

Magnetic Resonance Imaging Measurement of Entorhinal Cortex in the Diagnosis and Differential Diagnosis of Mild Cognitive Impairment and Alzheimer's Disease

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Research

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Abstract

Background: Several Magnetic Resonance Imaging (MRI) studies have shown that the entorhinal cortex (ERC) is the first brain area related to pathologic changes of Alzheimer's disease (AD), even before atrophy of hippocampus (HP). However, Change of ERC morphology (thickness, surface area and volume) in the progression from aMCI to AD, especially in the subtypes of aMCI (single domain and multiple domain, aMCI-s and aMCI-m), however, is still unclear.

Methods: ERC thickness, surface area and volume were measured in 29 people with aMCI-s, 22 people with aMCI-m, 18 patients with AD and 26 age-/sex-matched healthy controls. Group comparisons of the ERC geometry measurements (including thickness, volume and surface area) were performed using analyses of covariance (ANCOVA). Furthermore, receiver operator characteristic (ROC) analysis and the area under the curve (AUC) were employed to investigate the classification ability (HC, aMCI-s, aMCI-m and AD from each other).

Results: There was a significant ERC thickness decreasing tendency from HC to aMCI-s to aMCI-m to finally AD in both left and right hemispheres (left hemisphere: $HC > aMCI-s > AD$; right hemisphere: $aMCI-s > aMCI-m > AD$). For ERC volume, both the AD group and the aMCI-m group showed significantly decreased volume in both sides compared with the HC group. Besides, the AD group also had significantly decreased volume in both sides compared with the aMCI-s group. As for the ERC surface area, no significant difference was identified among the four groups. Furthermore, the AUC results demonstrated that combined ERC parameters (thickness and volume) can better discriminate the four groups from each other than ERC thickness alone. Finally, and most importantly, relative to HP volume, the capacity of combined ERC parameters was better at discriminating between HC and aMCI-s, as well as aMCI-m and AD.

Conclusion: ERC atrophy, particularly combination of ERC thickness and volume, might be regarded as a promising candidate biomarker in the early diagnosis of aMCI.

Background

Alzheimer's disease (AD) is one of the most common progressive neurodegenerative diseases. So far, there is no cure for AD. The early diagnosis, timely intervention and treatment can improve the prognosis of patients[1], so it is important to make ad diagnosis in Preclinical stage.

Amnesic mild cognitive impairment (aMCI), a probable transitional stage between normal aging and early dementia, is associated with a high risk of developing AD[2]. However, the group of aMCI is a heterogeneous clinical entity[3]. Some MCI individuals convert to AD rapidly, some keep stable state for many years, and others return to normal cognition[4]. Based on the patterns of cognitive impairment, aMCI can be classified into two subtypes: single domain aMCI (aMCI-s), those with isolated memory impairment and multiple domain aMCI (aMCI-m), those with multiple cognitive domain decline, such as language, attention, visuospatial or executive function[5]. It has been suggested that subjects with aMCI-

m are more likely to progress to AD than subjects with aMCI-s[3, 6]. From this perspective, we reckon that aMCI-s may represent an earlier stage of aMCI and classification of aMCI subtypes is important to identify individuals at high risk for developing AD.

Morphological indexes, based on high-resolution structural magnetic resonance imaging (sMRI), have become a standard method for the detection of incipient AD. It is well documented that hippocampal (HP) volume loss plays an important role in the early diagnosis of AD[7, 8]. According to the new diagnostic criteria for MCI due to AD, MRI-based measures of medial temporal lobe atrophy, especially HP volume loss, has been considered as important research criteria to enhance the specificity of the diagnosis[9]. However, several MRI studies have shown that the ERC is the first brain area related to pathologic changes of AD, even before HP atrophy occurs[10, 11]. Moreover, the morphological indexes of ERC generally included thickness, surface area and volume. These indexes have been derived by special neurophysiological basis[12–14]. Generally, thickness of the cerebral cortex likely represents not limited to neuron numbers but also many other elements of the neuropil, such as dendrites, axons and so on[13, 15]. Surface area, which is correlated with head size, may reflect local subcortical size[13]. As for the volume of ERC, it is a composite measure associated to both thickness and surface area. To date, it is still unclear how ERC thickness, volume and surface area changes among AD, aMCI and HC entities, especially for aMCI subtypes (aMCI-s and aMCI-m). In addition, different morphological indexes have been proven to be affected differently in the course of disease[13, 16] and cortical thickness and volume were demonstrated to have differentials among AD, aMCI and healthy controls in distinct cortical regions[17]. Therefore, combining multiple morphological indexes may effectively reveal subtle structural alterations in the early stage of AD and improve classification accuracy of aMCI subtypes.

In the current study, change of ERC thickness, volume and surface area were first assessed among HC, aMCI-s, aMCI-m and AD. Then, the capacity of single ERC indexes (thickness, volume or surface area) or combined them to discriminate the four groups from each other was separately identified. Based on previous studies, we hypothesized that combined ERC indexes may have an advantage over hippocampal volume to detect AD in the preclinical stage.

Materials And Methods

Participants

69 participants were recruited from Memory Disorders Clinic and Department of Neurology, Xuanwu Hospital, Capital Medical University, including 29 people with aMCI-s (14 females, mean age 71.21 ± 6.4 years), 22 people with aMCI-m (10 females, mean age 71.09 ± 8.4 years), 18 patients with AD (11 females, mean age 70.94 ± 9.7 years). The 26 age- and sex-matched healthy controls (15 females, mean age 70.38 ± 5.36 years) were recruited from community near Xuanwu Hospital. All participants or their guardians signed informed consent before participating in the study in accordance with the Institutional Review Board of Xuanwu Hospital, Capital Medical University, and gained compensation for their participation.

The clinical diagnosis of AD was established according to the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) criteria for Alzheimer's Dementia and the National Institutes on Aging and Alzheimer's Association (NIA-AA) Diagnostic Guidelines for AD[9, 18]. aMCI participants were diagnosed and classified according to Petersen's clinical diagnostic criteria and the NIA-AA criteria for MCI due to AD[5, 9]. The exclusionary criteria included depression, seizures, stroke, Parkinson disease, neurosurgery history, head trauma, and contraindications to MRI (e.g., aneurysm clip(s), cardiac pacemaker, any metallic fragment or foreign body, implanted cardioverter-defibrillator). Patient characteristics are summarized in Table 1.

All participants underwent a standard battery of neuropsychological tests that included the Clinical Dementia Rating (CDR)[19] the Mini-mental State Examination (MMSE)[20] and the Montreal cognitive assessment (MoCA)[21]. Four specific cognitive domains were assessed: (1) the visuospatial skill was measured with the clock drawing test (CDT, 3-point)[22]; (2) the executive function was evaluated with the trail making test (TMT)[23]; (3) language skill was assessed with the Boston naming test (BNT)[24]; (4) the memory function was evaluated with the Auditory Verbal Learning Test (AVLT of Chinese version)[25].

MRI acquisition

3D high-resolution structural T_1 -weighted images was obtained by magnetization prepared rapid acquisition gradient echo (MP-RAGE) pulse sequence on a 3.0 Tesla scanner (Trio + tim, Siemens, Medical Solutions, Erlangen, Germany). MP-RAGE indexes were as followed: repetition time (TR)/echo time (TE)/inversion time (TI)/flip angle (FA) = 1900 ms/2.2 ms/900 ms/9°, acquisition matrix = 224×256×176, voxel size = 1×1×1mm³. The acquisition time was about 3 mins. Suitable foam padding was used to limit head movement, and earplugs were employed to minimize scanning noise.

MR morphometric image analysis

The data were exported from scanner to a personal computer to perform morphometric analysis. Automatic segmentation of ERC was performed with FreeSurfer version 5.0, which is documented and freely available for download online (<https://surfer.nmr.mgh.harvard.edu/>). The technical details of FreeSurfer procedures were described elsewhere. Briefly, the processing included motion correction, removal of non-brain tissue, automated Talairach transformation, intensity normalization, estimation of grey matter/white matter boundary and pial surface. Cortical thickness was then defined as distance from the GM/WM boundary and the pial surface. The volume measures of left and right ERC were derived from the standard stats directory using the Desikan-Killiany-Atlas.

Statistical analyses

SPSS (version 20.0, IBM) was utilized for statistical analyses. Demographic features were compared using one-way analysis of variance (ANOVA). Gender difference was tested using the Chi-square test. Group comparisons of the left and right ERC were performed using analysis of covariance (ANCOVA), in which thickness, volume and surface area of the ERC were dependent variables respectively. Gender, age,

and years of education were used as covariates. Moreover, head size, as estimated by estimated total intracranial volume (eTIV), was also considered as a covariate in all analyses for correcting head size variation in regional brain volume measurements. Although head size does not associate with thickness, the same covariates were used to attain formal statistical equivalency. P values of less than 0.05 were considered to indicate statistical significance.

ROC analyses

Furthermore, to investigate the classification ability (HC, aMCI-s, aMCI-m and AD from each other) of the ERC single index (including thickness, volume and surface area), or ERC combined indexes (combining thickness, volume or surface area), or HP measure (volume), the receiver operating characteristic (ROC) analyses were performed. The area under the curve (AUC) was calculated and used as a differentiating indicators. MedCalc software (version 19, <http://www.medcalc.org>) was used for ROC curve analysis.

Results

Demographics features of patients and healthy controls were showed in Table 1. The four groups were comparable in terms of age [$F(3, 91) = 0.064, P = 0.979$] and gender distribution ($\chi^2 = 1.461, P = 0.691$). Education level [$F(3, 91) = 9.342, P < 0.001$] was significantly lower in the AD ($P < 0.001$) and aMCI-s ($P = 0.001$) groups than in the HC group. There were significant differences across the four groups in all cognitive measures ($P < 0.001$ for all). Specifically, based on post-hoc comparisons, the AD group had the worst performance on all behavioral measures relative to the other three groups. The aMCI-m group showed significant impairment in all cognitive domains compared with the HC group and worse performances on BNT, TMT and CDT compared with the aMCI-s group. Moreover, the aMCI-s group showed significantly impaired cognitive abilities compared with the HC group, reflected in the MMSE, MoCa and AVLT scores.

Table 1
Demographic and neuropsychological assessments of participants

	AD	aMCI-m	aMCI-s	HC	P Value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Gender (Females/Males)	11/7	10/12	14/15	15/11	0.69 [#]
Age	70.94 (9.77)	71.09 (8.41)	71.21 (6.48)	70.38 (5.36)	0.979 [*]
Education (years)	7.06 (3.69)	10.32 (3.72)	8.07 (3.85)	12.19 (3.26)	< 0.001 [*]
MMSE	15.89 (7.05)	24.45 (4.04)	24.07 (3.47)	28.19 (1.47)	< 0.001 [*]
MoCa	11.56 (5.35)	20.36 (4.47)	19.45 (4.24)	26.58 (1.70)	< 0.001 [*]
AVLT	12.06 (7.21)	29.50 (11.12)	27.14 (5.74)	48.08 (9.29)	< 0.001 [*]
CDR (0, 0.5, 1–2)	0.5 = 1, 1–2 = 17	0.5 = 22	0.5 = 29	0 = 26	< 0.001 [#]
BNT	11.94 (6.26)	23.36 (2.15)	27.76 (1.35)	28.96 (0.96)	< 0.001 [*]
TMT	260.89 (49.53)	114.09 (29.88)	79.55 (23.35)	86.27 (34.51)	< 0.001 [*]
CDT (0, 1, 2, 3)	2 = 6, 1 = 7, 0 = 5	1 = 6, 2 = 9, 3 = 7	2 = 5, 3 = 24	2 = 1, 3 = 25	< 0.001 [#]

Differences in ERC thickness, volume and surface area among the aMCI-s, aMCI-m, AD and HC groups were first assessed. As shown in Fig. 1B, there was significant difference in the ERC thickness across the four groups ($P < 0.01$). Post hoc analyses revealed significant ERC thickness decreasing tendency from HC to aMCI-s to aMCI-m to AD in both left and right hemispheres. Specifically, for left hemisphere ($F(3, 87) = 6.134, P < 0.001$), with multiple comparison tests: p value of AD versus aMCI-s was 0.016, p value of AD versus HC was less than 0.001, p value of aMCI-m versus HC was 0.008, p value of aMCI-s versus HC was 0.024. For right hemisphere [$F(3, 87) = 10.933, P < 0.001$], with multiple comparison tests: p value of AD versus aMCI-m was 0.016, p value of AD versus aMCI-s was less than 0.001, p value of AD versus HC was less than 0.001, p value of aMCI-m versus aMCI-s was 0.027, p value of aMCI-m versus HC was 0.005.

For the ERC volume, the AD group had significantly decreased volume in both sides compared with the HC group (right: $p < 0.001$; left: $p = 0.002$) and the aMCI-s group (right: $p = 0.012$; left: $p = 0.016$) after multiple comparison (Fig. 1B). In addition, the aMCI-m group also showed significantly decreased volume in both sides compared with the HC group (right: $p = 0.002$; left: $p = 0.02$; Fig. 1B). But as for the ERC surface area, no significant difference was identified among the four groups ($P > 0.4$; Fig. 1C).

The ERC location of left and right hemisphere in coronal slices (A). The figure showed group difference of ERC thickness (B), volume (C) and surface area (D). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Abbreviations: L: left, R: right

The AUC of single ERC index (including thickness, volume and surface area) were summarized in Supplemental Table S1. Relative to ERC surface area or ERC volume, ERC thickness is the best index to distinguish the four groups, the discriminating ability of ERC thickness and combination of ERC thickness and volume was compared (shown in Table 2), AUC value of thickness and volume in combination was higher than that in thickness only..

Table 2
The AUC of ERC thickness and ERC thickness and volume combined

	right thickness	left thickness	combined thickness and volume
HC vs aMCI-s	0.558	0.711	0.760
HC vs aMCI-m	0.736	0.729	0.788
HC vs AD	0.908	0.876	0.919
aMCI-s vs aMCI-m	0.647	0.505	0.687
aMCI-s vs AD	0.824	0.711	0.833
aMCI-m vs AD	0.694	0.707	0.725

Finally, the discriminating ability of combined ERC indexes (combination of ERC thickness and volume) was further compared to that of hippocampal volume, which is the most studied and used MRI biomarker of AD. By comparison, classification accuracy of HC from aMCI-s (ERC: AUC = 0.760; HP: AUC = 0.676) as well as aMCI-m from AD (ERC: AUC = 0.725; HP: AUC = 0.631) using combined ERC indexes the AUC value was higher than that of hippocampal volume, indicating a superior ability of combined ERC indexes to differentiate HC from aMCI-s as well as aMCI-m from AD (Fig. 2). In addition, the ability of combined ERC indexes was similar to that of hippocampal volume in discriminating between HC and aMCI-m, HC and AD, aMCI-s and aMCI-m, as well as aMCI-s and AD (Supplemental Figure S1).

Discussion:

In this study, the alterations in ERC morphological indexes (including thickness, volume and surface area) were first assessed among AD patients, aMCI-m, aMCI-s and HC participants. The ERC thickness, rather than the ERC volume and surface area showed a significant tendency in the conversion from aMCI to AD. Then, the AUC results demonstrated that combining ERC thickness and volume could better discriminate the four groups from each other than single ERC index alone. Furthermore, relative to the hippocampal

volume, combination of ERC thickness and volume had better discriminating capacity between HC and aMCI-s, as well as aMCI-m and AD.

The ERC atrophy has been regarded as early potential biomarker in patients with MCI and AD[10, 26–30]. Our findings suggested that ERC thickness showed more significant changes than ERC surface area among AD, aMCI-m and aMCI-s, which was consistent with a previous study that showed AD appearing to have different effects on thickness and surface area[13]. To be more precise, both hemispheres of ERC thickness showed a decrease trend from HC to aMCI-s to aMCI-m to AD. These results add to the evidence that aMCI-m is more likely a transitional stage between aMCI-s and AD[5, 6, 17, 31]. More importantly, our AUC results further proved that ERC thickness had superiority over ERC surface area and volume in discriminating among the four groups. So, on the basis of previous studies, our study found that aMCI-s and aMCI-m showed different magnitudes of decreased cortical thickness in the bilateral ERC relative to the HC group. In that, ERC thickness may serve as a potential diagnosis index in patients with aMCI.

ERC thinning is sensitive to the early pathological process of AD, which may due to its own neurophysiological mechanism. In one aspect, early structural changes in AD are limited to specific laminae within ERC (layer II is particularly vulnerable)[32]. In the other aspect, the thickness of the cerebral cortex was calculated as the average distance between the gray/white boundary and the pial surface[33, 34]. It likely represents cytoarchitectural features or many components of the neuropil, such as intra-cortical axons, dendrites, synaptic elements, and glia, not limited to neuron numbers[13, 34–36]. It was reported that AD-related pathological alterations first resulted in synaptic neurodegeneration and then neuronal loss[37]. In addition, no significant neuronal loss in ERC was detectable in cognitively normal participants, while a very severe neuronal loss was seen in ERC in the very mild AD cases[38]. On account of above reasons, the ERC thickness, rather than the ERC surface area and volume appeared significant change even in the stage of aMCI-s.

Our results also revealed that ERC surface area was minimally affected in the conversion from aMCI to AD. To our surprise, aMCI-s group even showed an increase trend. This may be explained by compensation for ERC thinning[38]. The increase of ERC surface area autonomously compensates for ERC thinning in patients at earliest preclinical stage (e.g., aMCI-s), whereas the absence of such compensation mechanism in patients at late clinical stage (e.g., AD). However, the neurophysiological correlates of cortical surface area are less clear. The ERC surface area may relate to local subcortical factors, such as subjacent white matter volume or global factors, such as the head size[13]. So, regionally analyses of cortical surface area must take into account the global effects of head size and brain size[13, 34]. Previous work has shown that aging was related with reduced surface area, rather than AD[13, 39]. In line with this, we found that ERC surface area was relatively unchanged in aMCI and AD after adjusting for head size.

By definition, ERC volume was a product of thickness and surface area[13, 33, 39]. The ERC volumetric decrease was the result of a combination of the ERC thinning and ERC surface area change. No

significant change in ERC surface area, even a slight increase in aMCI-s may weaken ERC volumetric reduction. That may explain why ERC volume atrophy was not significant in subtypes of aMCI.

As discussed above, the alteration of different ERC morphological indexes varied among the four groups. Combining multiple ERC indexes (e.g., volume, thickness, and surface area) may provide a complete understanding of progressive structural brain changes during the conversion of aMCI to AD. Moreover, the different morphological features had unique contributions to the classification of aMCI patients and healthy controls[34]. Thus, multi-parametric indexes may have the ability to detect subtle alteration in the progression of AD. The multivariate method, which combined certain indexes together, allows us to determine the relationships among different features beyond their individual values. Consistent with prior studies, the AUC results showed that the combination of ERC thickness and volume further improved discrimination among the four groups.

Memory impairment is the earliest and most prominent symptom of aMCI and AD[40–42]. Since the medial temporal lobe structures (ERC and HP) are specialized for memory functions, alteration of the medial temporal lobe, especially hippocampal volume loss, has been considered to be a key feature for early diagnosis of AD[43–45]. However, the ERC atrophy may be more closely associated with the pathologic processes of AD than HP atrophy[38]. Thus, the ERC atrophy could have an advantage over HP atrophy in discriminating among HC, subtypes of aMCI and AD.

The AUC results verified the above-mentioned assumption and showed that combination of ERC thickness and volume had a superior differential power than hippocampal volume for discriminating between HC and aMCI-s. The results also coincided with pathologic study stating that the pathology of AD starts in ERC, providing in vivo evidence for the Braak stages (Stages 1 and 2 represent the entorhinal phase of the disease with minimal involvement of the hippocampus)[46]. In addition, combination of ERC thickness and volume had a better discriminating capacity than hippocampal volume between aMCI-m and AD. According to a longitudinal MRI study, atrophy rates in AD were significantly higher for ERC than for HP[29]. Considering that ERC was affected earlier and had higher atrophy rate than HP in AD[28, 29], the combination of ERC multiple morphometric indexes should reflect more comprehensive information during the process from aMCI to AD. Therefore, it is quite understandable that combination of ERC thickness and volume had an advantage regarding early diagnosis of aMCI and predicting conversion from aMCI to AD.

There were still some limitations in this study. First, although we use education level as a covariate for covariance analysis to reduce its impact on ERC evaluation, it is not as convincing as choosing subjects with similar education level, but because our study is based on real clinical data, there is no perfect control obtained. Second, although the present study revealed an ERC thickness decreasing tendency from HC to AD, however, this trend needs to be further confirmed by longitudinal studies.

Conclusions

In conclusion, this study demonstrated that the ERC thickness, rather than the ERC surface area or volume showed a significant decrease tendency from aMCI to AD group. Based on the study, combination of ERC thickness and volume had a superior differentiate power than single ERC index alone or hippocampal volume for discriminating between HC and aMCI-s, as well as and aMCI-m and AD. These findings suggest that ERC atrophy, particularly multi-index (combination of ERC thickness and volume) might be regarded as a promising candidate biomarker in the early diagnosis of aMCI as well as in the prediction of conversion from aMCI to AD.

Abbreviations

MRI: Magnetic Resonance Imaging; ERC: entorhinal cortex; HP: hippocampus; ANCOVA: analyses of covariance; ROC: receiver operator characteristic; AUC: area under the curve; aMCI-s: single domain aMCI; aMCI-m: multiple domain aMCI; DSM-V: Diagnostic and Statistical Manual of Mental Disorders-V; NIA-AA: National Institutes on Aging and Alzheimer's Association; CDR: Clinical Dementia Rating; MMSE: Mini-mental State Examination; MoCA: Montreal cognitive assessment; CDT: clock drawing test; TMT: trail making test; BNT: Boston naming test; AVLT: Auditory Verbal Learning Test; MP-RAGE: magnetization prepared rapid acquisition gradient echo; TR: repetition time; TE: echo time; TI: inversion time; FA: flip angle; ANOVA: analysis of variance

Declarations

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Author contributions

KCL,PPL,and JHL were responsible for the study concept and design. JHL and PPL contributed to the acquisition of MRI data. QQL, JKW and PPL assisted with data analysis and interpretation of data. QQL, JKW, PPL and KCL drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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Availability of data and materials

The datasets analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants or their guardians signed informed consent before participating in the study in accordance with the Institutional Review Board of Xuanwu Hospital, Capital Medical University.

Consent for publication

Not applicable.

Competing interests

All authors report no biomedical financial interests or potential conflicts of interest.

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Figures

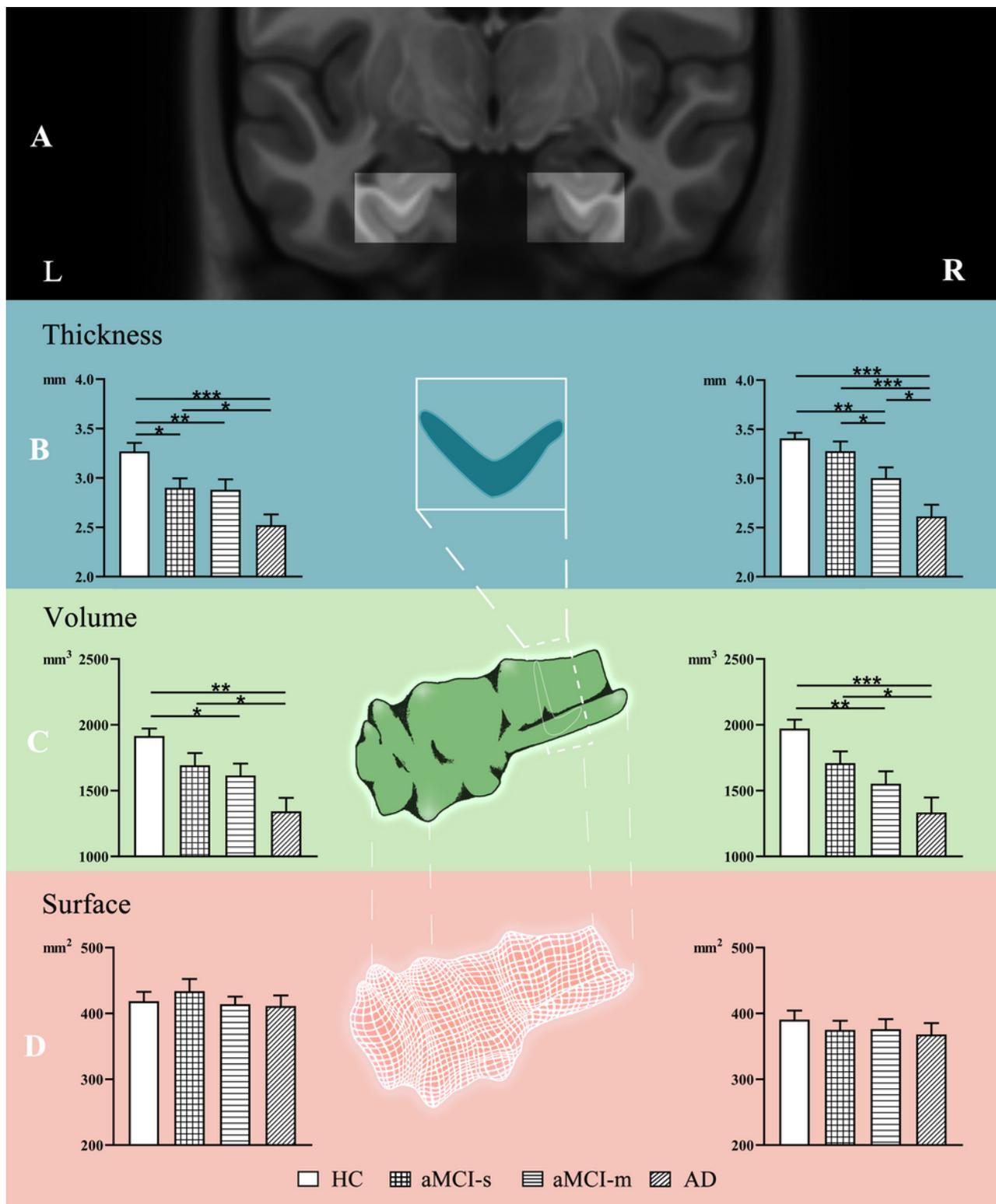


Figure 1

Alterations of ERC thickness, volume and surface area among HC, aMCI-s, aMCI-m and AD group. The ERC location of left and right hemisphere in coronal slices (A). The figure showed group difference of ERC thickness (B), volume (C) and surface area (D). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Abbreviations: L: left, R: right

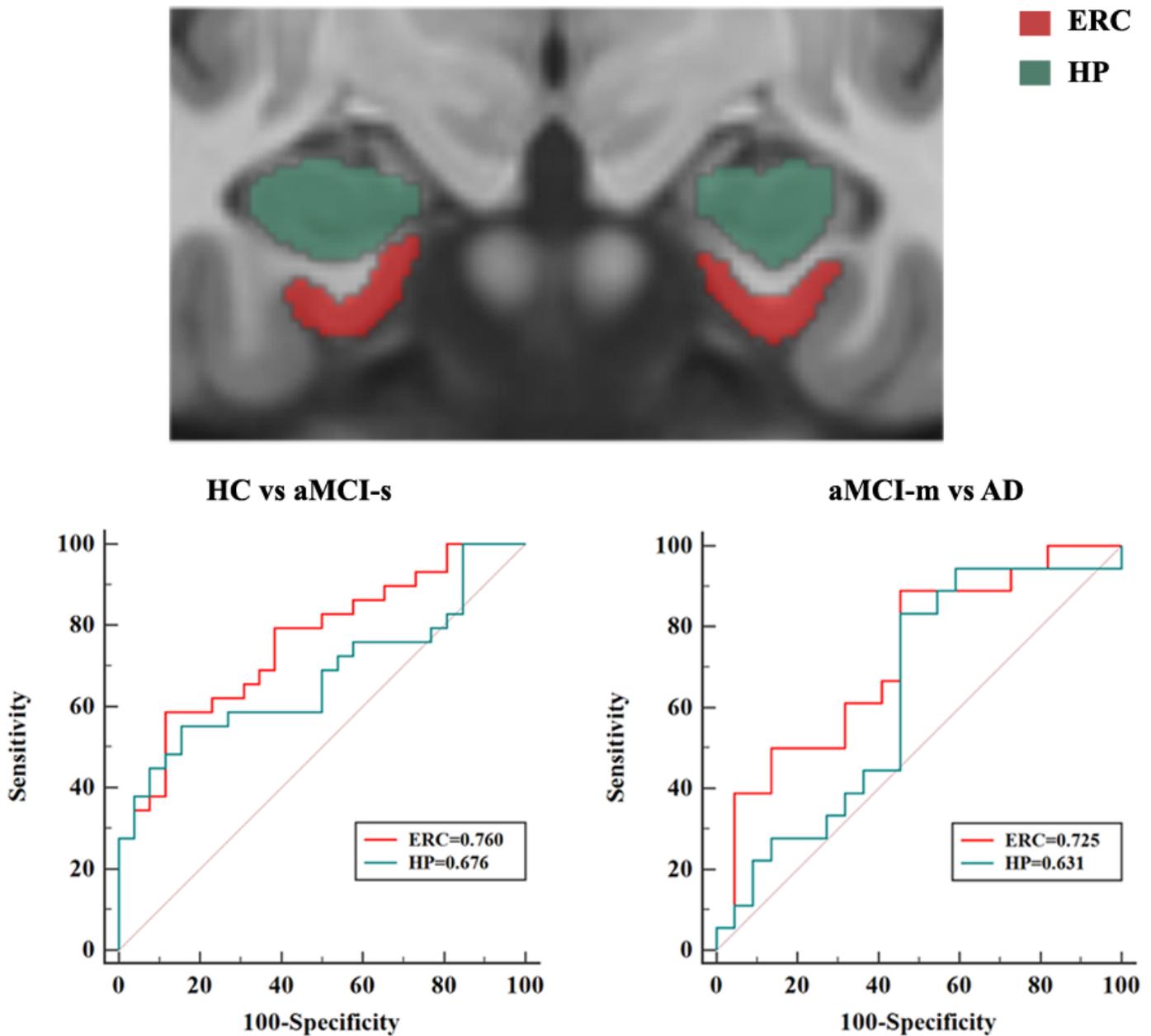


Figure 2

The ERC versus HP in discriminating HC and aMCI-s, aMCI-m and AD. Red: entorhinal cortex; green: hippocampus.

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