based brain network to analyze the cognitive and motor development of infant's brain. A 3-D patch-based end-to-end learning approach has been proposed by Christian Wachinger et al., [25] to segment and classify 26 ROIs from MRI data. This model simultaneously learns a multiclass classification and an abstract feature extraction. This complicated operation is performed using two hierarchical networks where one network separates the foreground from background and second network identifies 26 ROIs from foreground. Similarly, 26 ROIs from MRI and Ultrasound images were automatically localized and segmented using Hough-CNN proposed by F. Melliti et al., in [26]. A 3-D CNN-based architecture [9] has been proposed to segment the subcortical regions from brain MRI scan. On the other hand, a two-phase colonial walk-based approach [27] has been proposed to detect 8 anatomical land marks from CT scans.

An ensemble-based deep learning model has been proposed to localize the left and right hippocampus in [14]. A simplified U-shape network architecture [28-29] has been proposed to segment the 2-D

[1] LH and RH stand for the left and right hippocampal model, respectively and they have dropout layer after first fully connected layer (25%) and second fully connected layer (35%).

Table 2. Network Architecture for Localization Models.

[2]Model Name	Network Architecture		Activation Function	Batch Normalization	Optimizer
GH-CNN	GMlh	$I_{32}, C_3^{16}, C_3^{32}, P_2^m, C_3^{64}, P_2^m, C_3^{128}, P_2^m, C_3^{256}, C_3^{512} F^{512}, F^{128}, F^3$	ReLU	All Layers	Adam
	GMrh	$I_{32}, C_3^{16}, C_3^{32}, P_2^m, C_3^{64}, P_2^m, C_3^{128}, P_2^m, C_3^{256}, C_3^{512} F^{512}, F^{128}, F^3$			
LH-CNN	LMlh	$I_{32}, C_3^{16}, C_3^{32}, P_2^m, C_3^{64}, P_2^m, C_3^{128}, P_2^m, C_3^{256}, C_3^{512} F^{512}, F^{128}, F^3$	ReLU	All Layers	Adam
	LMrh	$I_{32}, C_3^{16}, C_3^{32}, P_2^m, C_3^{64}, P_2^m, C_3^{128}, P_2^m, C_3^{256}, C_3^{512} F^{512}, F^{128}, F^3$			

$I_{sample\ size}$ = Network input, $C_{kernel\ size}^{\#filter}$ = Convolutional layer, $P_2^m = Max\ Pooling$ with stride 2, $F^{\#filter}$ = Fully connected layer.

and 3-D medical images. A novel 3-D CNN-based model [30] was proposed to diagnose Alzheimer's disease from rs-fMRI. Similarly, a 3-D CNN architecture [31] was constructed to evaluate the functional decline in Alzheimer's dementia from rs-fMRI measurements.

We have organized this research work in the following manner. In section III, we explained the methodology, network architecture, and loss function and localization procedures. In the following section, we described the dataset, soft-segmented pure volume measurement procedures, error calculation process and provided an overview about the proposed method with its limitation. We summarized this research work in section V.

III. PROPOSED METHOD

If a 3-D image patch contains the complete hippocampal volume and it is possible to quantitatively estimate the volume externally, then 3-D CNN can extract appropriate features automatically using the 3-D images patches and the numerical values of the volumes to train a model that can later be used to predict volumes for new 3-D image data. Furthermore, the voxels attributed to hippocampus are the target voxels, where the overlapping voxels in the boundary region can simultaneously represent the neighbor ROIs that must need to be separated to accurately measure the volume. CNN is good at extracting automatic features from input image. The overlapping neighbor voxels' issue can be resolved using the strength of CNN. Therefore, to measure the pure volume from MRI data in one-step, an ensemble model of 3-D CNN has been constructed. The 3-D patches were extracted from the MRI scans by locating the left and right hippocampi with the help of two-stage ensemble Hough-CNN [14]. Using 3-D patches,

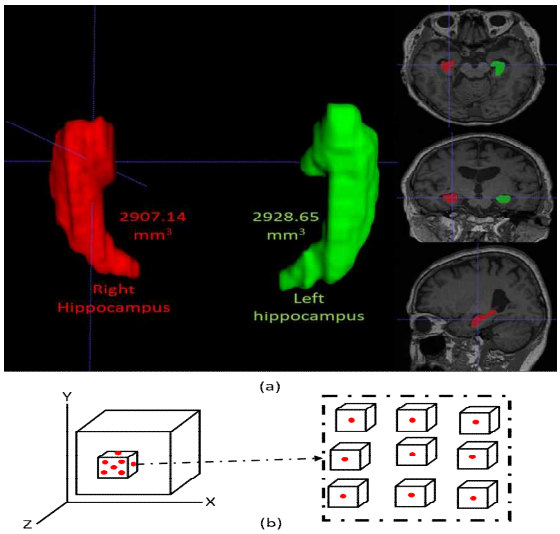

Fig. 2. (a) The voxel location determined by the two-stage ensemble Hough-CNN in the axial, coronal and sagittal views and 3-D visualization of left and right hippocampi of an MRI scan with their respective volumes are displayed above. (b) The 3-d patch extraction process is shown, where red dot denotes as the patches' centers.

the 3-D CNN models were trained and the trained models were used to construct the ensemble model. In the test phase, the preprocessed 3-D patches were fed to the ensemble 3-D CNN model to predict the volumes.

[2] GH-CNN and LH-CNN stand for global Hough-CNN and local Hough-CNN, respectively. GM and LM stand for global model and local model, where the subscript rh and lh stand for left and right hippocampus, respectively.

1. Patch Generation and Ground Truth Preparation

From 326 MRI scans of GARD dataset, 325 MRI scans were used in this study. Using patient identification number, the MRI scans were separated into training (195), validation (65) and testing (65) sets. The 3-D patches were extracted from the vicinity of the hippocampus. The left and right Hippocampi were localized using a two-stage ensemble Hough-CNN model [14] from MRI scans. Using the localized voxel position, the 8x8x8 cubic region was selected to extract 3-D patches with a dimension of 96x96x96. The 3-D patches were resized into a dimension of 32x32x32. The patches were then separated to the axial, coronal and sagittal slices. The slices were normalized using mean of zero and the standard deviation of one. Then, the randomly selected axial, coronal and sagittal patch slices were rotated by a θ-degree angle and reconstructed back into 3-D patches of the axial, coronal and sagittal views. These preprocessed patches were used to train three different 3-D CNN models. The ground truth volumes were prepared by FreeSurfer using original T1-weighted MRI scans. 3-D CNN models were trained against the ground truth volumes. The representative localization of the hippocampus with patch extraction process as well as the respective volumes are shown in Fig. 2.

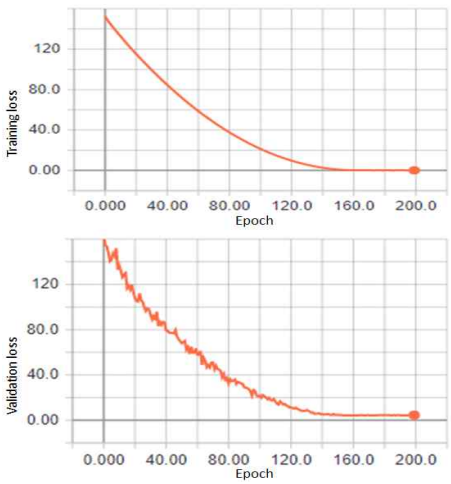

Fig. 3. Training and validation loss curves. The representative loss curve is shown in above for the axial model of the left hippocampus. The models were trained with 200 epochs.

2. Network Architecture

The ensemble model was constructed using three 3-D CNN models. Each model has the same numbers of convolutional layers with a predefined kernel size. The constructed each model has four convolutional layers and three fully connected layers. First and third convolutional layers have 3x3x3 kernel whereas second and fourth convolutional layers have 5x5x5 kernel. The number of filters were different in different layers. The convolution layers are followed by a batch normalization layer [32] and a ReLU activation function [33]. A max-pooling layer was added after second and third convolutional layers. The fully connected layers were also followed by a batch normalization and ReLU activation function except for the last fully connected layer. Only a batch normalization layer was concatenated with the last fully connected layer.

Adam [34] optimizer was used with its default parameters setting with one modification. We have changed the learning rate to 1e-4. Adam is an optimization algorithm, which can be used in place of classical stochastic gradient descent algorithm to update the weights iteratively based on training data. Adam simultaneously uses the benefits of AdaGrad and RMSProp and it offers many facilities, such as it is computationally efficient, required less memory, appropriate for very noisy/sparse gradient and so on. However, the proposed network parameter detail is shown in table 1.

3. Loss Function

The mean squared error (MSE) was used to observe the training progress. If the measured volumes by the FreeSurfer and the proposed method are (V_{af}, V_{cf}, V_{sf}) and (V_{ap}, V_{cp}, V_{sp}) respectively, then the loss function can be expressed in the following way.

$$MSE_{Pure\,Volume} = \frac{1}{k*n}\left(\sum_{j=1}^{j=k*n}\frac{1}{3}\left(\begin{array}{l}\left(V_{af_j}-V_{ap_j}\right)^2\\+\left(V_{cf_j}-V_{cp_j}\right)^2\\+\left(V_{sf_j}-V_{sp_j}\right)^2\end{array}\right)\right) \quad (1)$$

Here, n is the number of samples used in the training process and k is the number of 3-Dpatches extracted from each sample MRI scan. The representative training and validation loss curves for the axial view of the left hippocampus are shown in fig. 3.

Table 3. Five Lowest errors for left hippocampus.

Measured Volume (mm^3) -FreeSurfer	Measured Volume (mm^3) -Our Method	Absolute Error %	Average Error %± STD
3638.3	3587.4	1.4	11.7±8.8
3755.0	3685.0	1.9	
4004.6	3924.9	2.0	
3799.6	3721.2	2.1	
3386.0	3467.5	2.4	

Table 4. Five Lowest errors for right hippocampus.

Measured Volume (mm^3) - FreeSurfer	Measured Volume (mm^3) -Our Method	Absolute Error %	Average Error %± STD
3805.7	3802.0	0.1	12.5±12.8
3966.6	3973.5	0.2	
4188.7	4171.7	0.4	
3728.8	3747.9	0.5	
3970.9	3997.2	0.7	

4. Hough-CNN

Hough-CNN learns the displacement vectors between the target location to the center of the patches extracted from a large image slice of an MRI scan. Uniformly distributed random points inside the MRI scans are used to extract patches to train the Hough-CNN model and the train model predicts the displacement vectors, which are added with the randomly generated points, where the resultants ultimately point to the target hippocampal location. Therefore, we have constructed two pairs of Hough-CNN model to locate accurately the left and right hippocampi by following [14].

5. Localization

Accurate localization of the target ROI is crucially important in the volume measurement process. We designed a two-stage ensemble Hough-CNN model similar to [14] with one modification. The global and local models were constructed with the similar number of convolutional and fully connected blocks. For both stage, we used only one model. The numbers of filters used in different layers are different but the numbers of filters are same in between global and local models. We constructed two sets of models to estimate the voxel location two sets of models to estimate the voxel location of left and right hippocampi. After each convolutional layer and fully connected layer, a batch normalization layer [32] and a ReLU [33] activation function was concatenated to build the 2-D CNN model except last fully connected layer. The last fully connected layer had only batch normalization layer. Adam [34] optimizer with default parameters setting was used to train the global and local models. Mean squared error is considered as loss function to observe the training process. In the test phase, the trained global and local models were amalgamated to estimate the hippocampus location. The estimated voxel location of the left and right hippocampi were used in the ensemble model to extract the 3-D patches where each patch contains complete hippocampal volume. The parameter detail of the two-stage ensemble Hough-CNN network is shown in table 2.

IV. EXPERIMENTAL RESULTS

1. Dataset

The Gwangju Alzheimer's and Related Dementia (GARD) cohort dataset was used in this study. The dataset consists of 326 MRI scans of 326 patients and it is divided into four classes: (a) Asymptomatic Alzheimer's Disease (aAD) (35) (b) Mild Alzheimer's Disease (mAD) (39) (c) Alzheimer's Disease Dementia (ADD) (81) (d) normal control (NC) (171). All MRI scans are T1-weighted and most of the MRI scans have the dimension of 320x212x240 with a voxel size of 0.512 mm^3. The range of patient age was from 49 to 87 years, where the average age was 70.0184 ± 6.074 (avg. age ± STD).

2. Pure Volume Measurement Procedures

If from each MRI scan k number of 3-D patches were extracted for the axial, coronal and sagittal views, where each 3-D patch contains the complete hippocampal volume, then one-step

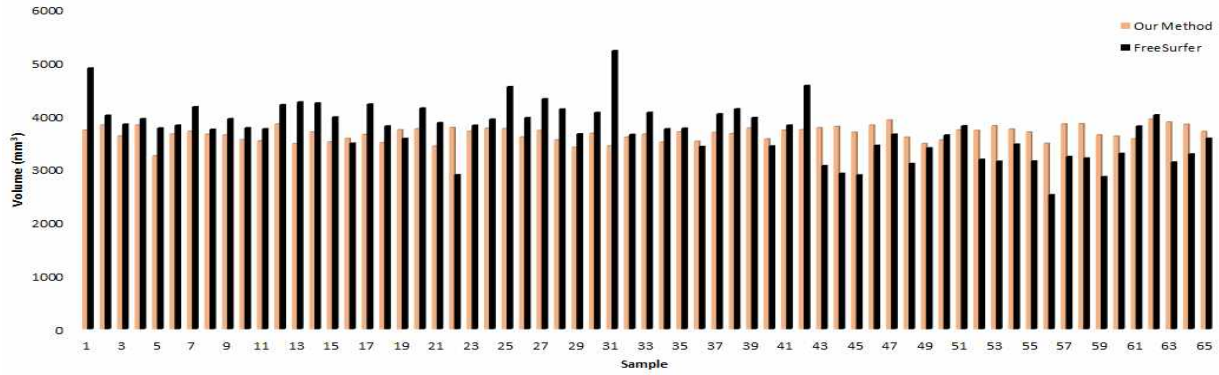

Fig. 4. Graphical representation of the estimated volume differences between our method and FreeSurfer. This bar graph represents the comparative estimation of the left hippocampal volumes of 65 test samples by the proposed method against the FreeSurfer.

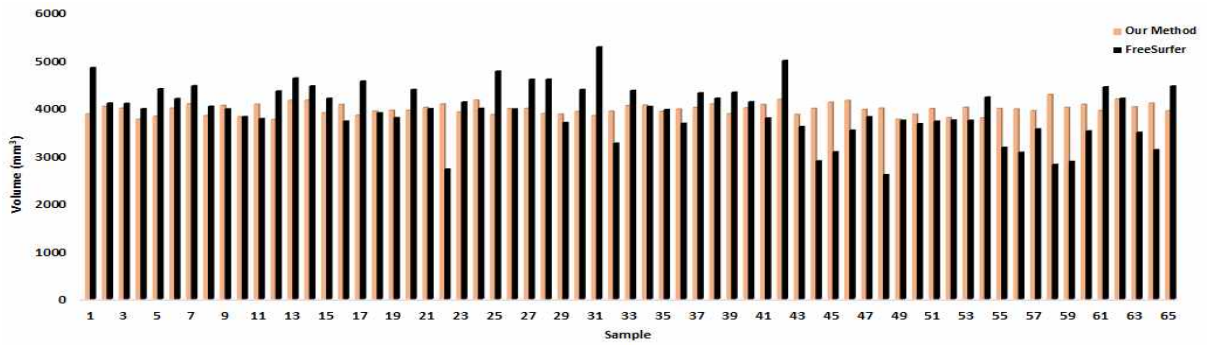

Fig. 5. Graphical representation of the estimated volume differences between our method and FreeSurfer. This bar graph illustrates the comparative estimation of the right hippocampal volumes of 65 test samples by the proposed method against the FreeSurfer.

predicted pure volume by the ensemble model can be expressed in the following way

$$V_p = \frac{1}{k}\left(\sum_{j=1}^{j=k}\left(\frac{1}{3}\left(V_{ap_j} + V_{cp_j} + V_{sp_j}\right)\right)\right) \quad (2)$$

Here, V_{ap}, V_{cp}, and V_{sp} are the predicted volumes of 3−D patches extracted from the axial, coronal and sagittal views. Moreover, V_p is the estimated pure volume by the ensemble model. The measured volumes for 65 test MRI scans by our method and FreeSurfer is reported using bar graph in fig. 4 and fig. 5.

3. Error Calculation

If V_p and V_f are the measured volume by our method and FreeSurfer, respectively, then the absolute error can be calculated using following expression.

$$E_{pv} = |V_f - V_p| \quad (3)$$

Here, E_{pv} is the absolute error. Next, we can express the error in percentage in the following manner.

$$E_{\%} = \left(\left(\frac{E_{pv}}{V_f}\right) * 100\right) \quad (4)$$

Here, $E_{\%}$ is the percentage error. The model performance can be verified through its percentage error. The average percentage errors for 65 test MRI scans of the left and right hippocampi are shown in tables 3 and 4.

We have conducted the training, validation, and testing on a HP workstation Intel Xeon Processor (3.10 GHz) with INVIDIA Quadro MD4000 GPU (8GB) along with 32GB RAM.

4. Discussion

Alzheimer's disease affected patients show a significant amount of hippocampal volume reduction by brain imaging, such as in MRI scan [35]. The proposed approach of an ensemble model of 3−D CNN is a promising alternative to the atlas−based method. The trained ensemble model of 3−D CNN is used to measure the hippocampal soft−segmented pure volumes. The preprocessed

3-D patches were fed to trained CNN models to predict the soft-segmented hippocampal pure volume. The motivation of this research work was to develop a deep learning model to estimate the soft-segmented pure volume and compared it with the atlas-based method, such as FreeSurfer to validate the proposed approach as a proxy. FreeSurfer estimates the pure volume in the soft segmentation period [36].

The hippocampal volume atrophy is one of the most significant biomarkers for Alzheimer's disease diagnosis, where one-step measurement can effectively reduce the diagnosis time and deliver on-site report of the volume. The proposed method estimates 88.3% and 87.5% accurate volumes for the left and right hippocampi, respectively.

5. Limitations

Although the proposed approach estimates the pure volume comparatively with a low error rate, however, it is required to observe the same cases against the manually measured volume. In addition, the inter-class imbalance problem as well as proper data distribution from different classes to the training, validation and testing sets need to be resolved.

V. CONCLUSION

In this research work, we propose an ensemble model of 3-D CNN to estimate the soft-segmented pure volume of the left and right hippocampi from MRI scan. Using our proposed method, we have reported the pure volumes for 65 test MRI scans. The measured pure volumes are compared with the ground truth volume to estimate the error in percentage. The estimated errors for the left and right hippocampi are 11.7±8.8 (error% ± STD) and 12.5±12.8 (error% ± STD), respectively. The quantitative studies showed us that the proposed method could be used as a proxy. The model performance can be improved by tuning the hyper parameters and increasing the number of training sample patches as well as distributing the inter-class data properly among the training, validation and testing sets. In our future study, we will study these aspects thoroughly.

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