Published in final edited form as:

J Neuroimaging. 2016 May ; 26(3): 278–282. doi:10.1111/jon.12297.

Entorhinal cortex thickness across the human lifespan

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Abstract

Background and Purpose—Human entorhinal cortex (ERC) connects the temporal neocortex with hippocampus and is essential for memory retrieval and navigation. Markedly, there have been only few quantitative MRI works on the ERC geometric measurements in pediatric and adult healthy subjects across the lifespan. Here, we sought to fill this gap in knowledge by quantifying the ERC thickness in a very large cohort of subjects spanning nine decades of life.

Methods—Using magnetic resonance imaging data from multiple centers (IXI, MMRR, NKI, OASIS combined with the NIH-Child Dev database and locally recruited healthy subjects), we analyzed the lifespan trajectory of ERC thickness in 1660 healthy controls ranging from 2 to 94 years of age.

Results—The ERC thickness increased with age, reached a peak at about 44 years and then decreased with age. ERC thickness is hemispherically rightward-asymmetric with no gender differences. Mean ERC thickness was found to vary between 2.943 ± 0.438 mm and 3.525 ± 0.355 mm across different age populations. Also more pronounced loss of the ERC thickness in healthy aging men was noticeable.

Discussion—Our report with high spatial resolution brain MRI data from 1660 healthy controls provided important clues about ERC thickness across lifespan. We believe that our report will pave the way for the future studies investigating distinct neural pathologies related with cognitive dysfunctions.

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Keywords

Cortical thickness; Entorhinal Cortex; MRI; FreeSurfer; Big data; Lifespan

INTRODUCTION

Human cerebral cortex architecture is determined by both genetic and environmental factors. The cerebral cortex can be characterized *in vivo* on magnetic resonance imaging (MRI) by geometric measures such as folding or gyrification, sulcal depth, cortical volume, surface area and thickness. [1] In particular, cortical thickness has been shown to mark brain healthy development and natural aging. [2-5] Some cortical structures such as entorhinal cortex (ERC) have been identified as potential early markers of pathological aging and Alzheimer's disease. [1,6-8] However the in vivo trajectory of the ERC thickness and its biological correlate have not been determined during the first 9 decades of life.

The Human entorhinal cortex (ERC) is a relay hub that connects the temporal neocortex with deep archicortex gray matter structures such as hippocampus. [1,6,7] Interestingly, the ERC tissue loss with age has been an important marker of early cognitive and degenerative disorders such as Alzheimer's disease associated with impaired spatial memory. [5,8] The ERC is among the regions whose thickness provided the best discrimination between cognitively intact subjects and patients with mild cognitive impairment/Alzheimer's disease.[9] Another study showed that thinning due to Alzheimer's disease is most prominent in the rostral medial temporal cortex.[10] Furthermore, ERC volume is found to be strong predictor of cognitive decline in progression from MCI to AD[11-12] and early AD.[13] Larger entorhinal cortex volume was also associated with better memory in AD.[14] Further, anxiety status in AD predicted greater rates of decrease in EC volume.[15] Thus, detailed *in vivo* knowledge of ERC cortical thickness variation across the lifespan would help advance knowledge on the role of the ERC in neural degeneration and natural aging

Markedly, there have been only few quantitative MRI works on the ERC geometric measurements in healthy children[16] and adults[5] and across the lifespan. [17, 18] Here, we sought to fill this gap in knowledge by quantifying the ERC thickness in a very large cohort of subjects spanning nine decades of life. Our data provide for the first time a universal normative measure of the ERC thickness variation with age, gender and lateralization.

METHODS

Subjects

We quantified ERC thickness in well characterized healthy cohorts with no history of neurological conditions using customized and validated methods[1, 18] (**Figure 1A**). We pooled data from different open access and publically available sources (i.e. IXI, [19] MMRR, [20] NKI (http://fcon_1000.projects.nitrc.org), OASIS[21] as described recently[18] combined with the NIH-Child Dev database[22] and healthy subjects recruited locally. [23] Overall, high spatial resolution brain MRI data from 1660 healthy controls (770 males and

890 females) aged 2-94 years were used to study age and gender effects on ERC thickness (**Table 1**).

Anatomical MRI Data Processing and Cortical Thickness Estimation

The MRI data processing pipeline used in this work is described in more detail elsewhere, [18] we provide below a brief account of the major processing steps on the T1-weighted data which was used to obtain cortical thickness. The T1-weighted brain data were automatically segmented into cortical, sub-cortical gray matter and lobar white matter, and cerebrospinal fluid compartments using FreeSurfer (version 5.3; http://surfer.nmr.mgh.harvard.edu/) software library. [1] In brief, MRI T1-weighted data were visually inspected to rule out artifacts and input to FreeSurfer's autorecon scripts for extraction of morphometric measurements. Specifically, processing consisted of removal of non-brain tissue, Talairach transformation, segmentation of subcortical structures (i.e. thalamus proper, caudate, putamen, hippocampus and amygdale; see **Fig. 1A**). Additional pre-processing steps included intensity normalization, tessellation of the gray-matter/white-matter boundary, and labeling based on probabilistic information. FreeSurfer provided the average cortical thickness and surface area using the cortical atlas labels (http://www.freesurfer.net/fswiki/CorticalParcellation).[24] In specific, the entorhinal cortical thickness procedure, validation and application have been detailed by Fischl and colleagues. [1]

Data Quality Assurance: Scanner Stability, Intrascan and Interscan Reliability using Serial Data

Detailed examples of MRI data quality of the major OpenAccess databases used here are provided by Tustison and colleagues. [18] We included the KIRBY center data set (http://mri.kennedykrieger.org/databases.htm) from which we used data from 20 healthy adults[20] who were scanned serially within hours. Analysis of this data assured reproducibity of cortical thickness results.[18] The NIH child brain data included serial scans over 4 years. The Houston data included some healthy subjects who were scanned over 2 years along with water phantom data to assure scanner stability. [23,25-26]

Statistical Analysis

Group comparisons (e.g. left vs. right) were conducted using paired t-tests. Comparisons between males and females and data from multicenter were modeled using generalized linear models and pooled as described previously. [2, 18] Statistical power analysis and randomization results are conducted using procedures described previously. [27] Statistical significance was considered at the level of $p<0.05$ adjusting for the number of comparisons. All computations, least-squares curve fitting analysis, goodness-of-fit, and statistical analyses were conducted using MATLAB (The Mathworks Inc, Natick, MA, USA).

RESULTS

The ERC thickness increased with age, reached a peak at about 44 years and then decreased with age (**Fig. 1B**). Using random permutation, analysis-of-variance, generalized linear model and goodness-of-fit tests, gender effects were not significant ($p>0.2$). The ERC thickness is rightward-asymmetric (ERC thickness in right hemisphere is greater than left) in

healthy adults (p<0.02), in agreement with previous reports (**Fig.1 B**).[8,28] We then assessed the difference between left and right ERC thickness, focusing on narrow age ranges (Table 2; **Fig. 1C**). The ERC thickness is rightward-asymmetric on all age groups between 13-80 years (p<0.02; see **Table 2**). The left and right ERC thickness values correlated strongly on all age groups (r > 0.5; p<0.00001). This stratification is only feasible because of the large sample used, which provided sufficient statistical power to test gender and age. [27] Finally, we calculated the rate of growth or atrophy with advancing age (**Fig. 1D**). More pronounced loss of the ERC thickness in healthy aging men is noticeable.[8]

DISCUSSION

Overall, the current study reports the ERC trajectory using a large sample size collected from open access datasets of healthy controls from different centers across the United Kingdom (IXI) and the United States of America (NKI, OASIS, MMRR, NIH-Child brain development database, and Houston). We analyzed the lifespan trajectory of ERC thickness in 1660 healthy controls ranging from 2 to 94 years of age. Consistent with a previous two-center study on 476 healthy controls aged 7-87 years from Australia that did not examine ERC asymmetry and gender by age interactions, [2] the ERC thickness in our study follows a quadratic trajectory with age bilaterally. The ERC thickness is hemispherically rightward-asymmetric, and with no gender differences. This asymmetry may be related with the rightward-asymmetry of some temporal lobe structures and in particular the hippocampus. The hippocampus volume asymmetry is well-documented using meta-analyses. [33] Some authors have speculated on the neurobiological and functional correlates of this observation which remains to have some unexplained function. [8] Also, the right hemisphere has been the “dominant” hemisphere for spatial memory and orientation. Probably that is the reason why cortical thickness of ERC that has been known to play crucial role along with hippocampus in spatial skills is greater in the right hemisphere. [34] However, a post-mortem report showed verrucae part of ERC shows leftward asymmetry across gender and age.[35] Lifespan trajectory of thickness of ERC verrucae could affect the global ERC thickness across gender and age. This region has been shown to be important in AD related cortical thinning.[36,37] The inconsistency between their report and ours might have resulted from the difference in analysis technique (post-mortem vs. in-vivo imaging) and the region of interest (ERC verrucae vs. global ERC).

Our finding of a more pronounced loss in the right ERC thickness is consistent with a recent report[28] in which the lack of the laterality shift in limbic system and early loss of asymmetry in entorhinal cortex have been suggested as biomarkers to identify preclinical Alzheimer’s among other dementia. [28] Our finding of a faster rate of decrease in the ERC thickness in males is also consistent with a recent longitudinal study on older adults. [38]. Some gene polymorphism such as apolipoprotein E might play role in right-left asymmetry in the aging brain especially clinically silent ε2 and ε4 polymorphism may also explain the wide variability in healthy controls. [39] Our findings of increased loss of ERC in healthy aging men may be also partly explained by the influence of androgens on cortical thickness. Androgens have been shown to relate with cortical thickness during early brain development. [40] 30% of men over the age of 60 and 50% over the age of 70 have been found to have androgens less than the lower limit of the normal range for healthy young men. [41]

This decrease might accelerate the cortical thinning process in a more prominent way compared to women. Berchtold and colleagues[42] have shown that gene expression changes in the course of normal brain aging are sexually dimorphic. Prominent change occurred in the sixth to seventh decades across cortical regions, suggesting that this period is a critical transition point in brain aging, particularly in males. Also globally across all brain regions, males showed more gene change than females. [42]

We speculate that such baseline trajectories across the human lifespan as presented in this report will help identify *in vivo* patterns of defects in neurogenesis, neuronal migration and synaptogenesis in neurologic and psychiatric disease populations[30,44-46]. The late peak in mid forties in men and women, the pattern of rise-plateau and then decrease of ERC thickness with age mimics the histological studies on synaptic[29, 30] and dendrite tree density[31] variation with age in humans. The continued thickening and rightward-asymmetry of this important cortical zone until the mid forties may reflect the pattern also observed in hippocampal volume, [32] which may be related to adult neurogenesis or synapse/dendrite growth and then subsequent regression due to aging. [7]

Also the definitions of cortical thickness and volume deserves an attention. Cortical thickness is one dimensional measurement whereas cortical volume is three dimensional. Cortical volume has two component; thickness and surface area. We specifically reported cortical thickness of ERC as cortical volume is to be affected by factors that might change cortical surface area such as gyrification index or total intracranial volume.[47]

The availability of a universal baseline data for healthy controls would help resolve inconsistent reports in literature that failed to predict the ERC thickness trajectory across the human lifespan due to exclusive inclusion of children and adolescents[16] or adult samples.[4,43] This trajectory across the lifespan combined with the expected rightward-asymmetry may be used as normative baseline in experimental design of studies on patients on one hand, and in studies targeting the biological markers and environmental modulators of cortical thickness variation as age advances. [2,3]

Our study highlights the importance of early intervention and potential strategies in middle adulthood to reduce ERC cortical thinning and subsequent effects on cognition in particular subjects with high risk of developing Alzheimer's disease. [48-50]

Limitations

Our study is limited as data on other variables related to subject hormonal activity, genetic risk factors, cognition, education, socioeconomics, anxiety, depression, body mass, diet, parent education, ethnic history, and alcohol intake were not provided or made uniform across the data bases, and therefore we did not attempt to study such covariates in this short communication.

Also our findings are trends derived from cross-sectional data and but not longitudinal observations. Results from cross-sectional observation should be carefully interpreted when drawing longitudinal conclusions.

Another limitation of our study is that the imaging data were acquired on different scanner platforms. The variability of local thickness measurements has been found to be about 0.15-0.17 mm in average across platforms and different field strengths.[51]

Acknowledgements

This work is funded by the National Institutes of Health (NIH/NINDS R01-NS052505-04) and the Dunn Research Fund to K.M.H., NS046565 to R.E.F, NIMH Grant R01 MH 085667 and the Pat Rutherford, Jr. Endowed Chair in Psychiatry to J.C.S. P.K. is supported by U54EB020403 and RO1EB015611.

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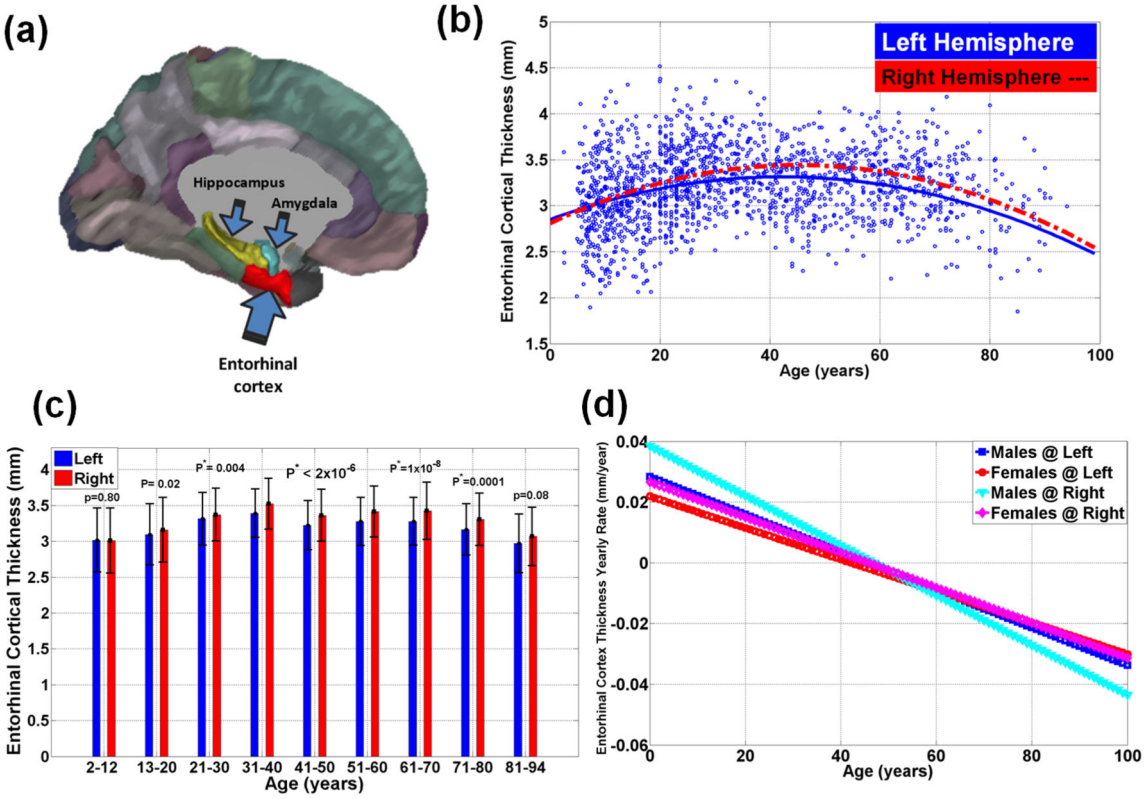

Figure 1.

(a) Three-dimensional view of the human medial temporal lobe showing the entorhinal cortex (Brodmann's area 28) with respect to hippocampus, and amygdala as anatomical landmark anterior to hippocampus (b) Scatter of the left ERC thickness variation with age along with the least-squares fit of left and right ERC using a quadratic model age trajectory on all subjects as gender effects were not significant ($p>0.1$). Note the rightward-asymmetric ERC especially in young and older adults ($p<0.02$; $F>94.9$). (c) Bar plots showing average and standard deviation of the left and right entorinal cortical thickness along with paired t-test comparisons using data grouped for ages 2-12, 13-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, and 81-94 years (see **Table 2**). (d) Rate of change of ERC thickness as function of age in both hemispheres for males and females. The best fit for the ERC cortical thickness in mm was:

Left = $(2.85 \pm 0.03) + (0.022 \pm 0.002)*\text{Age}-(0.00026\pm0.00002)*\text{Age}^2$ (peak ~ 44 years)

Right = $(2.81 \pm 0.03) + (0.028 \pm 0.002)*\text{Age}-(0.00031\pm0.00002)*\text{Age}^2$ (peak ~ 47 years)

Table 1

Basic information and web-location on healthy control anatomical MRI data sets used in our analyses.

Data base	N(Females)	Age (years)	Scanner	Voxel size (x, y, z) mm
I. IXI	563(313)	20-86	Philips 3T&1.5T GE 1.5T	1,1,1
II. NKI	183 (74)	5-83	Siemens 3T	1,1,1
III. OASIS	311 (193)	18-94	Siemens 1.5T	1,1,1.33
IV. KIRBY	20 (10)	22-61	Philips 3T	1,1,1.2
V. NIH-Child	306 (165)	2-18	Siemens 1.5T GE 1.5T	1,1,1 1,1,1.4-1.8
VI. Houston	277(135)	6-86	Philips 3T	~1,1,1
Total	1660(890)	2-94		

Web links to the five open data sets used are listed below. For the first four databases please see representative data samples, quality assurance measures and other details provided by Tustison and colleagues[11]:

I. http://biomedic.doc.ic.ac.uk/brain-development

II. http://fcon_1000.projects.nitrc.org/

III. http://oasis-brains.org/

IV. http://www.nitrc.org/projects/multimodal

V. http://pediatricmri.nih.gov/nihpd/info/index.html

Table 2

Entorhinal cortical thickness average and standard deviation of the left and right entorinal cortical thickness along with paired t-test comparisons and percentage difference using multicenter data from healthy controls grouped for ages 2-12, 13-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, and 81-94 years.

Age Group (years)	Total Number (# Females)	Left ERC Thickness Mean ± S.D. (mm)	Right ERC Thickness Mean ± S.D. (mm)	P (Left vs. Right)	Percentage difference Between Right and Left (%)
2-12	297 (158)	3.018 ± 0.446	3.012 ± 0.454	0.80	−0.19
13-20	187 (84)	3.096 ± 0.427	3.159 ± 0.452	0.02	2.03
21-30	341 (183)	3.314 ± 0.369	3.372 ± 0.366	0.004	1.73
31-40	180 (76)	3.391 ± 0.338	3.525 ± 0.355	2.4×10^{-7}	3.86
41-50	187 (95)	3.225 ± 0.341	3.362 ± 0.363	2.1×10^{-7}	4.19
51-60	158 (95)	3.276 ± 0.336	3.416 ± 0.354	1.8×10^{-6}	4.16
61-70	158 (98)	3.277 ± 0.333	3.425 ± 0.398	9.5×10^{-9}	4.41
71-80	87 (61)	3.165 ± 0.356	3.308 ± 0.365	9.6×10^{-5}	4.41
81-94	44 (27)	2.943 ± 0.438	3.055 ± 0.411	0.08	3.70