International Journal of Research in Medical Sciences
Jilowa S et al. Int J Res Med Sci. 2020 Jul;8(7):2487-2494
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20202884

Original Research Article

MRI based volumetric analysis of entorhinal cortex in elderly subjects with mild cognitive impairment and in subjects with normal cognition to see effects of aging on volume of ERC

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Received: 02 May 2020
Accepted: 28 May 2020

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ABSTRACT

Background: MCI is a transitional period between normal ageing and clinically probable early Alzheimer's Dementia (AD). ERC volumes show early reduction in cases of MCI in comparison to the normal ageing subjects. Early cognitive impairment can be documented with ERC atrophy on MR volumetry. Aim of the study was to evaluate the volume of entorhinal cortex in patients of MCI and to compared the volume with patients of normal cognition. Secondarily, we studied changes in the volume of entorhinal cortex with increasing age

Methods: In this study 30 patients of 60 years and above with MCI and 30 controls of normal cognition (age and sex matched) underwent brain examination on 3T MRI. Volume of entorhinal cortex was measured on 1 mm thick T1 coronal oblique MR scans by manually tracing the boundaries defined by two widely used methods i.e. Insausti et al and Goncharova et al.

Results: Patients with MCI showed 17.2% decline in the entorhinal cortex volume compared to controls (p value = 0.001). Patients of older age showed significantly more ERC volume reduction, reaching up to 30.4% in comparison to younger subjects suggesting atrophy of ERC in normal aging and in MCI both, but more so in patients with cognitive impairment.

Conclusions: ERC atrophy was found in MCI cases more than controls, increase atrophy trend was noted with increasing age. MR volumetry may play a role for documentation of ERC atrophy in cases of MCI.

Keywords: Cognition, Dementia, Entorhinal, Impairment, MR volumetry

INTRODUCTION

Mild cognitive impairment (MCI) is a functional syndrome involving the onset and evolution of cognitive impairment beyond those expected, based on the age and education of the individual which are not significant enough to interfere with their daily activities.[1-3] Post mortem pathological studies have implicated ERC as an early site of involvement in MCI, suggesting that the pathology starts in ERC first and then spreads to the region of hippocampus.[4]

ERC is a bilateral structure located deep in medial temporal lobe dorsolateral to hippocampus and has a role in learning and memory.Past studies have indicated that in patients with MCI, the entorhinal cortex volume start declining before hippocampus indicating superior relevance of entorhinal cortex volume.[5] The volume of the ERC is not much affected in normal aging as much as of the hippocampus. Studies have also suggested that the longitudinal shrinkage of the ERC predicts lower memory performance much earlier than volume decline of the hippocampus within healthy aging.

The concept of MCI is to identify cognitive decline in these individuals at an earlier stage. This early detection of ERC atrophy may be of help such as if therapeutic interventions for neuro-regeneration become available, clinicians might intervene at this early stage and prevent further decline of cognitive changes. MRI based volumetry of entorhinal cortex is a good non-invasive diagnostic modality which can help in finding the patients who are at risk of developing debilitating dementia in future.[6]

We calculated the ERC volumes in cases of MCI and controls using MRI protocols developed by Insausti and Goncharova.[7,8] The results are in concordance to previous studies, reduced volume of ERC was found in MCI patients compared to control group, more so with increasing age. Combining MRI volume with age and cognitive measures leads to high levels of predictive accuracy that may have potential clinical applications.

METHODS

This study comprised of 30 patients of 60 years and above who reported to department of Neurology of a tertiary care hospital during the study period (from November 2018 to March 2019) with memory complaints with a clinical diagnosis of mild cognitive impairment diagnosed as per Petersen's criteria. All the study subjects underwent battery of neuropsychological tests, administered by a trained examiner.

Our study individuals had the Montreal Cognitive Assessment (MoCA) score of 26 and above, GDS score of less than 10 as per the Geriatric Depression Scale (GDS) and a global deterioration score of 3 which coincides with the diagnosis of MCI more relevantly.

These patients were referred for MRI brain study in Radio-Diagnosis department.Patients with epilepsy, major psychiatric illness, history of alcohol or substance abuse were excluded from study.

Healthy controls

A total of 30 (age and sex matched) cognitively normal controls were recruited from the patient population reported for other MRI examinations (for example backache) with no memory complaints to obtain the comparative data which is not available in Indian population. A written and well informed consent was taken from all study participants. The study was approved by the Institutional Ethics Committee. Healthy controls were subjected to MRI of brain using the same protocol as cases.

This is a prospective study in which ERC volumes of MCI patients is compared with those who are cognitively normal controls (age and sex matched) by two methods Insausti and Goncharova.

MRI protocol

MRI brain was performed using 3 Tesla MR System (Siemens "Magnetom Skyra"), using a 16 channel head coil. The procedure was explained to the patient in his/ her language of understanding to allay fear and anxiety. The subjects were scanned in a non-emergent setting. No sedation was required before MRI examination.

A dedicated protocol was followed and images were acquired covering whole of ERC with tilted coronal T1W, 3-D magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence (4.5min) with a slice thickness of 1.0 mm and inter-slice gap of 0.5 mm and flip angle of 10-12°. This resulted in acquisition of multiple contiguous T1 weighted partitions oriented perpendicular to the long axis of the hippocampus and ERC. For detailed visualization and anatomical characterization of ERC, the images were magnified. ERC volumes were calculated using region of interest (ROI) approach, using manual segmentation sequence. Volume of the entorhinal cortex was obtained by manually drawing the boundary of the structure as seen in the coronal oblique T1 weighted MRI.

Measurements of ERC were performed according to the protocols developed by Insausti and Goncharova. The borders of the entorhinal cortex were manually traced sequentially with a mouse-driven cursor on each slice from the anterior to posterior till the entire length of the entorhinal cortex. Total area was calculated by summing up the area of all the sections. The area thus obtained was multiplied by 1.5 (1 mm slice thickness and 0.5 mm inter-slice gap), giving volume in cubic millimeters. The ERC volumes were calculated for the both study groups (cases and controls) and the data analyzed.

Data analysis was done using SPSS software licensed version 21. All the variables were analyzed using descriptive statistics to calculate frequencies, mean, range etc. Bi-variate analyses were done using the Chi square test and Fischer exact test, to determine the association between various demographic variables and ERC volumes. A p-value <0.05 was used to test level of significance.

RESULTS

A total of 30 patients of age 60 or above (M=16: F=14) diagnosed as MCI by neurologist of a tertiary care hospital of India were assessed. 30 controls, age and sex matched (M=16: F=14) were also included to measure the entorhinal cortex volumes in cognitively normal patients. The mean age of the cases was 67.27±6.17 years and of controls was 66.56±4.57 years. The patients were divided into two age groups; group I with age of 60 to 70 years and group II with age of 71 to 80 years. Table 1 gives demographic profiles of study subjects.

In both study group the majority (22, 73.33%) of patients fell in group I while 8 were in group II (26.67%).The mean MoCA score was 27.50±1.41 in MCI cases and 29.03±1.10 in controls. In cases the mean geriatric depression scale score was 4.0 and in controls it was 3.67 (Table 1).

The ERC volumes were taken for both the study groups according to the boundaries defined by Insausti and Goncharova. Both right and left ERC volumes were measured separately, later volumes of both sides were added to give combined bilateral ERC volume.

Table 2 gives volume of ERC in study subjects (both cases and controls) using Insausti method while table 3 gives volume by Goncharova method. Table 4 shows ERC volumes in cases and controls by both methods. The mean bilateral ERC volume in controls is 2607.0± 233.7mm^3 by Insausti method while volume in cases is 2158.5±186.4 mm^3.

Table 1: Demographic profile of study subjects.

		Cases (n=30)	Controls (n=30)
Age group	I (60-70 years)	22 (73.33%)	22 (73.33%)
	II (71-80 years)	08 (26.67%)	08 (26.67%)
Mean age		67.27±6.17	66.56±4.57
Sex	Male	16 (53.3%)	16 (53.3%)
	Female	14 (46.7%)	14 (46.7%)
MoCA score		27.50±1.41	29.03±1.10
Geriatric Depression Scale score		4.0	3.67

Table 2: ERC volumes (mm^3) in study subjects using Insausti method.

		Cases(n=30)			Controls(n=30)		
		RT ERC	LT ERC	B/L ERC	RT ERC	LT ERC	B/L ERC
Mean ERC volumes		1110.6±95.76	1047.9±93.41	2158.5±186.4	1332.7±122.8	1274.3±113.7	2607.0±233.7
Male (n=16)		1169.5±72.64	1103.9±75.87	2273.4±143.84	1435.8±51.03	1362.7±60.46	2798.5±107.64
Female (n=14)		1043.3±72.26	983.9±67.55	2027.2±137.23	1215±51.65	1173.1±60.86	2388.1±108.23
Age group	I	1138.1±80.7	1073.4±85.9	2211.5±163.81	1349.4±114.5	1288.9±107.2	2638.3±219.5
	II	1034.9±90.5	977.7±79.7	2012.6±174	1287±141.2	1234±126.8	2521±265

Table 3: ERC volumes (mm^3) in study subjects using Goncharova method.

		Cases (n=30)			Controls (n=30)		
		RT ERC	LT ERC	B/L ERC	RT ERC	LT ERC	B/L ERC
Mean ERC volumes		870.2±81.4	817.4±73.7	1687.6±152.2	1045±96.8	998.4±83.1	2043.4±177
Male (n=16)		916±63.4	859.3±61.1	1775.3±119.4	1125.4±39.5	1060.1±47.4	2185.5±83.2
Female (n=14)		818±63.2	769.5±52	1587.5±113.3	953±42.1	927.8±49	1880.8±86.6
Age group	I	891.4±72.5	835±69.7	1726.4±136.6	1058.8±88.6	1011.8±74.8	2070.6±160.2
	II	811.9±75.5	768.6±55.9	1580.5±130.1	1006.8±102.2	961.5±88	1968.3±188

Table 4: Mean Entorhinal Cortex volumes (mm3) in cases and controls.

Protocol	Group	Right ERC Volume	Left ERC volume	Bilateral ERC Volume
Insausti	Cases	1110.69	1047.9	2158.5
	Controls	1332.7	1274.3	2607.0
Goncharova	Cases	870.2	817.4	1687.6
	Controls	1045.0	998.4	2043.4

The mean bilateral ERC volume of controls is 2043.4±177.0 mm^3 while this volume in cases is 1687.6±152.2 mm^3 by Goncharova method. Bilateral ERC volumes in cases and controls by both Insausti and Goncharova are depicted as graph in figures 1 and 2.

Figure 3 to 5 depict box and whisker plots; Figure 3 shows ERC volumes in male and female cases. Figure 4 represents ERC volumes in male and female controls and Figure 5 shows ERC volumes in cases and controls by Insausti method.

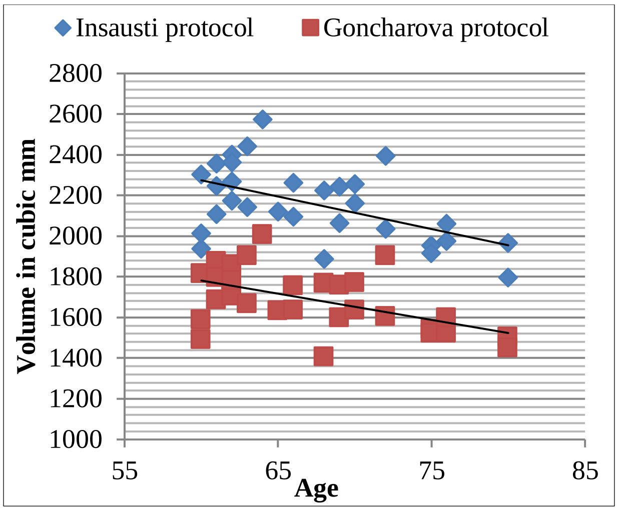

Figure 1: Bilateral ERC volumes by Insausti and Goncharova protocols in MCI cases.

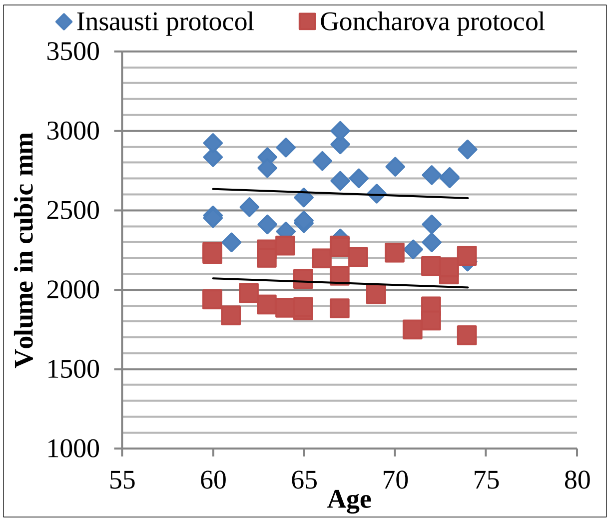

Figure 2: Bilateral ERC volume by Insausti and Goncharova protocols in controls.

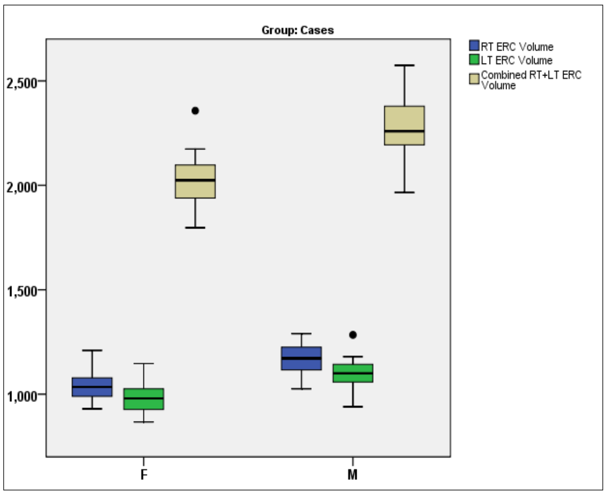

Figure 3: ERC volumes in male and female cases.

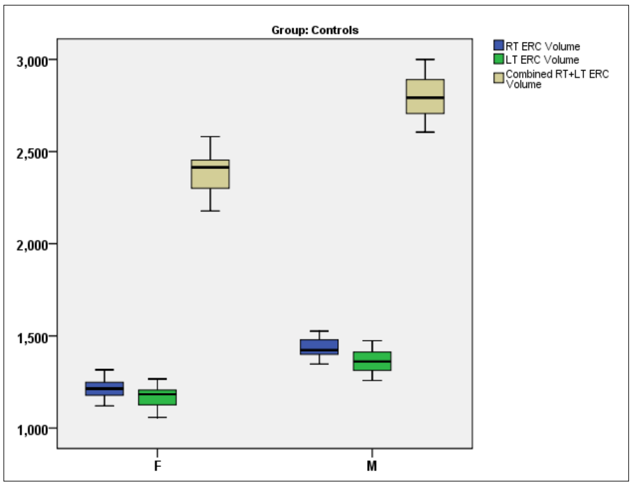

Figure 4: ERC volumes in male and female controls.

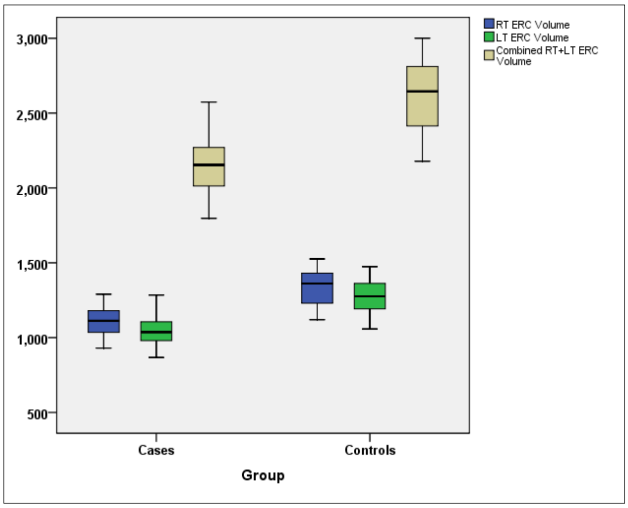

Figure 5: ERC volumes in cases and controls (Insausti method).

DISCUSSION

Subjective memory impairment is first clinical manifestation of dementia. Mild cognitive impairment is a functional syndrome involving the onset and evolution of cognitive impairment beyond those expected, based on the age and education of the individual which are not significant enough to interfere with their daily activities.[9]

Over the last decade much of the focus has turned towards the MCI to find the individuals at risk of developing debilitating dementia in future. MRI based volumetric analysis of the entorhinal cortex has emerged as a valuable tool to identify the individuals with MCI and their further progression to frank dementia.[10]

The ERC is an area of the brain located in the medial temporal lobe and functioning as a hub in a widespread network for memory, navigation and perception of time. The ERC is the main interface between the hippocampus and neocortex. It is located at the rostral end of the temporal lobe and stretches dorsolaterally.[11]

The boundaries of ERC defined by Insausti are as follows; the most rostral section containing the entorhinal cortex lies on average 2 mm posterior to limen insulae. The medial border of the entorhinal cortex is the ventral border of the gyrussemilunaris that is the fundus of the sulcus semilunaris.[12] The rostrocaudal midpoint of the ERC is at the level of the hippocampal fissure (the choroid fissure). The caudal end of ERC is taken at one MRI section behind the caudal most portion of the uncus (Figure 6).

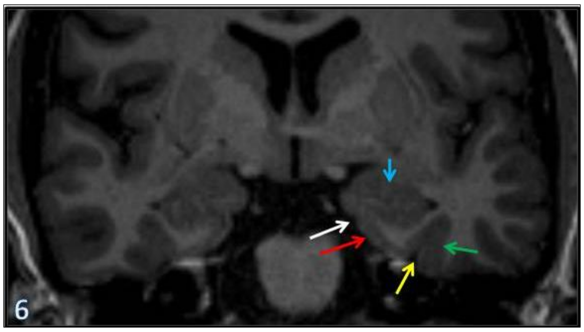

Figure 6: MR image showing boundaries of left ERC (red arrow) at the level of gyrus intralimbicus (white arrow), Perirhinal cortex (green arrow), collateral sulcus (yellow arrow) are visualized. Hippocampus is shown by blue arrow.

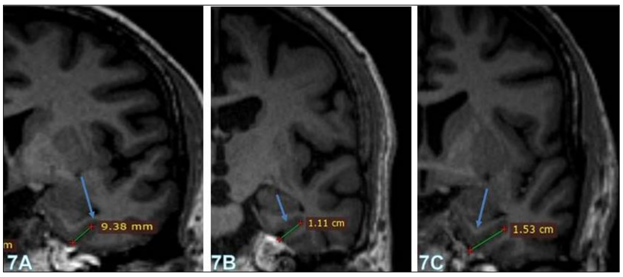

Figure 7: Measuring ERC in different Collateral Sulcus (CS) depths by Insausti method. A) shallow CS, B) regular CS , C) Deep CS. Blue arrow is depicting the lateral boundary of ERC.

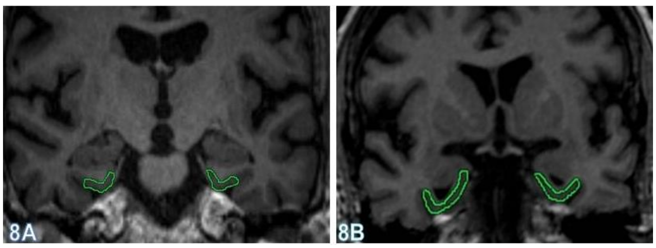

Figure 8: Measuring ERC using the Insausti method. A) 62 year old control with regular CS, B) 65 year old MCI case with shallow CS. ERC atrophy with prominent temporal horns are seen in MCI case.

Laterally, the entorhinal cortex extends to the medial bank of the collateral sulcus, where it borders the perirhinal cortex. In Insausti protocol the lateral border of the ERC was defined to be variable according to the depth of the collateral sulcus (CS) (Figure 7 and Figure 8). In shallow CS (less than 1 cm) the lateral border is taken at fundus of CS, in regular CS (depth 1 to 1.5 cm) lateral border of the ERC is taken at the midpoint of the medial bank of the CS and in deep CS (more than 1.5cm) it's taken at the medial edge of the CS.[13]

In Goncharova method, the collateral sulcus variations were not taken into account. Here the lateral border of the entorhinal cortex is independent of the depth of the collateral sulcus. In their protocol the lateral ERC involved the infero-medial point of the medial bank of the CS (Figure 9).

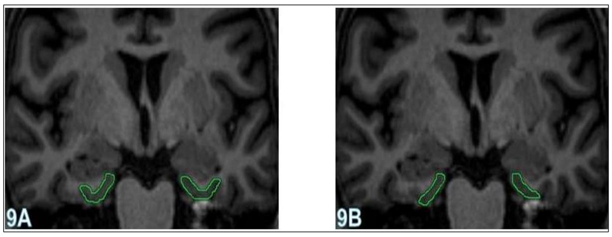

Figure 9: A) Measuring ERC using the Insausti method. In shallow CS, the ERC lateral border is at fundus of CS. B) Measuring ERC using the Goncharova method. The ERC lateral border is independent of CS depth, measured till medial bank of CS.

In this study, a total of 30 elderly cases with MCI and 30 age and sex matched controls with normal cognition underwent MRI volumetry to know any change in ERC volume in early cognitive impairment (MCI) compared to controls.

On neurophysiological testing the MCI cases had mean MoCA score of 27.5, with range of 25 to 30. The non MCI controls had mean MoCA score of 29, ranging from 26 to 30. This showed higher MoCA scores suggesting better task performance in controls compared to the MCI cases.

The mean geriatric depression scale score in MCI cases was 4.0, ranging from 2 to 8. While in non MCI controls the mean GDS score was 3.67, with a range of 1 to 7. The GDS score was used to exclude the patients with depression because depression is taken as an independent risk factor for MCI.[14]

Male MCI cases vs female MCI cases

Male patients of MCI had greater bilateral ERC volume compared to female MCI cases. The right ERC volume was 12.09% higher in males while the left ERC volume was 12.19% higher. The bilateral ERC volume was

12.14% more in male cases of MCI. Insausti found raw volume of the ERC cortices to be 16% lesser in females than in males.[7] He concluded, this difference might be associated with variability in brain size and not due to more atrophy in size of ERC in females since this gender difference was eliminated after normalizing the volume according to head size.

Male controls vs female controls

In male controls the right ERC volume was 18.17% more compared to female controls, while the mean left ERC volume was 16.16% greater. The bilateral ERC volume measured 17.18% more in male controls. This further showed consistent smaller volumes in females irrespective of presence or absence of MCI. This suggested that there is no gender dependent effect of aging on the volumes of the entorhinal cortex.

Owing to the differences in ERC volumes in male and female subjects it was necessary to compare the volumes in sex matched groups.

Male cases vs male controls

Using the Insausti protocol derived values, in male cases the right ERC volume was 18.54% lesser in comparison to male controls. The ratio of right ERC volume between cases and controls was 1:1.22. The left ERC volume was 19.0% lesser in cases with ratio of 1:1.23. In male cases the bilateral ERC volume was 18.76% lesser compared to male controls with ratio of 1:1.23. In male subjects maximum volume decline was 29.75%, seen in an 80 year old MCI case (Figure 10).

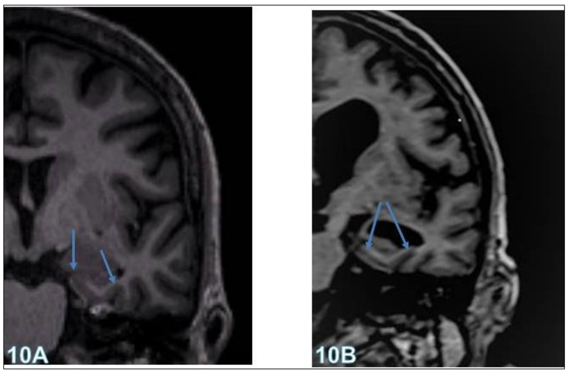

Figure 10: Coronal oblique T1W image of 63 year old control (A), and 80 year old male MCI case (B). Marked atrophy of ERC (blue arrows) is seen in MCI case with markedly dilated temporal horn (ERC volume -1966mm^3).

Female cases vs female controls

The female cases showed on average 15.11% decline in the bilateral ERC volumes when compared to the female controls using Insausti derived values. The ratio between cases and controls was 1:1.18. The right entorhinal cortex volume was 14.13%, and left entorhinal cortex volume was 16.12% lesser in female cases with ratio between cases and controls being 1:1.16 and 1:1.19 respectively. In females maximum reduction in ERC volume was 24.7%, noted in an 80 year old MCI case. It is evident from our results that the male patients showed slightly more volume reduction of the ERC than the female patients when compared to sex matched controls. This may be attributed by unequal distribution of mean ages and other factors among them.

Authors, further divided both cases and controls into 2 age groups. This was done to ensure better comparison between the cases and controls as ERC volume is clearly affected by increasing age as per our hypothesis.

Group I cases vs. group I controls (60-70 years of age)

When compared among both study groups the cases with MCI in Group I had 16.17% lesser volume of bilateral ERC when compared to the Group I controls. The right ERC was 15.6% and left ERC was 16.7% smaller in Group I cases.

Group II cases vs. group II controls (71-80 years of age)

In Group II MCI cases bilateral ERC volume was 20.16% lesser than the controls of age group II. The right ERC was 19.6% and left ERC was 20.8% smaller in volume in group II MCI cases.

In this study, subjects in both age groups showed reduction in the volume of ERC on both sides, however the age group II had more decrease in the volume of ERC (20.16%). This suggested a rapid progression of the volume loss in MCI subjects with increasing age in comparison to the normal ageing.

Our results are also in concordance to study by Du et al who studied age effects on atrophy rates of ERC and hippocampus in 42 subjects and found that age was significantly associated with increased per year atrophy rates of 0.04±0.02% for ERC.[15]

Steady atrophy in the bilateral ERC was found with increasing age and rate of atrophy was noticed more in MCI subjects compared to the normal ageing controls.[16] Changes in the ERC in elderly individuals seemed to be predictive of the transition from normal cognition to MCI.[17] The volume of the entorhinal cortex differentiated the subjects from those destined to develop dementia with considerable accuracy (84%) on 3 years follow up study.[18]

In this study bilateral ERC volumes negatively correlated with increasing age in MCI cases (Figure 1) with a Pearson’s coefficient (r) of -0.530 by Insausti method and -0.524 by Goncharova method. A significant correlation was found (p=0.002), suggesting that the age is major factor in the atrophy of ERC in MCI cases.

ERC volumes were also correlated with increasing age in non MCI control group (Figure 2). In them too, negative correlation was found with Pearson's coefficient (r) of -0.08 using the Insausti protocol and -0.106 using the Goncharova method. However this correlation was found not significant (p = 0.673).

These results suggested that ERC volume loss is directly related to increasing age, however, MCI cases show a stronger correlation between the increasing age and volume decline on comparison to subjects with normal cognition, suggesting higher rate of atrophy in the MCI subjects.

For final comparison of the results, the measurements were taken using two different methods. The first was Insausti protocol and second was Goncharova protocol, the differences between these imaging protocols have been discussed earlier. This resulted in two sets of data (Table 4).

The two imaging protocols used, provided different volumes of the ERC. The Goncharova protocol resulted in smaller volumes of bilateral ERC. In MCI cases the ratio of mean bilateral volumes by Insausti and Goncharova methods was 1.28:1. In non MCI controls this ratio was 1.27:1.

When the both study groups (cases and controls) were compared, both measuring methods showed similar decrease in the volume. The bilateral volume decrease according to Insausti protocol was 17.2% (Figure 5). The bilateral volume decrease by Goncharova method this was 17.4%. The left ERC showed slight more decline in volume than the right ERC by both methods.

The results of present ERC volume analysis are in agreement with study done by Du et al who used the Insausti method for measuring the ERC and found 13% ERC volume decline in cases of the MCI while the total decline in cases of Alzheimer's disease was 39%.[19] On average 15% reduction in volume of bilateral entorhinal cortices in MCI subjects was found by using Insausti method on follow up to see for development of AD.[20]

The Goncharova method however was easier to implement in comparison to the Insausti, mainly due to the fact that lateral boundary of entorhinal cortex is a well-defined in former method and is not affected by the depth of the collateral sulcus. Goncharova conducted a rigorous comparison of their technique to that of Insausti in their publication. They demonstrated that while this simplified approach resulted in smaller ERC volume overall relative to the Insausti approach, both techniques had a similar distribution and correlated highly. The Goncharova approach also described as reducing the measurement time and disagreements between lateral boundary endpoints. On Comparing the validity of the both measuring protocols, moderate to strong inter-rater reliability was found for Goncharova protocol mainly due to ERC lateral boundary end point being consistent and moderate reliability for the technique which required consideration of depth of collateral sulcus (Insausti method).[21]

The possible limitation of the Goncharova method is that this technique omits portions of the ERC.

However, no significant difference was found in the atrophy rates of ERC when calculated by either the Insausti method or the Goncharova, suggesting that both methods are reliable to examine the ERC volume loss in subjects with cognitive decline.

CONCLUSION

MRI volumetric study done on 3T scanner with dedicated sequence demonstrated the presence of abnormally decreased entorhinal cortex volumes in patients of MCI, compared to normal ageing controls. The study also demonstrated higher atrophy rates in older subjects and rapid progression in MCI cases. Thus, ERC volume gives a fair idea about cognition decline, may be used in clinical practice for documentation in cases of MCI. Both methods, Insausti and Goncharova showed good reliability.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Jilowa S, Kumar H, Singh Y, Anand KS. MRI based volumetric analysis of entorhinal cortex in elderly subjects with mild cognitive impairment and in subjects with normal cognition to see effects of aging on volume of ERC. Int J Res Med Sci 2020;8:2487-94.