ARTICLE

ANALYSIS OF SURFACE-BASED MORPHOMETRIC OF HIPPOCAMPAL SUBFIELD VOLUMETRY IN ALZHEIMER'S DISEASE AND MCI

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ABSTRACT

Background: *Changes in Hippocampal subfield volumeof patients with Alzheimer's Disease and Mild Cognitive Impairment from structural Magnetic Resonance Imaging using the techniques like free surfer and FIRST. The Hippocampus is one of the main areas used in neuroimaging studies. Hippocampus is responsible for memory and learning because of which it can be considered as one among the important biomarker for the neuro diseases. Hippocampal subfield even though being an important region for diagnosis of the AD diseases, is not being used in most of the study because of the complexities such as semi-automated segmentation and manual segmentation.* ***Methods:*** *To overcome existing problems we have modeled a novel subfield segmentation pipeline which consists of three stages. Those are Subfield information extraction, hippocampal segmentation and atlas mean surface calculation.* ***Results:*** *Experimental implementation on ADNI dataset it is proved that our model provides high accuracy than the other models comparatively for diagnosing the disease.* ***Conclusions:*** *Our proposed approach successfully analyzed the hippocampus subfield volume from MRI scan for AD and MCI disease.*

KEY WORDS
Hippocampus, subiculum, presubiculum, Magnetic Resonance Imaging (MRI), Alzheimer's disease, pre-processing.

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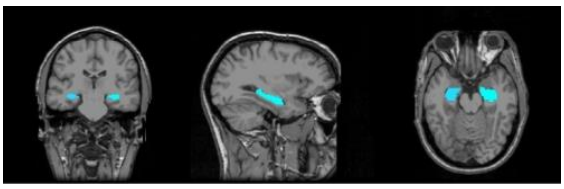
INTRODUCTION

Alzheimer Disease is one among the dreadful disease with has caused 700000 death in the year 2017 and It's estimated that the percentage may increase in the future.This disease effects the elders who are is aged more than 65 years. This disease is not been diagnosed properly it may also be fatal. Huge populations of about 40 million people are being after by this disease. It is also estimated that the growth maybe alarming such that in 2030, the affected populous maybe 76 million and in 2050 it may even nearly double to be 135 million. If this ratio continues nearly 30% of the world's population will be affected by this disease within the year 2080 [1,2].

The study of the hippocampus plays a vital role in the diagnosis of brain-related disorders such as Alzheimer's disease. Hippocampus is the area which summaries the long-term to short-term memory it is also one among the main part which gets affected by the Alzheimer's disease. Hippocampus is mainly used for learning and memory and it can be widely studied using neuroimaging Technologies [3]. Subfield volume grey matter surface deformation and total volume are the measures which are considered for the hippocampus [4].

The subfield hippocampus information is mostly ignored as it is mostly related to the long-term study which is mostly done using semi or manual segmentation [5][6].Itis mostly not suitable for large-scale studies. The subfield scans is still challenging for 1.5T and 3T scans of MRI. The regional volume segmentation and cortical thickness is derived using the freesurfer tool. On using the volume, boundary error exists which makes it hard to analyze the image safe. FIRST is another software which gives good results for the hippocampus segmentation than the freesurfer tool [7][8]. Surface Atlas is constructed using both the freesurfer and the first which identify the hippocampus structural changes and different conditions.



(a) (b) (c)

Fig.1: The Hippocampal area for some relevant blue slice on the (a) coronal view (b) sagittal view (c) axial view for AD subject from MRI scan

The organization of this paper is as follows. Section II focuses on the background of the related works. It presents the technique of subfield volume changes, surface modeling using SPHARM and building a surface atlas in section III. Section IV discusses experimental and results of AD/MCI. Section V concludes the paper.

RELATED WORKS

The ADNI dataset is a 3D sMR image which comprises of the complete brain's structure. In the surface based morphometric analysis features the complete surface brain is considered for feature extraction. Various analyzing techniques and machine learning algorithms have been used along with these features for diagnosing the AD.Many clinical data is reorderedonly for few diseases such as Alzheimer's disease (AD), mild cognitive impairment (MCI),

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depression, schizophrenia and many other neurological disorders based on hippocampal subfield can be analyzed. By combining hippocampal subfield with clinical data high accuracy could be achieved. Many weighted MRI scans are used to identifying the AD and MCI such as T1,T2, 1.5T, 3T, 4T and 7T. Hippocampal subfield analysis is done based on age, gender, subfield volume, education, cognitive functions, cortical sub regions and diseases. In this work, ADNI dataset has been used for classification of AD and MCI. This work has been compared with the existing work that uses cortical features and has achieved good accuracy. There are many classifier approaches for the AD and MCI patients using various hippocampal subfield volumes exists for different subjects(aMCI, HC, AD, MCI and LMCI) using different metrics (1.5, 3T and 7T) and different weighted MR images(T1, T2)[9-16,3]

Table -1: Classifier approach of the AD and MCI patients using different subfield volume

Author & year	Subfield Volume	Datasets	Metrics	Results
Dong woo kang et al.2018[9]	Education, Cognitive functions	77 subjects(aMCI-38,HC-39)	3T scan	Education years (hc&aMCI) Std.β=0.74,p-value<0.001,aMCI=Std.β=0.3,aMCI=0.041
Fabian Bartel et al.2016[10]	Regional volume & Outline Reproducibility, cube algorithm	ADNI 80 subjects:HC-20,MCI-40, AD-20	T1 weighted MRI scans	Region Method (Manual: anterior-0.794, Middle-0.828, Posterior-0.756) FSL-FIRST: anterior-0.829, Middle-0.855, Posterior-0.798, Freesurfer: anterior -0.756, Middle-0.784, Posterior-0.721.
Paul .A.Yushkevich et al. 2015[11]	Cortical subregions& hippocampal subfields.	83 aMCI subjects.	T2 weighted MRI scans	Corrective learning from left part Mean-0.780, SD-0.027, Min-0.701, Max-0.853 and right part Mean- 0.777, SD-0.034, Min-0.689, Max-0.847
Stine K. Krogsrud et al.2014[12]	Hippocampal subfield regions age from 4 to 22 years	244 healthy subjects.	1.5T MRI scans. Validation(1.5 T & 3T MRI scans	-
Renaud la joie et al.2013[13]	Subfield volume(Complementary analyses, operating characteristic analyses and Non-parametric group comparisons)	ADNI 75 subjects:HC-40,aMCI-17, AD-18	-	ROC curve = 0.88 and 0.76,p=0.05
Laura E.M. et al.2013[14]	Linear regression and continuous independent variable	ADNI 54 patients with HC-29,aMCI-16, AD-9	7T MRI scan(ultra high speed0.7mm^3)	Linear regression: ERC(CI=-0.07,B=-0.04) SUB(CI=-0.16,B=-0.04)
John Pulta, P. Yushkevich et al.2012 [15]	Template- based approach	Subjects 45: 28 Normal control,17 aMCI,	T2 weighted images	Hippocampal volume CA1 left p=0.001 right p=0.038,CA4/DG left p=0.002 right p=0.043. Reduced volume CA4/DG left p=0.029 right p=0.221.
Li shen et al. 2010[16]	Intraclass and Pearson correlations calculated and statistical analysis.	125 adult subjects with HC-38, aMCI=37, AD=11.	T1 weighted MRI scans	Freesurfer(p=0.004) manual method(p=0.428)range from 0.76-0.90. ICC range from 0.75-0.89.
SG Muller et al. 2011[3]	Stepwise regression analysis Pearson correlations.	50 elder subjects 25 NC, 25 AD.	4T MRI scans	ERC=IFRD-0.17, SFRD-0.29, DRD-0.20, Sub= IFRD-0.26, SFRD-0.31, DRD-0.22, CA1= IFRD-0.31, SFRD-0.41, DRD-0.41,CA1-2= IFRD-0.12, SFRD-0.16, DRD-0.15, CA3&DG= IFRD-0.35, SFRD-0.38, DRD-0.35.

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From the above survey, we could infer that various surface-based analysis techniques are used for hippocampal analysis and hippocampal subfield volume segmentation. Most of the researchers use high dimensional scanned features which have increased the cost of memory and data redundancy. It's noted that subfield volume is high. But Segmentation of hippocampal subfield volume is analyzed and surface atlas of hippocampal subfield is built to reduce the data, high accuracy and memory usage to a far extent. Thus surface atlas is deployed along with the freesurfer and FIRST and their respective accuracies are being analyzed.

SUBJECTS AND METHODS

We have used a three-stage pipeline model. (a) From MRI scan Subfield information is extracted using freesurfer, (b)hippocampus segmentation is done using the FIRST, and (c) spherical harmonic basis functions is used for hippocampus surface modeling and calculating the mean surface [17]. Using the above three methods the surface Atlas is created for the hippocampal subfield using normal control people from the ADNI dataset.

Adni Neuroimaging Data

MRI image data set is downloaded from theAlzheimer's disease [18] Neuroimaging Initiative database (ADNI) (http://adni.loni.usc.edu/). ADNI website which also comprises the Magnetic resonance imaging,PET image datasets, SPECT, CSF, blood biomarkers combined with clinical assessment to improve the ad process. Adni database has images of three different stages in the Alzheimers disease [19]. From this database, the data can be downloaded where this database also monitors the regular research works done. Consist of totally 800 subjects which have been divided into subjects with early AD early or late MCI and normal control based on the age which must be within the range55 to 90. The primary goal of the adni is to improve the ad progress using these biomarkers[18]. The proposed work we use the MRI images. The MRI image is primarily classified into a fMRI and a sMRI where we utilize the sMRI images.

Analysis datasets

The baseline MR images downloaded from the ADNI (adni.loni.usc.edu) site using 1.5T and 3T scanners with the help of DICOM. This downloaded MR images incorporate with Mini-Mental State Examination (*MMSE*) score and Clinical Dementia Rating Scale(*CDR*) (or *CDR* = 0) for each and every subjects. The given subjects are primarily classified into three categories such as HC, MCI and AD based on the age which must be within the range55 to 90. We organize the dataset consisting of 687 subjects as follows.

1. 172 HC subjects: 93 male and 79 female; age SD=75.3±7.4 years, range = 55 -90; Mini-Mental State Examination(MMSE)=29.±1.2; the range= 25 -30.
2. 407 MCI subjects: early MCI 267 patients not converted into AD with 18 months(EMCI) and late MCI 140 (LMCI) patients who changed over to AD ; 212 male and 195 female; age ± SD=75.3±7 years, range 58-88 years; Mini-Mental State Examination (MMSE)=27.1±1.7; the range from = 24 - 30
3. 108 AD subjects: 65 male and 43 female; age SD=75.3±7.4 years, range = 55 -90; Mini-Mental State Examination(MMSE)=23.8±2; the range = 18 – 27.

Structural MRI analysis

Surface-BasedAnalysis is a method where the Cortical surface's geometrical model is used to derive the morpho metric measures. Among the numerous implementation of SBA we primary use free surfer brain visa and brain voyager. Taking the input as T1 weighted MRI image the SBA extracts cortical surface. Coronal surface displays two surfaces which are the Yellow line and the red line. Yellow line depicted as the inner boundary of the cortex which can also be called as a white surface. The Yellow line which acts as a surface boundary lies in between of the cortical grey matter and white matter. Whereas the Red Line boundary lies in between grey matter and CSF which can also be termed as pial surface[20]. Cortex is the composition of highly dense Triangles each of which are known as a face is being interconnected as a mesh which is being modeled as a surface model. The junction of each face is called a vertex. The three-dimensional coordinates X,Y and Z which are the parameters are being deducted from the extraction process of MRI. The surface can be subjected to many manipulations among which one is inflating it. All the area or being exposed during the inflation which is equivalent to unfolding the surface. Combining the area of the Triangles we get the cortex's surface area. Cortical thickness is the distance between the white and pial surfaces.

Segmentation of the subfield volume

On doing Hippocampus Subfield segmentation using the free surfer will we concentrate 8 volumes. The 8 volume represented as a probability maps each of which are a subfield all of them are listed below. The subfield volumes are CA1, CA2-3, CA 4-DG, Fimbria, Hippocampal -fissure Parasubiculum, Subiculum and others.

Using the first software hippocampus is split into two parts which are the left and right. Over this processing, the topology fix is then which verifies the spherical property and object connectivity of the hippocampus. All the probability maps are being masked. After the masking area outside the mask is assigned to be zero and there must be no zero values inside the mask for converting the zero values to non-zero values which are present inside the mask the Gaussian kernel is used. The size of the Gaussian kernel is [5 5 5] in our work. Updated values are assigned to the voxel in the hole. Thus we can obtain the updated probability map which is from P1 to P8. These are the next step of input data.

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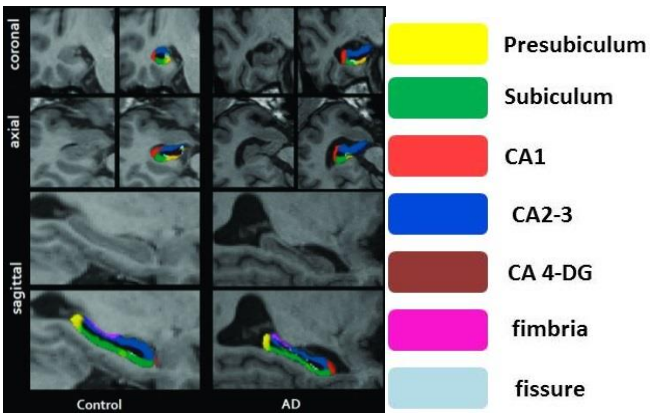

Fig. 2: Hippocampal subfield segmentation from freesurfer: Coronal view, axial view and sagittal view. The left images are healthy control and right images are ad subjects. The abbreviations are CA- Cornu'sammonia;DG-dentate gyrus.

Surface modeling using SPHARM

The binary object can be compared for the diagnosis directly. So we apply the spharm basic function to model the surfaces. This spharm method was developed by La Joie et al [13] to shape the 3D objects. Thus we use the three processing methods are spherical parameterization, expansion and registration. We should perform the bijective mapping between spherical coordinates and surface. The coordinates represented as ø and θ and surface point represented as V.

$V(\theta,\phi)=(x(\theta,\phi), y(\theta,\phi), z(\theta,\phi))^T$TheFourier transform is this used the preprocessing to define the three-dimensional surface from the three spherical functions[21]. Three spherical functions are transferred to three sets of Fourier coefficients. The hippocampal surface is expanded and registered.

Building surface atlas of hippocampal subfield mapping

Using the freesurfer we segmented 8 subfield volumes: The subfield volumes are CA1, CA2-3, CA 4-DG, Fimbria, Hippocampal -fissure Parasubiculum, Subiculum and others. This subfield segmentation on the basis of the Bayesian approach.Each 8 volume represented as a probability maps. Then we employ the spharm basic function to model the surfaces.

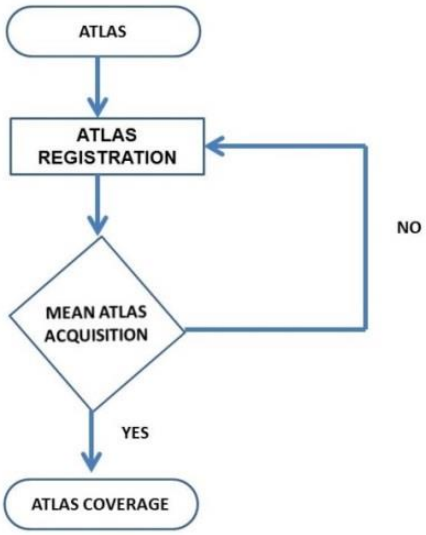

Fig.3: The flowchart for creating a surface atlas of the subfield.

Our example is as follows: atlases is the starting point of the surface, then register the atlas for aligning, then mean atlas acquisition for all the data. Then repeat atlas registration until the stopping point of the coverage of the atlas.

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RESULTS

Shown in [Fig. 1] is the hippocampal area from the brain images from different view,(coronal view, sagittal view and axial view) for ad patients from MR images. And [Fig. 2] displays the five hippocampal subfield segmentation with atlas color mapped. [Fig. 3] shows the process of creating a surface atlas of the subfield. Below we briefly discuss about the three categories, which is age and gender for surface signals. In this experiment, we have used a three-stage pipeline model. MRI scan Subfield information is extracted, hippocampus segmentation and spherical harmonic basis functions is used for hippocampus surface modeling and calculating the mean surface.

Table 2 shows the surface vertices for five various analyses obtained from adnidatasets such as CA1, CA2-3, CA4-DG, SUB and Tail. Below table, we briefly discussed about three categories from original surface signals.(I) EMCI vsHC. There was no change in both regions and entire surface. (II) LMCI vs HC :some changes in these atrophy patterns .the pattern of the tail is 26%,SUB is 43%, CA4-DG is 30%, CA2-3 is 33%, and CA1 is 28.(III)AD vs HC shows changes atrophy pattern in of tail is 52%, SUB is 56% , CA4-DG is 32%, CA2-3 is 31% and CA1 is 90%, while subiculum is the top most region and important regions at both AD stages and LMCI stages. Age is affected 39% of CA1, 83% OF subiculum, 39% of CA2-3, and 38% of CA4-DG and tail affected 50- 57%. The entire pattern was same diagnostic method of AD stages and LMCI stages. Regarding the gender, 45-60% of CAI and Tail part, 13-15% of CA2-3, Subiculum was affected is 13-15%, and finally CA4-DG is affected 5%.

DISCUSSION

In this approach, we have presented the analysis ofsurface-based morphometric of hippocampal subfield volumetry in Alzheimer's Disease and MCI. We also used 1.5T and 3Tscans to segment the hippocampal volume and we have identified that early stages of AD and compared with the mid-term stages of MCI patients. The major three strength follows in this apprach (1) we analyzed subfield of hippocampal size (2) most important and hippocampal subfield information (3)and MR image scans with weighted images from ADNI datasets for our proposed approach. We have identified the most dominant region like subiculum and pre-subiculum. The SUB part merged into SUBICULUM and PRE-SUBICULUM, Which is a top region of AD stages and LMCI stages, after controlling the gender and age of AD patients. But the remaining region of CA4-DG and CA1 is the prudent atrophy at the LMCI stage and serious atrophy at the stage of AD. Within this control DG-CA4 and CA1 automatically reduced with increasing the age of AD patients. Volume loss of CA1 and pre-subiculum and subiculum patients in AD has been noted[22][23].another sub region of volume loss of CA4 & DG patients in AD has been noted[24][25]. And volume loss of CA3 region not yet reported till now. Moreover some hippocampal region has been combined together and reported some vivo studies For example CA3, DG & CA2. In our approach we separately identified both CA4 and CA3&DG.

The proposed surface-based analysis shows better accuracy and better diagnosis of the patients with AD and MCI diseases compared to the existing method.

Table 2: FIVE different subfield information and their analysis for existing and proposed method. **(**The SUB part merged into SUBICULUM and PRE- SUBICULUM.)

	Hemisphere		Left					Right				
Existing Method	Hippocampal subfields		CA1	CA2-3	CA4-DG	SUB	Tail	CA1	CA2-3	CA4-DG	SUB	Tail
	Number of vertices		389	728	91	956	398	362	735	119	941	405
	Regions	EMCI vs HC	0	0	0	0	0	0	0	0	0	0
		LMCI vs HC	135	236	33	550	89	151	210	35	494	112
		AD vs HC	195	346	52	803	223	307	365	110	762	193
Proposed Method	Hippocampal subfields		CA1	CA2-3	CA4-DG	SUB	Tail	CA1	CA2-3	CA4-DG	SUB	Tail
	Number of vertices		380	721	92	920	398	340	730	114	932	406
	Regions	EMCI vs HC	0	0	0	0	0	0	0	0	0	0
		LMCI vs HC	130	231	27	440	70	120	210	34	481	110
		AD vs HC	340	325	77	821	221	225	370	28	746	93

CONCLUSION

In this work, the surface atlas is created using free surfer and FIRST from sMRI. We have modeled a novel subfield segmentation pipeline which consists of three stages which are Subfield information extraction from MRI scan, hippocampus subfield segmentation and hippocampus surface modeling. Those are successfully surface based morphometric analyzed the AD disease with health control (HC). For the experiment, we have considered the ADNI dataset that comprises of the proposed approach. Thus it is proved that our model provides high accuracy than the other models comparatively for diagnosing the disease. The future enhancement of our work can be carried out as a robust model that can incorporate 3D hippocampal structure.

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CONFLICT OF INTEREST
None

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FINANCIAL DISCLOSURE
None

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