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S.I. : LOW RESOURCE MACHINE LEARNING ALGORITHMS (LR-MLA)

An evaluation on changes in hippocampus size for cognitively normal, mild cognitive impairment, and Alzheimer's disease patients using fuzzy membership function

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Abstract
Alzheimer's disease (AD) is a neurological disorder where the hippocampus, an essential part of the limbic system in the brain, gets affected severely. The transition from cognitively normal (CN) to AD has one intermittent stage, popularly known as mild cognitive impairment (MCI). Since physical changes in the human brain may occur during aging, sometimes it is challenging to predict dementia stages based on the hippocampus size. To solve this uncertainty, the concept of the fuzzy membership function has been used in this study, where all the data are acquired from the online public dataset "Alzheimer's disease neuroimaging initiative" and found that the average difference in the hippocampus size between CN and MCI is 17.05%, between CN and AD is 31.90%, and between MCI and AD is 18.24%. The average atrophy per year in the hippocampus is 4.62% for AD, 2.33% for MCI, and 1.10% for CN subjects. From the study, it is also observed that, for AD patients, hippocampus atrophy is the highest, and hence they experience the highest memory loss, followed by the MCI and CN patients.

Keywords Alzheimer's disease · Hippocampus · Mild cognitive impairment · Hippocampus atrophy · Brain image segmentation · Magnetic resonance imaging · Cognitively normal

1 Introduction

Alzheimer's disease (AD) AD is a progressive brain disorder caused by the damage of brain cells, which leads to memory loss and a decline of intellectual ability [1]. According to the research report by the National Institute on Aging, about 6 million people from the USA, aged about 60–70, are suffering from AD [2]. AD is ranked as the sixth major cause of death for older people in the USA, which may reach the third rank in the coming years [2]. According to the Alzheimer's and Dementia Resources report, more than 4 million people

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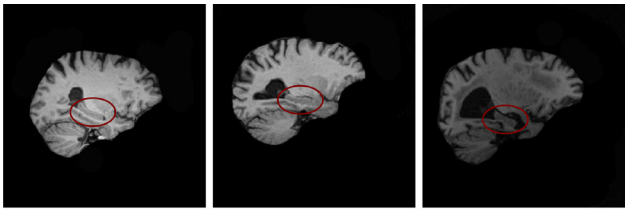

Fig. 1 Sample brain images with hippocampal regions for **a** CN, **b** MCI, **c** AD patients

in India have some form of dementia, including AD. Worldwide, at least 44 million people are living with dementia [3].

Mild cognitive impairment (MCI) MCI is an intermediate stage when a person is considered to be in between CN and AD [4]. Although the symptoms of a person having MCI are not as severe as having AD, they experience memory loss more than normal people of their age [5]. According to the researchers, although all people with MCI may not develop AD, patients with MCI develop AD faster than CN people [6]. According to a research article by Davis et al. [7], the approximate probability of developing AD by the MCI subjects is around 22%.

In most neuropsychiatric disorders, including AD and MCI, the hippocampus is one of the severely affected areas in the brain [8]. Hippocampus is a small, curved, complex structure in the brain that plays a significant role in regulating emotional responses, forming memories and navigation, etc. [9]. Hippocampus is also an essential part of the limbic system, located in the medial region of the temporal lobe [10]. The damage to the hippocampus causes amnesia and is incapable of forming new memories, primarily related to time as well as the location [11, 12]. Sample brain images (without skull) with hippocampal regions for CN, MCI, and AD subjects are shown in Fig. 1.

Although the decay in the hippocampus occurs over the ages, the hippocampal atrophy in AD and MCI is higher than in standard aging [13]. According to a research, the average difference in the hippocampus size between AD and CN patients is 32%, between MCI and CN patients is 19%, and between MCI and AD patients is 15% [14]. According to some other researchers, the average hippocampal atrophy in AD is between 20 and 52% compared to CN patients, and the average hippocampal atrophy in AD is between 16 and 27% compared to the MCI patients [15, 16]. According to research, the atrophy in hippocampus volume is greater in AD subjects, followed by the MCI and then the CN subjects [17]. According to research, the annual atrophy in the hippocampus is 1.4% for CN subjects and 4.6% for AD subjects [18]. According to another literature, the hippocampus atrophy per year for MCI patients is 2.53%, whereas 1.12% for CN patients [19]. Figure 1 shows a sample brain MR image containing the left and right hippocampus for AD, MCI, and CN subjects.

Although many researchers have done similar works, they have not performed the comparison according to the subject's age and gender. In this paper, we have performed the comparison separately for different aged groups for both male and female subjects. The main contributions to this work can be summarized below:

- To evaluate the changes in the hippocampus, a segmentation operation is performed using the MATLAB tool.
- From the segmented region, the number of major and minor pixels are calculated. Using the major and minor axis, an appropriate formula is used to determine the hippocampus area for different subject groups.
- By comparing the hippocampus area of different years, average atrophy (per year) is calculated for different subject groups.
- For better estimation of hippocampus size and atrophy, the concept of Fuzzy Membership Function is utilized.

The rest contents of the article are organized as follows: (a) In Sect. 2, some related works are discussed. (b) In Sect. 3, pre-processing works and the process of hippocampus segmentation are described. (c) A detailed discussion about the results are presented in Sect. 4. (d) In Sect. 5, a concluding remark is explained.

2 Related works

AD causes damage in the hippocampus cells [20]. Many researchers have been doing research on the size as well as the atrophy of the hippocampus in the human brain. A few of the related research works are described below.

Henneman et al. [21] conducted a hippocampal size study with a total number of 64 AD, 44 MCI, and 34 CN subjects. The coronal three-dimensional T1-weighted gradient-echo sequence data are acquired from the 1.0 Tesla (Siemens Magnetom Impact Expert System, Siemens AG, Erlangen, Germany). The authors used the ShowImages 3.7.0 software package for selecting and segmenting the region of interest (ROI). The structural image evaluation, using normalization, of atrophy, cross-sectional (SIENAX), and structural image evaluation, using normalization, of atrophy (SIENA), both are part of FMRIB's Software Library is used to calculate the hippocampal volumetric changes per year. The authors concluded that the hippocampus atrophy for the CN subjects is around 2.2%, for the MCI subjects' atrophy is around 3.8%, and for AD subjects the atrophy is around 4.0%.

Similarly, Seab et al. [22] conducted a hippocampal volumetric study. The authors acquired 10 AD subjects and 7 CN subjects for the study. However, the authors did not mention

any information about the dataset they used. The study was done using the IBM/MIT/LBL 0.5-T NMR imager software. After selecting the ROI, considered the hippocampus as an elliptical shape, and calculated the volume of the ROI over the years. Finally, the authors concluded that an AD patient experiences a loss of around 40% of the hippocampal volume in his/her lifetime than a normal subject.

A similar hippocampal study is done by Liedes et al. [23]. The authors acquired the MRI data from ADNI 1 and the Australian Imaging Biomarkers and Lifestyle flagship study of aging (AIBL) databases. The authors used tensor-based morphometry (TBM), and voxel-based morphometry (VBM) was used to extract the features from the baseline MRI. Hippocampal volume change is determined by observing the changes that occurred in the intensity levels of the hippocampus using the extended boundary shift integral (eBSI) method. According to the authors, the annual atrophy in the hippocampus for the CN subjects is around $(1.17 \pm 1.11)\%$, and for Stable MCI (SMCI) subjects the annual atrophy in the hippocampus is around $(2.47 \pm 2.30)\%$, for Progressive MCI (PMCI) subjects the atrophy in the hippocampus is around $(4.43 \pm 2.36)\%$, and for the AD subjects the annual atrophy in the hippocampus is around $(5.84 \pm 2.97)\%$.

Uysal and Ozturk [24] proposed a novel approach for the classification of AD based on the hippocampus volume. The T1-weighted MRI data are acquired from the ADNI data set. The hippocampal volumetric information is obtained by using a semi-automatic separation software ITK-SNAP. The borders of both the hippocampus are determined and labeled by the software in order to segment it accurately. According to the research, the average size of the left hippocampus in AD is approximately 26% smaller than MCI, and 42% smaller than CN subjects, whereas the average size of the right hippocampus in AD is approximately 24% smaller than MCI, and 39% smaller than CN subjects. The average size of the left hippocampus in MCI is approximately 20% smaller than CN, and the average size of the right hippocampus in MCI is approximately 20% smaller than CN subjects.

A study on hippocampal atrophy in AD, and MCI subjects is conducted by Mueller et al. [25]. For the study, the authors acquired 91 T-2 weighted MR images. From the input images, the ROI (i.e, the hippocampus) is manually selected and segmented by using the FreeSurfer software. multiple-linear-regression (MLR) analyses through the subfields, correspondingly hippocampus volume, as well as the intracranial volume (ICV) as autonomous variables are used for identifying the volumes. According to the authors, the average size of the hippocampus in AD is approximately 10% smaller than MCI, and 16% smaller than CN subjects. The average size of the hippocampus in MCI is approximately 7% smaller than in CN subjects.

A hippocampal study is conducted by Wang et al. [26]. The authors acquired the data from 20 aMCI, 20 AD, and 20 normal control subjects. The authors concluded that there is a significant hippocampal volumetric difference between NC, MCI, and AD subjects. However, the number of subjects (60) for the study is relatively small. Moreover, the authors did not perform any volumetric comparison among the subject groups.

A research on hippocampal size is conducted by Belleville et al. [27]. In that study, they tested the memory of 108 older adults from the Quebec Consortium. After memory analysis, they analyzed the hippocampal sizes. It is concluded from the study that individuals experiencing more memory loss have a smaller hippocampus than patients with less memory loss.

Zhang et al. [28] performed a study on overall brain atrophy for different subjects. By taking brain images as data, the overall size of the brain is analyzed. By analyzing the brain sizes in different age variations, the atrophy is measured. It is revealed that patients with AD have the highest atrophy than normal subjects.

3 Materials and methods

3.1 Pre-processing

Since after the segmentation of 3D MRI, some post-processing steps are required to be performed, which may be time-consuming, most of the researchers prefer to segment the MRI on 2D images [29]. In our work, we converted the 3D MR images to 2D for the particular slice where the hippocampus is located. All the images are resized to 256×256 pixels.

The brain MR images also contain some unwanted pixels, which are also known as the skull [30]. For accurate segmentation of a region in the brain, it is necessary to strip the skull part from the MR images [31, 32]. After comparing the performance of five popular segmentation techniques namely region-growing [33], region splitting and merging [34], K-means algorithm [35], histogram-based algorithm [36], and fuzzy C means [37] for 50 MRI images, it is found that the histogram-based thresholding technique gives the highest accuracy among all these algorithms [38]. Hence, for skull stripping, we have used the histogram-based thresholding technique. Python tool is used for skull stripping. In Fig. 2, a sample input image and the corresponding skull-stripped output image are shown.

3.2 Hippocampus segmentation

Segmentation is an operation to separate the important parts from an object [39]. Segmentation of the hippocampus from the brain is very important in order to study the changes that occur in different neurological disorders like AD, MCI,

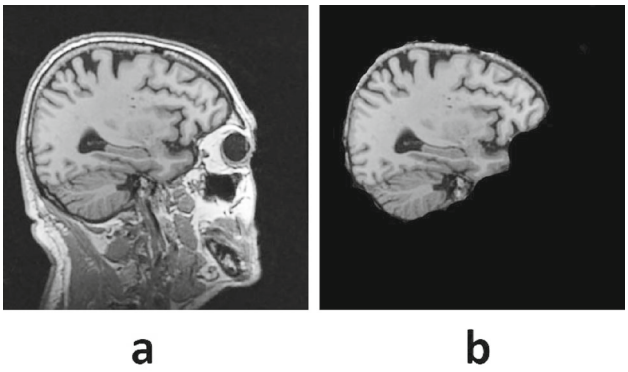

Fig. 2 Sample MRI of **a** input, **b** skull-stripped image

etc. [40]. Although many researchers have proposed different hippocampus segmentation techniques, accurate hippocampus segmentation is still considered as a challenge for the researchers [41]. Matrix Laboratory (MATLAB) is a well-known tool in the area of medical image processing, including the segmentation of medical images [42] (Fig. 3).

For analyzing the hippocampus size for different subject groups, we have segmented the hippocampus using MATLAB tool. All skull-stripped MR images are resized to 256×256 pixels and used as input images. From the input images, the region of interest (ROI), i.e., the hippocampus is selected and segmented automatically by the MATLAB tool as shown in Fig. 6. The shape of the hippocampus can be related to the shape of an ellipse [43]. With the help of a radiologist and 3D-slicer tool, the hippocampal ground-truth images are extracted. Output images are then compared with their corresponding ground-truth images. The segmentation performances are achieved as shown in Table 1.

The next step is to analyze the size of the segmented hippocampus. For hippocampal size analysis, the following algorithm is used:

Step 1 Determine the number of pixels in the major axis of the segmented area, $N1$.

Step 2 Calculate the number of pixels in major radius, $m1 = (N1/2)$.

Step 3 Determine the number of pixels in the minor axis of the segmented area, $N2$.

Step 4 Calculate the number of pixels in minor radius, $m2 = (N2/2)$.

Step 5 Convert the number of pixels in $m1$ and $m2$ to the size in millimeters (mm), by using the following formula:

$$r1 = \left(\frac{25.4}{D}\right) \times m1 \tag{1}$$

$$r2 = \left(\frac{25.4}{D}\right) \times m2 \tag{2}$$

where D = dot per inch (DPI) of the image, which is 96 for all the input images considered in this work.

Step 6 Calculate the approximate area of the segmented region by using the following formula:

$$a = \pi \times r1 \times r2 \tag{3}$$

4 Results and discussion

A total of 2008 numbers of brain MR images for 210 numbers of different subjects are acquired from the ADNI dataset [44]. After segmenting the hippocampus (both left and right), we

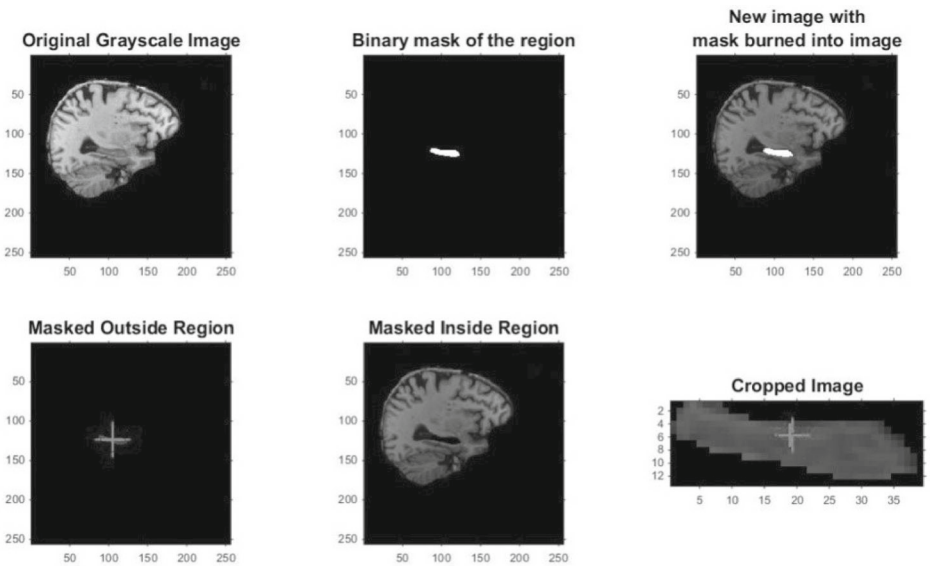

Fig. 3 Segmentation of hippocampus from brain MRI

Table 1 Performance of hippocampus segmentation

Average no. of pixels in confusion matrix		Accuracy	Sensitivity	Specificity	Precision	Dice coefficient (DIC)	Jaccard Index (JI)	Average performance
TP	25,000	0.9872	0.9246	0.9424	0.9090	0.9270	0.8576	0.9118
	2250							
	35,886							
FN	1950							

Table 2 Data distribution

Class	Age group	Gender wise data samples	
		Male: no. of sample images	Female: no. of sample images
CN: (total subjects = 70, male: 35, female: 35)	60–64	57	57
	65–69	58	57
	70–74	56	56
	75–79	55	55
	80–84	55	55
	85–90	55	55
MCI: (total subjects = 70, male: 35, female: 35)	60–64	57	57
	65–69	57	57
	70–74	56	56
	75–79	55	55
	80–84	55	55
	85–90	55	55
AD: (total subjects = 70, male: 35, female: 35)	60–64	57	56
	65–69	56	56
	70–74	56	56
	75–79	55	55
	80–84	55	55
	85–90	55	55

have analyzed the size and the average atrophy for CN, MCI, and AD subjects (male/female) of different aged groups (i.e., 60–64, 65–69, 70–74, 75–79, 80–84, and 85–90 years). Age-wise data distribution is presented in Table 2.

The difference in hippocampus size among CN, MCI, and AD subjects are shown in Tables 3, 4, and 5.

The average atrophy in hippocampus size among CN, MCI, and AD subjects is presented in Tables 6, 7, and 8.

The average hippocampus (left and right) size and the average hippocampal atrophy per year of all the subjects (male and female) are shown graphically in Figs. 4, 5, 6, and 7.

Figures 4 and 5 show how the hippocampus size varies over the ages in CN, MCI, and AD subjects (male and female). We can also observe that for some points in the x-axis (subject's age), the hippocampus size is almost identical or very near to each other.

By following up on the hippocampus size of the same subject for more than two consecutive years, we have analyzed the size of hippocampus loss per year, also known as the hippocampal atrophy rate. The average hippocampal atrophy per year for CN, MCI, and AD subjects is shown graphically in Figs. 6 and 7. Figures 6 and 7 show that the atrophy curve is almost identical for CN, MCI, and AD subjects (male and female) at some points.

From Figs. 4, 5, 6, and 7, it can be concluded that if a subject's age and hippocampus size or hippocampal atrophy per year is known, from the graphs, sometimes it may be a challenge to decide the subject's stage (CN/MCI/AD). Some zones in the graphs are marked by a rectangular shape, making it challenging to determine the subject's dementia stage (CN/MCI/AD). To solve this issue, a fuzzy membership function can be used. From the membership value, the subject's stage can be predicted.

Based on the average hippocampal (left/right) size, three fuzzy sets are created, namely AD, MCI, and CN, for subjects of different aged groups. The combination of triangular and trapezoidal membership functions is used in this study. The

Table 3 Difference in hippocampus size of CN versus MCI subjects

Sex	Age	Difference in hippocampus size of CN versus MCI subjects			Average difference in hippocampus size of CN versus MCI subjects		
		Left (%)	Right (%)	Total (%)	Left (%)	Right (%)	Total (%)
M	60–64	18.48	17.52	18.00	17.27	17.42	17.34
	65–69	23.62	24.79	24.21			
	70–74	21.14	22.12	21.64			
	75–79	13.54	13.45	13.49			
	80–84	11.39	9.76	10.55			
	85–90	15.43	16.86	16.15			
F	60–64	15.53	15.44	15.48	16.79	16.73	16.76
	65–69	18.35	18.50	18.43			
	70–74	14.69	14.54	14.62			
	75–79	17.99	17.16	17.57			
	80–84	16.62	17.27	16.94			
	85–90	17.58	17.46	17.52			

Table 4 Difference in hippocampus size of CN versus AD subjects

Sex	Age	Difference in hippocampus size of CN versus AD subjects			Average difference in hippocampus size of CN versus AD subjects		
		Left (%)	Right (%)	Total (%)	Left (%)	Right (%)	Total (%)
M	60–64	32.12	32.34	32.23	32.37	32.87	32.63
	65–69	33.49	33.59	33.54			
	70–74	33.69	34.36	34.03			
	75–79	33.41	31.71	32.56			
	80–84	29.15	31.84	30.53			
	85–90	32.33	33.41	32.87			
F	60–64	23.29	23.37	23.33	30.81	31.53	31.18
	65–69	31.01	34.15	32.62			
	70–74	30.51	31.98	31.26			
	75–79	32.90	33.06	32.98			
	80–84	29.77	28.41	29.10			
	85–90	37.39	38.18	37.79			

trapezoidal membership function is used for the fuzzy sets AD and CN, whereas the triangular membership function is used for the fuzzy set MCI. The mathematical expression for the triangular membership function is shown in Eq. (4).

$$\mu_{MCI}(x) = \begin{cases} 0, & \text{if } x < a \\ \frac{x-a}{m-a}, & a \le x < m \\ \frac{b-x}{b-m}, & m \le x < b \\ 0, & \text{if } x \ge b \end{cases} \tag{4}$$

where a is the lower limit and b is the upper limit. In Eq. (4), m is a value that lies in between a and b, for which the degree of the membership function is 1 (or 100%), and $\mu_{MCI}(x)$ denotes the membership value for any input x in the fuzzy set 'MCI'.

The mathematical expression for the trapezoidal membership function can be expressed as Eq. (5).

$$\mu_{AD}(x) = \begin{cases} 0, & \text{if } (x \le a) \text{ or } (x \ge d) \\ \frac{x-a}{b-a}, & a \le x < b \\ 1, & \text{if } b \le x < c \\ \frac{d-x}{d-c}, & c \le x < d \end{cases} \tag{5}$$

where a is the lower limit, d is the upper limit, b is the lower support limit, and c is the upper support limit such that $a < b < c < d$, and $\mu_{AD}(x)$ denotes the membership value for any input value x in the fuzzy set 'AD'.

The fuzzy membership functions for the average hippocampus (left + right) size are shown graphically in Figs. 8, 9, 10, 11, 12, and 13.

Table 5 Difference in hippocampus size of MCI versus AD subjects

Sex	Age	Difference in hippocampus size of MCI versus AD subjects			Average difference in hippocampus size of MCI versus AD subjects		
		Left (%)	Right (%)	Total (%)	Left (%)	Right (%)	Total (%)
M	60–64	16.73	17.96	17.35	18.10	18.48	18.30
	65–69	12.92	11.71	12.32			
	70–74	15.92	15.73	15.82			
	75–79	22.98	21.10	22.04			
	80–84	20.04	24.46	22.34			
	85–90	19.99	19.90	19.94			
F	60–64	14.24	14.39	14.32	17.71	18.63	18.18
	65–69	15.50	19.20	17.39			
	70–74	18.55	20.41	19.49			
	75–79	18.18	19.20	18.69			
	80–84	15.77	13.47	14.63			
	85–90	24.03	25.10	24.58			

Table 6 Average atrophy in hippocampus for CN subjects

Sex	Age duration	Subjects: CN	
		Total atrophy in hippocampus (%)	Average atrophy per year in hippocampus (%)
M	60–64	3.50	1.09
	65–69	3.98	
	70–74	5.06	
	75–79	5.45	
	80–84	6.53	
	85–90	7.34	
F	60–64	4.55	1.11
	65–69	4.09	
	70–74	4.57	
	75–79	5.56	
	80–84	6.20	
	85–90	8.46	

From Figs. 8, 9, 10, 11, 12, and 13, if a subject's age and hippocampal (left/right) size are known, the degree of membership in the fuzzy sets CN, MCI, and AD can be obtained. Based on the degree of membership value, it can be determined how much a subject belongs to a particular fuzzy set. If the membership value for a fuzzy set 'A' is 1, then it implies that the subject is in the fuzzy set 'A' with 100% belongingness. If the membership value is 0, then the subject will not be considered in the fuzzy set 'A', or the subject is said to be in the fuzzy set 'A' with 0% belongingness. For any other membership value (between 0 and 1), the subject will be partially considered in the fuzzy set 'A'. From these three fuzzy sets, the dementia stage of any subject (CN/MCI/AD) can be predicted.

From Fig. 8, it is found that a subject (male or female) 'z' aged between 60 and 64 years can be included in fuzzy set CN with membership value 1, if the size of its hippocampus (left + right) 'h' is more than or equal to 48.68101 mm^2, whereas the membership value of the subject is 0, if 'h' is less than 41.71 mm^2, and for any other value of 'h', the subject will be considered in the fuzzy set CN partially with any membership value in between 0 and 1. Subject 'z' can be included in fuzzy set MCI with a degree of membership value as 1 if its 'h' is 41.71 mm^2. The degree of membership function in MCI is 0 if 'h' is less than 35.29 mm^2 and more than 48.67 mm^2. The subject 'z' can be considered in fuzzy set AD with the degree of membership 1, if 'h' is less than or equal to 35.29 mm^2, whereas the degree of the membership function is 0 if 'h' is greater than or equal to 41.70 mm^2.

Table 7 Average atrophy in the hippocampus for MCI subjects

Sex	Age duration	Subjects: MCI	
		Total atrophy in hippocampus (%)	Average atrophy per year in hippocampus (%)
M	60–64	9.80	2.32
	65–69	11.14	
	70–74	14.00	
	75–79	10.51	
	80–84	12.25	
	85–90	11.90	
F	60–64	10.67	2.34
	65–69	10.05	
	70–74	12.28	
	75–79	10.67	
	80–84	13.33	
	85–90	13.25	

Table 8 Average atrophy in hippocampus for AD subjects

Sex	Age duration	Subjects: AD	
		Total atrophy in hippocampus (%)	Average atrophy per year in hippocampus (%)
M	60–64	22.13	4.70
	65–69	18.29	
	70–74	20.78	
	75–79	27.96	
	80–84	24.90	
	85–90	26.96	
F	60–64	22.26	4.54
	65–69	20.77	
	70–74	20.05	
	75–79	23.35	
	80–84	23.43	
	85–90	26.37	

Similarly, from Fig. 9, a subject '$z1$' aged between 65 and 69 years is considered to be in fuzzy set CN with a degree of membership 1 if the size of the hippocampus (left + right) '$h1$' is more than 45.70 mm^2. If '$h1$' is less than 36.35 mm^2, then '$z1$' can be included in CN with a degree of membership of 0. Subject '$z1$' is said to be in fuzzy set MCI with membership value as 0, if '$h1$' is less than 30.93 mm^2 and greater than 45.70 mm^2, whereas the membership value is 1 if the value of '$h1$' is 36.34 mm^2. If '$h1$' is smaller than 30.93 mm^2, then '$z1$' can be included in fuzzy set AD with a degree of membership value as 1. If the value of '$h1$' is more than 36.33 mm^2, then the membership value of '$z1$' in the fuzzy set AD is 0.

From Fig. 10, for a subject '$z2$' aged between 70 and 74 years, if its hippocampus (left + right) size '$h2$' is more than 39.90 mm^2, then it can be considered that '$z2$' is in the fuzzy set CN with a membership value of 1. If '$h2$' is less than 32.64 mm^2, then the membership value of '$z2$' in fuzzy set CN is 0. If '$h2$' is determined as 32.64 mm^2, then '$z2$' can be included in the fuzzy set MCI with a membership value of 1. For '$h2$' less than 26.88 mm^2 and greater than 39.90 mm^2, the membership value of '$z2$' in MCI is 0. In the fuzzy set AD, '$z2$' can be included with a membership value of 1 if '$h2$' is less than 26.88 mm^2. If '$h2$' is more than 32.63 mm^2, then the degree of membership value for '$z2$' in AD is 0.

From Fig. 11, a subject '$z3$' of aged between 75 and 79 years can be included in the fuzzy set CN with a degree of membership value of 1, if its hippocampus (left + right) size '$h3$' is more than 32.03 mm^2. If the value of '$h3$' is less than 28.63 mm^2, then the degree of membership value of '$h3$' in the fuzzy set CN is 0. For '$z3$', if '$h3$' is found to be as less than 22.79 mm^2 and greater than 32.03 mm^2, then

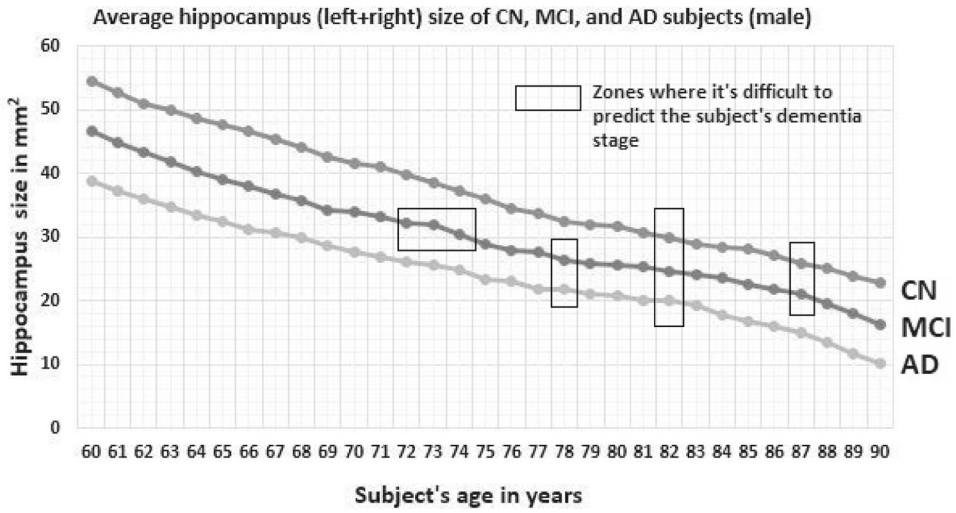

Fig. 4 Average size of the hippocampus for CN, MCI, and AD male subjects

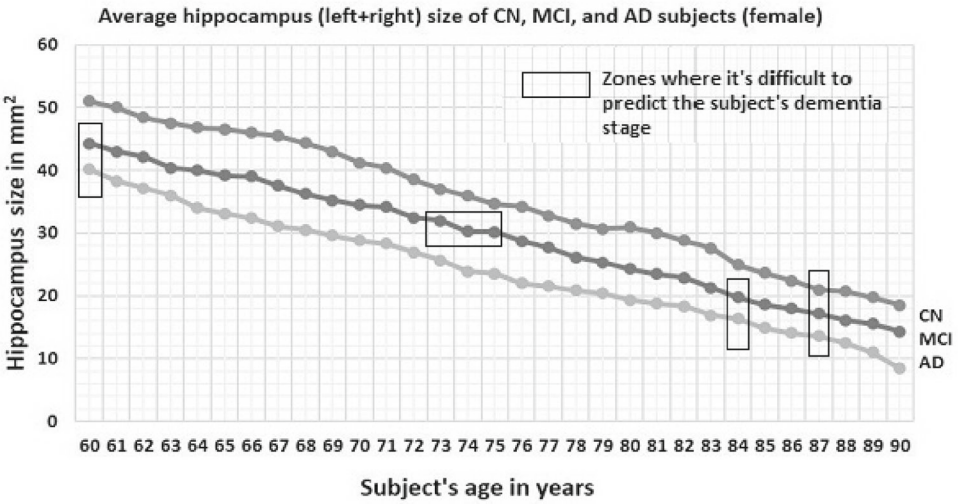

Fig. 5 Average size of the hippocampus for CN, MCI, and AD female subjects

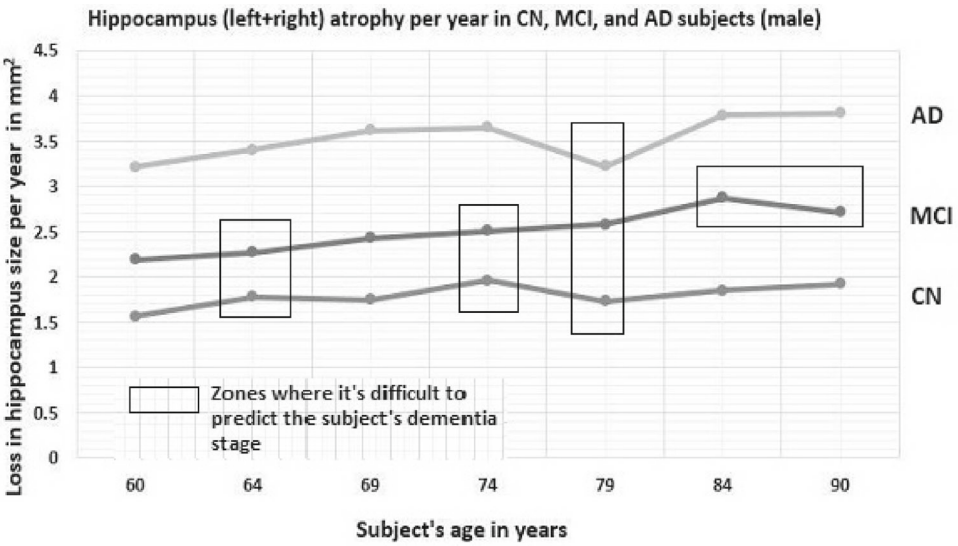

Fig. 6 Average atrophy per year in hippocampus for CN, MCI, and AD male subjects

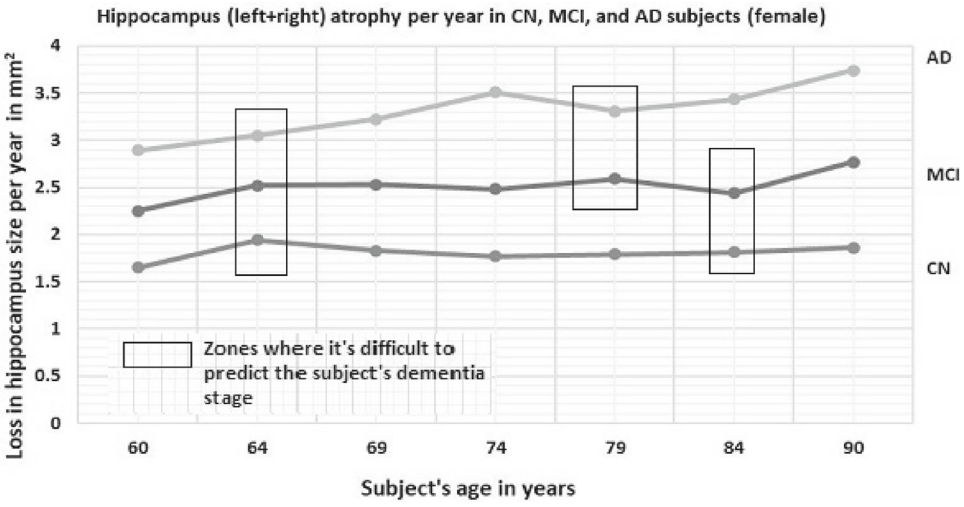

Fig. 7 Average atrophy per year in hippocampus for CN, MCI, and AD female subjects

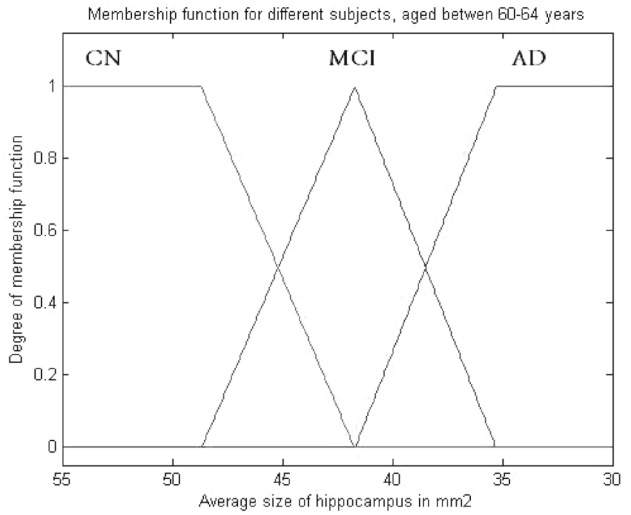

Fig. 8 Degree of membership in fuzzy set AD, MCI, and CN for any subject (male/female) aged between 60 and 64 years, based on their hippocampus (left/right) size

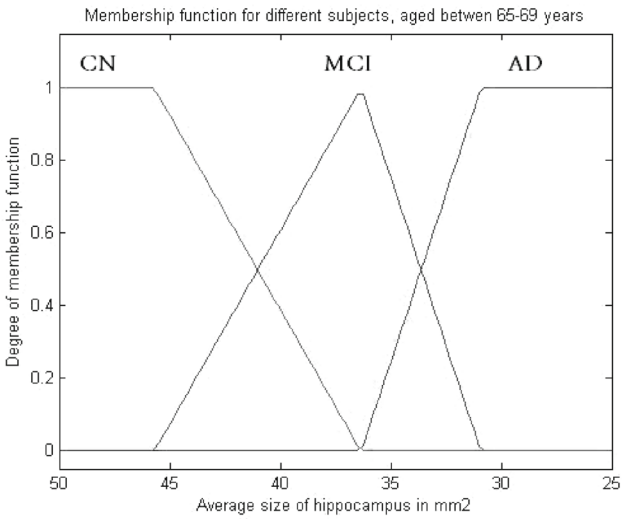

Fig. 9 Degree of membership in fuzzy set AD, MCI, and CN for any subject (male/female) aged between 65 and 69 years, based on their hippocampus (left/right) size

its membership value in the fuzzy set MCI is 0, whereas for '$h3$' equals 28.62 mm^2, the degree of membership value in MCI is 1. If the value of '$h3$' is less than 22.79 mm^2, then '$z3$' can be included in the fuzzy set AD with a degree of membership value of 1, whereas for any value of '$h3$' which is more than 28.61 mm^2, the degree of membership of '$z3$' in AD is 0.

From Fig. 12, if the hippocampus (left + right) size '$h4$' of a subject '$z4$' aged between 80 and 84 years is more than 28.72 mm^2, then the membership value of the subject in the fuzzy set CN is 1, whereas if the value of '$h4$' is below 24.79 mm^2, then the membership value of '$z4$' in CN is 0. If '$h4$' equals 24.78 mm^2, then '$z4$' is in the fuzzy set MCI with a degree of membership value 1, whereas for '$h4$' is less than 20.17 mm^2 and more than 28.72 mm^2, '$z4$' is in the fuzzy set MCI with a degree of membership value of 0. If '$h4$' is less than 20.17 mm^2, then '$z4$' can be considered in the fuzzy set AD with a membership value of 1, whereas if '$h4$' exceeds 24.77 mm^2, the degree of membership value in the fuzzy set AD is 0.

From Fig. 13, it can be observed that, for a subject '$z5$' of aged between 85 and 90 years, if its hippocampus (left + right) size '$h5$' is found to be as more than 24.10 mm^2, then the subject can be included in the fuzzy set CN with a degree of membership value of 1, whereas if '$h5$' is less than 21.49 mm^2, then the degree of membership value for '$z5$' in the fuzzy set CN is 0. If the value of '$z5$' equals 21.48 mm^2, then '$z5$' is considered in the fuzzy set MCI with a degree of membership value of 1, whereas if '$h5$' is less than 15.71 mm^2 and more than 24.10 mm^2, then the degree of membership value for '$z5$' in the fuzzy set MCI is 0. For the

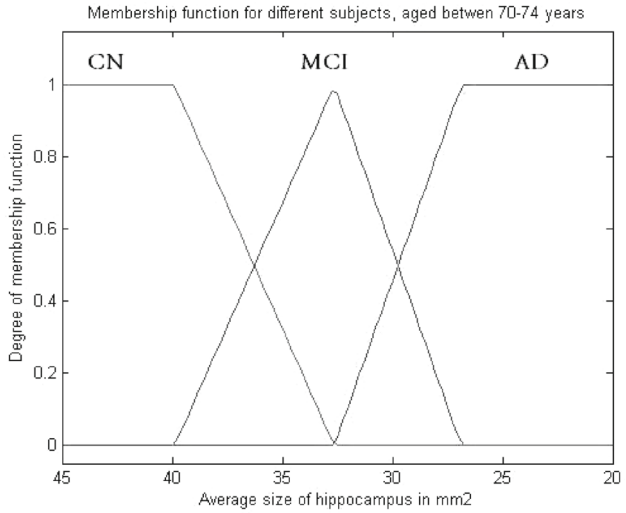

Fig. 10 Degree of membership in fuzzy set AD, MCI, and CN for any subject (male/female) aged between 70 and 74 years, based on their hippocampus (left/right) size

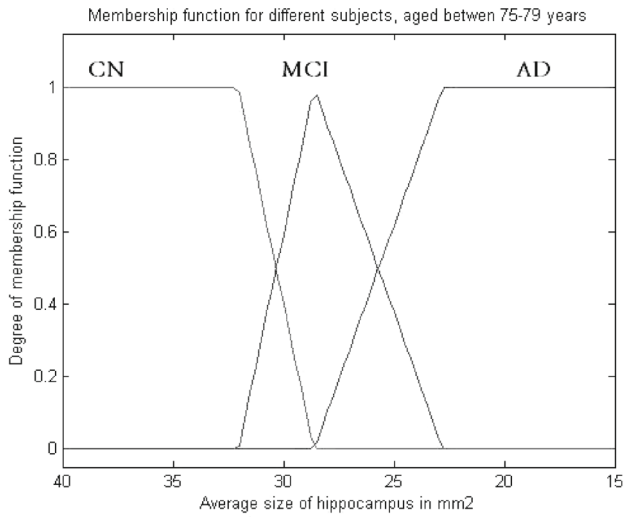

Fig. 11 Degree of membership in fuzzy set AD, MCI, and CN for any subject (male/female) aged between 75 and 79 years, based on their hippocampus (left/right) size

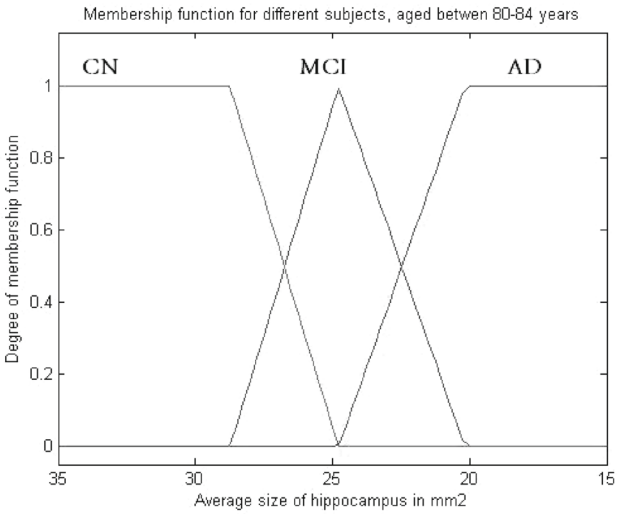

Fig. 12 Degree of membership in fuzzy set AD, MCI, and CN for any subject (male/female) aged between 80 and 84 years, based on their hippocampus (left/right) size

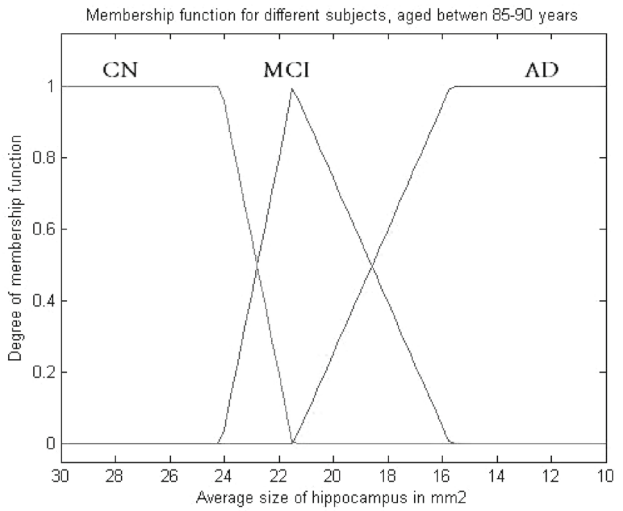

Fig. 13 Degree of membership in fuzzy set AD, MCI, and CN for any subject (male/female) aged between 85 and 90 years, based on their hippocampus (left/right) size

subject '$z5$', if '$h5$' is less than 15.71 mm^2, then the subject is considered in the fuzzy set AD with a degree of membership value of 1, whereas for the value of '$h5$' more than 21.47 mm^2, the degree of membership value for '$z5$' in AD is 0.

The hippocampal atrophy is observed separately for the left and right hippocampus, for male and female subjects, and for the subjects of different aged groups. Based on the hippocampal (left + right) atrophy value, we have created three more fuzzy sets, namely CNS, MCIS, and ADS separately. The fuzzy set CNS represents the CN subjects, MCIS represents the MCI subjects, and ADS represents the AD subjects. The membership function of different subjects in the fuzzy sets CNS, MCIS, and ADS is shown in Figs. 14, 15, 16, 17, 18, and 19.

From Fig. 14, it can be observed that a subject (male or female) 's' aged between 60 and 64 years can be included in fuzzy set CNS with membership value 1, if its average loss in hippocampus (left + right) size 'a' is less than or equal to 1.96 mm^2 per year, whereas the membership value of the subject is 0, if 'a' is more than 2.39 mm^2 per year, and for any other value of 'a', the subject will be partially considered in the fuzzy set CNS.

Subject 's' in Fig. 14 can be included in fuzzy set MCIS with a degree of membership value as 1 if its 'a' is 2.40 mm^2 per year. The degree of membership function in MCIS is 0

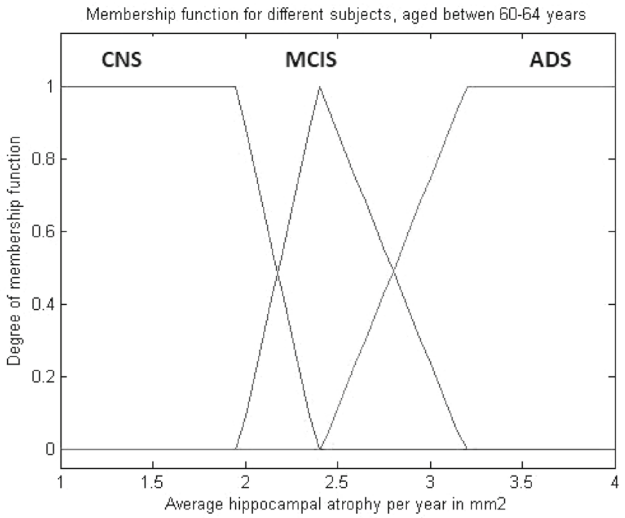

Fig. 14 Degree of membership in fuzzy set ADS, MCIS, and CNS for any subject (male/female) aged between 60 and 64 years, based on their hippocampus (left/right) atrophy per year

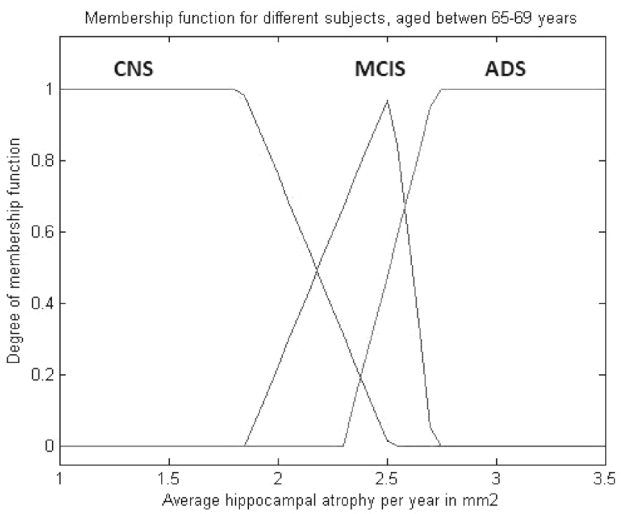

Fig. 15 Degree of membership in fuzzy set ADS, MCIS, and CNS for any subject (male/female) aged between 65 and 69 years, based on their hippocampus (left/right) atrophy per year

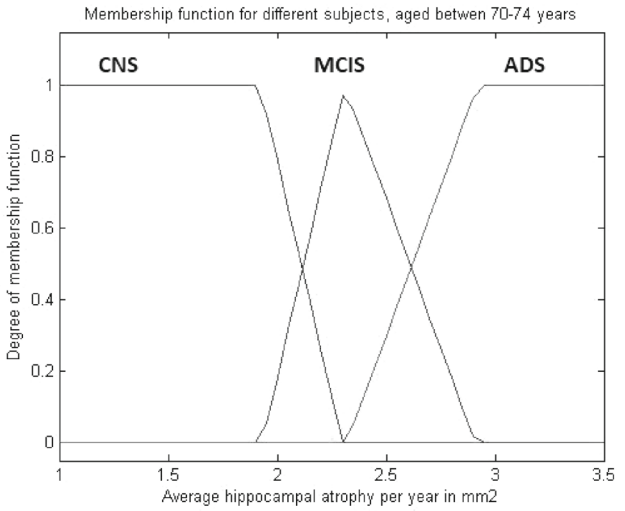

Fig. 16 Degree of membership in fuzzy set ADS, MCIS, and CNS for any subject (male/female) aged between 70 and 74 years, based on their hippocampus (left/right) atrophy per year

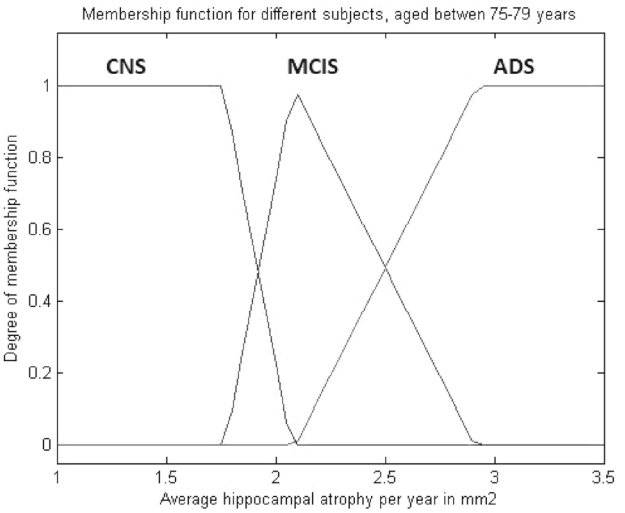

Fig. 17 Degree of membership in fuzzy set ADS, MCIS, and CNS for any subject (male/female) aged between 75 and 79 years, based on their hippocampus (left/right) atrophy per year

if 'a' is less than 1.96 mm^2 and more than 3.21 mm^2. The subject 's' can be considered in fuzzy set ADS with a degree of membership 1 if 'a' is more than or equal to 3.20 mm^2 per year, whereas the degree of the membership function is 0 if 'a' is less than or equal to 2.41 mm^2 per year.

From Fig. 15, a subject '$s1$' aged between 65 and 69 years is considered to be in fuzzy set CNS with a degree of membership 1 if the hippocampal (left + right) atrophy rate per year '$a1$' is less than 1.85 mm^2. If '$a1$' is more than 2.51 mm^2, then '$s1$' can be included in CNS with a degree of 0. The subject '$s1$' is said to be in fuzzy set MCIS with a membership value of 0 if '$a1$' is less than 2.73 mm^2 and greater than 1.85 mm^2, whereas the membership value is 1 if the value of '$a1$' is 2.52 mm^2. If '$a1$' is more than 2.71 mm^2, then '$s1$' can be included in fuzzy set ADS with the degree of membership value as 1. If the value of '$a1$' is less than 2.53 mm^2, then the membership value of '$s1$' in the fuzzy set ADS is 0.

From Fig. 16, for a subject '$s2$' aged between 70 and 74 years, if its hippocampus (left + right) size loss per year '$a2$' is less than 1.93 mm^2, then it can be considered that '$s2$' is in the fuzzy set CNS with a membership value of 1. If '$a2$' is more than 2.30 mm^2, then the membership value of '$s2$' in the fuzzy set CNS is 0. If '$a2$' is determined as 2.31 mm^2, then'$s2$' can be included in the fuzzy set MCIS with a membership value of 1. For '$a2$' more than 2.91 mm^2 and

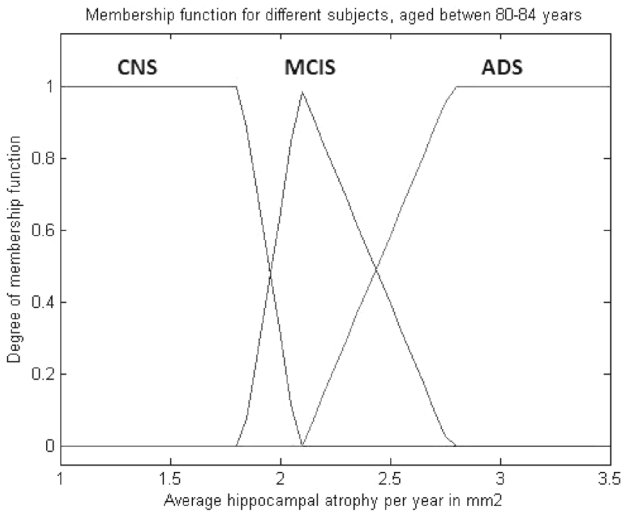

Fig. 18 Degree of membership in fuzzy set ADS, MCIS, and CNS for any subject (male/female) aged between 80 and 84 years, based on their hippocampus (left/right) atrophy per year

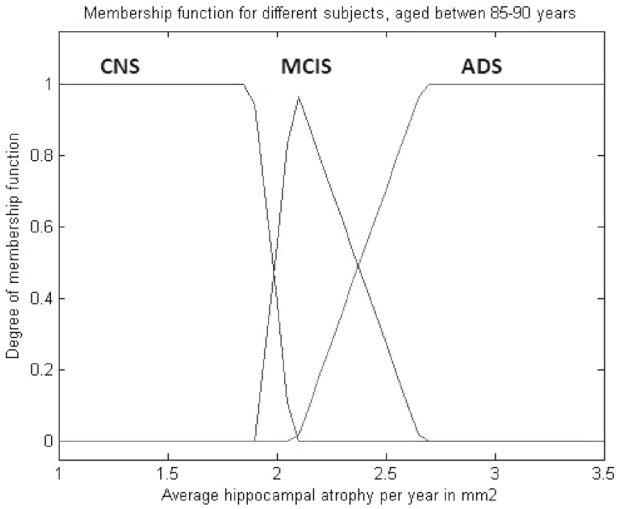

Fig. 19 Degree of membership in fuzzy set ADS, MCIS, and CNS for any subject (male/female) aged between 85 and 90 years, based on their hippocampus (left/right) atrophy per year

less than 1.91 mm^2, the membership value of '$s2$' in MCIS is 0. In the fuzzy set ADS, '$s2$' can be included with a membership value of 1 if '$a2$' is more than 2.91 mm^2. If '$a2$' is less than 2.30 mm^2, then the degree of membership value for '$s2$' in CNS is 0.

From Fig. 17, a subject '$s3$' of aged between 75 and 79 years can be included in the fuzzy set CNS with a degree of membership value of 1 if its hippocampus (left + right) size loss per year '$a3$' is less than 1.77 mm^2. If the value of '$a3$' is more than 2.07 mm^2, then the degree of membership value of '$s3$' in the fuzzy set CNS is 0. For '$s3$', if '$a3$' is found to be as more than 2.91 mm^2 and less than 1.77 mm^2, then its membership value in the fuzzy set MCIS is 0, whereas for '$a3$' equal to 2.08 mm^2, the degree of membership value in MCIS is 1. If the value of '$a3$' is more than 2.91 mm^2, then '$s3$' can be included in the fuzzy set ADS with a degree of membership value of 1, whereas for any value of '$a3$' which is less than 2.09 mm^2, the degree of membership of '$a3$' in ADS is 0.

From Fig. 18, if the atrophy per year in the hippocampus (left + right) size '$a4$' of a subject '4' aged between 80 and 84 years is less than 1.83 mm^2, then the membership value of the subject in the fuzzy set CNS is 1, whereas if the value of '$a4$' exceeds 2.08 mm^2, then the membership value of '$a4$' in CNS is 0. If '$a4$' equals 2.09 mm^2, then '$s4$' is in the fuzzy set MCIS with a degree of membership value 1, whereas for '$a4$' less than 1.83 mm^2 and more than 2.77 mm^2,'$s4$' is in the fuzzy set MCIS with a degree of membership value of 0. If '$a4$' is more than 2.77 mm^2, then '$s4$' can be considered in the fuzzy set ADS with a membership value of 1, whereas if '$a4$' is below 2.10 mm^2, the degree of membership value in the fuzzy set ADS is 0.

From Fig. 19, it can be observed that, for a subject '$s5$' of aged between 85 and 90 years, if its hippocampus (left + right) size atrophy per year '$a5$' is found to be as less than 1.90 mm^2, then the subject can be included in the fuzzy set CNS with a degree of membership value of 1, whereas if '$a5$' is more than 2.07 mm^2. The degree of membership value for '$s5$' in the fuzzy set CNS is 0. If the value of '$s5$' equals 2.08 mm^2, then '$s5$' is considered to be in the fuzzy set MCIS with a degree of membership value of 1, whereas if '$a5$' is less than 1.90 mm^2 and more than 2.66 mm^2, then the degree of membership value for '$s5$' in the fuzzy set MCI is 0. For the subject '$s5$', if '$a5$' is less than 2.68 mm^2, then the subject is considered in the fuzzy set ADS with a degree of membership value of 1, whereas for the value of '$a5$', which is less than 2.09 mm^2, the degree of membership value for'$s5$' in ADS is 0.

The overall practical implementation procedure of this work can be summarized below:

- After acquiring the brain MRIs, the first implementation we performed was skull stripping.
- After skull stripping, we performed a hippocampus segmentation operation.
- Next, we analyzed the hippocampal size and atrophy for all the segmented images.
- From the hippocampal comparison graph, it is observed that for some particular variants of ages and genders, it is difficult to differentiate the classes. To solve this issue, we have used fuzzy membership functions that can predict the classes based on the membership values.

5 Concluding remarks

The average size of the hippocampus in the brain is studied for three subject groups, namely CN, MCI, and AD, with an adequate number of MR images for both males and females separately. The age group of the subjects further categorizes the study. The mean area of the hippocampus is determined by analyzing the average number of major axis and minor axis pixels. It is found that the average size of the hippocampus in the brain (both left and right hippocampus) declined over age in the order of AD > MCI > CN subjects; hence, the average size of the hippocampus is in the order of CN > MCI > AD subjects. It is found that the average atrophy per year for the CN subjects is approximately 1.10%. For the MCI subjects, it is nearly 2.33%, and for the AD subjects, the atrophy per year is approximately 4.62%. From the study, it is also observed that the difference in the size of the hippocampus between CN and MCI subjects is approximately 17.05%. In contrast, this difference between CN and AD subjects is nearly 31.90%, and between MCI and AD subjects is 18.24%. For better analysis of hippocampus size and atrophy, the concept of the fuzzy membership function is utilized where the maximum height of the hippocampus size fuzzy functions is the maximum size of hippocampus found in that particular class, and base values are the minimum sizes. Similarly, maximum heights are the top atrophy values for fuzzy atrophy functions, and base values are the minimum atrophy values found in a particular class.

More data from different sources can be acquired in future works to validate this study. Moreover, more variants of dementia classes, such as Progressive MCI (PMCI) and Stable MCI (SMCI), can also be added to this extended study. After knowing hippocampal changes, the same can be used to develop a machine learning-based AD classification framework.

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Declarations

Conflict of interest The authors declare no potential conflict of interest.

Preprints The preprint version of this article is available at OSF Preprints: https://osf.io/wujfn/.

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