Entorhinal Cortex Thickness Predicts Cognitive Decline in Alzheimer’s Disease

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Abstract. Biomarkers for Alzheimer’s disease (AD) based on non-invasive methods are highly desirable for diagnosis, disease progression, and monitoring therapeutics. We aimed to study the use of hippocampal volume, entorhinal cortex (ERC) thickness, and whole brain volume (WBV) as predictors of cognitive change in patients with AD. 120 AD subjects, 106 mild cognitive impairment (MCI), and 99 non-demented controls (NDC) from the multi-center pan-European AddNeuroMed study underwent MRI scanning at baseline and clinical evaluations at quarterly follow-up up to 1 year. The rate of cognitive decline was estimated using cognitive outcomes, Mini-Mental State Examination (MMSE) and Alzheimer disease assessment scale–cognitive (ADAS-cog) by fitting a random intercept and slope model. AD subjects had smaller ERC thickness and hippocampal and WBV volumes compared to MCI and NDC subjects. Within the AD group, ERC > WBV was significantly associated with baseline cognition (MMSE, ADAS-cog) and disease severity (Clinical Dementia Rating). Baseline ERC thickness was associated with both longitudinal MMSE and ADAS-cog score changes and WBV with ADAS-cog decline. These data indicate that AD subjects with thinner ERC had lower baseline cognitive scores, higher disease severity, and predicted greater subsequent cognitive decline at one year follow-up. ERC is a region known to be affected early in the disease. Therefore, the rate of atrophy in this structure is expected to be higher since neurodegeneration begins earlier. Focusing on structural analyses that predict decline can identify those individuals at greatest risk for future cognitive loss. This may have potential for increasing the efficacy of early intervention.

Keywords: Alzheimer’s disease, biomarker, cognitive decline, entorhinal cortex, hippocampus, whole brain volume

INTRODUCTION

Alzheimer’s disease (AD) is the most common form of dementia and its prevalence is set to rise in the coming decades [1]. Biomarkers for AD, based on non-invasive methods are highly desirable for diagnosis, disease progression, and monitoring therapeutics.
A range of neuroimaging techniques provide insight into AD-related neurodegeneration, including structural magnetic resonance imaging (MRI), positron emission tomography (PET), and functional MRI. Neuroimaging techniques can improve early detection and aid in identifying individuals at risk of developing AD. In particular, structural MRI has provided insight into the neuroanatomical profile of pre-clinical and early AD. MRI has demonstrated significant value in the prediction of conversion and disease progression [4].

From a neuropathological perspective, it has been suggested that the medial temporal lobe is the anatomical site of the first pathological alterations in AD [5, 6]. It has been shown that MRI is useful for detecting atrophy in the medial temporal structures affected early in the neurodegenerative process [4]. Decreased volumes of hippocampus and entorhinal cortex are connected to AD and to individuals at risk of developing the disease. It has been shown that atrophy of the medial temporal lobe can predict conversion in subjects in the prodromal stages of the disease, referred to as mild cognitive impairment (MCI) [4, 7–9]. Atrophy also correlates with memory impairment. Numerous studies have used baseline and serial MRI measures to predict future cognitive decline but mostly for conversion from MCI to AD [9–12], and there is need for assessing these MRI measures as potential markers of disease progression in AD.

We have previously reported from the European Union AddNeuroMed multi-center MRI study that structural MRI measures discriminated AD from controls and MCI; and also demonstrated potential for prediction of conversion from MCI to AD [13–18]. The aims of the current study were to examine (a) the relationship between baseline hippocampal volume, entorhinal cortex thickness, and whole brain volume with baseline cognitive measures in (i) AD (ii) MCI, and (iii) age matched non-demented controls (NDC); and (b) to assess the associations of the baseline MRI measures with subsequent cognitive change over one year period. Our hypothesis was that smaller brain structures would be associated with worse baseline cognition and greater cognitive decline.

METHODS
Participants and clinical assessment

This study included data from 120 AD, 106 MCI, and 99 NDC participants from the AddNeuroMed study, a European Union funded FP6 program. AddNeuroMed is a longitudinal, multi-center study of biomarkers for AD [19]. All subjects underwent MRI scanning at baseline and cognitive testing at baseline and every 3 months up to one year.

Data was collected from six different sites across Europe: University of Kuopio, Finland; University of Perugia, Italy; Aristotle University of Thessaloniki, Greece; King’s College London, United Kingdom; University of Lodz, Poland; and University of Toulouse, France. Written consent was obtained where the research participant had capacity, and in those cases where dementia compromised capacity, then assent from the patient and written consent from a relative, according to local law and process, was obtained. This study was approved by ethical review boards in each participating country. The inclusion and exclusion criteria were as follows.

Alzheimer’s disease
Inclusion criteria. Patients with probable mild to moderate AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s disease and Related Disorders Association [NINCDS-ADRDA] criteria) [20] and Mini-Mental State Examination (MMSE) [21] score range between 12 and 28, age 65 years or above.

Exclusion criteria. Significant neurological or psychiatric illness, significant unstable systematic illness, or organ failure.

Mild cognitive impairment
Inclusion criteria. MMSE score range between 24 and 30, Clinical Dementia Rating (CDR) [22] scale score of 0.5, Geriatric Depression Scale score less than or equal to 5, age 65 years or above, medication stable, and good general health.

Exclusion criteria. Met the DSM-IV criteria for dementia, significant neurological or psychiatric illness, significant unstable systematic illness, or organ failure. The distinction between MCI and NDC was based on two criteria: CDR = 0 labeled the subject as control and a CDR = 0.5 labeled the subject as MCI. For the MCI subjects it was preferable that the subject and informant reported occurrence of memory problems.

Non-demented control
Inclusion criteria. MMSE score range between 24 and 30, CDR = 0. Geriatric Depression Scale score less
than or equal to 5, age 65 years or above, medication stable, and good general health.

Exclusion criteria. Met the DSM-IV criteria for dementia, significant neurological or psychiatric illness, significant unstable systematic illness, or organ failure.

The clinical assessment and cognitive testing of the AddNeuroMed subjects followed a standard protocol described previously [13, 23, 24]. Assessments included a structured interview including a detailed case and family history, Cambridge Examination for Mental Disorders of Older People (CAMDEX) [25]; cognitive testing with MMSE and Alzheimer disease assessment scale – Cognitive (ADAS-cog) [26] and stage of dementia with CDR sum of boxes score. The cognitive testing with ADAS-cog and MMSE were repeated every 3 months for a period of a year.

Genotyping
Venous blood was obtained for DNA extraction and genotyping for the apolipoprotein (APOE) alleles using standard methods [27]. The APOE haplotype (rs7412 and rs429358) was determined using two allelic discrimination assays based on fluorogenic 5′ nuclease activity: TaqMan single nucleotide polymorphism Genotyping Assays (Applied Biosystems.).

Magnetic resonance imaging
Data acquisition for the AddNeuroMed study was designed to be compatible with the Alzheimer Disease Neuroimaging Initiative (ADNI) [28]. The imaging protocol included a high resolution sagittal 3D T1-weighted MPRAGE volume (voxel size 1.1 × 1.1 × 1.2 mm3) and axial proton density/T2-weighted fast spin echo images. The MPRAGE volume was acquired using a custom pulse sequence specifically designed for the ADNI study to ensure compatibility across scanners [28]. Full brain and skull coverage was required and detailed quality control was carried out on all MR images according to the AddNeuroMed quality control procedure [23, 29].

Regional volume segmentation
We applied the Freesurfer pipeline (version 4.5.0) to the MRI images to produce regional cortical thickness and subcortical volumetric measures. Cortical reconstruction and subcortical volumetric segmentation includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure [30], automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) [30-32], intensity normalization [33], tessellation of the grey matter white matter boundary, automated topology correction [34, 35], and surface deformation following intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class [36-38]. Once the cortical models are complete, registration to a spherical atlas takes place which utilizes individual cortical folding patterns to match cortical geometry across subjects [39]. This is followed by parcellation of the cerebral cortex into units based on gyral and sulcal structure [40, 41]. This segmentation approach has been used for multivariate classification of AD and healthy controls [16, 17, 42, 72], neuropsychological-image analysis [15, 18], imaging-genetic analysis [43, 44], and biomarker discovery [24, 73, 74]. The current study focused on regional brain volumes and cortical thickness measures, specifically hippocampal volume, entorhinal cortex (ERC) thickness, and whole brain volume (WBV) which have been proposed to be related to AD and have received high level of attention in the recent literature [4, 7-12, 16, 17]. Volumes from the left and the right hemisphere were averaged together. All volumetric measures from each subject were normalized by the subject’s intracranial volume. Cortical thickness measures were not normalized and were used in their raw form [45].

Statistical analysis
Non-parametric and t-test analyses were used to test for differences in continuous outcomes such as MRI-based measures, cognition, severity measures, age, and education between AD, MCI, and NDC. The chi-square test was used to test for differences in categorical outcomes such as gender and the presence of the APOE ε4 allele. Correlation analysis (Spearman non-parametric test) was used for associations between brain region volumes, cognitive scores (MMSE, ADAS-cog), and CDR for illness staging within the groups.

Rates of cognitive decline were determined by change in the cognitive measures (MMSE and ADAS-Cog total scores). These measures were estimated by fitting a random intercept and slope model using xtmixed in STATA 10 (Stata Corporation, College.
Station, TX, USA). The average baseline cognitive outcome and the average change in the cognitive outcome over the follow-up time were calculated for all the AD patients, MCI, and NDC as a group (fixed effects). Subject-specific intercept and slope terms which reflected deviation from the group average (random effects) were also calculated. Follow-up time was defined as the number of years (days/365.25) passed since the baseline visit, and up to 5 time points (three months apart) was recorded for each patient. Time squared was also used to assess nonlinear cognitive decline.

Adjustment for age at baseline, education years, gender, cholinesterase inhibitors, center, and APOE genotype was made. Continuous outcomes were centered to their mean to aid interpretation of the model. As the main focus of the study was to study associations for cognitive decline in AD, we did not differentiate MCI into converters and non-converters and used all MCI as a group.

An interaction between the MRI-based brain volumes and follow-up time (Entorhinal Cortex × TIME, Whole Brain × TIME, or Hippocampus × TIME) was used to test the null hypothesis that there was no difference in the rate of cognitive function, i.e., in slopes for different baseline brain volumes. The coefficient of the time variable in this case (TIME) would indicate the association between follow-up time with cognitive decline for average brain volume (since the variables are centered around their mean); the coefficient of the brain volume for each subject (Entorhinal Cortex, Whole Brain, or Hippocampus) would indicate the association of baseline brain volume with baseline cognitive assessment score and the coefficient of the interaction term (MRI brain volume × follow-up time) would indicate the effect of brain volume on cognitive decline over time. The results were based on using the brain measures as continuous variables and the quartiles for graphical view.

RESULTS

Demographics, brain region, and baseline cognition

The subject characteristics are shown in Table 1. Predictably the AD patients had smaller regional brain measures and lower cognitive scores compared to age-matched MCI and NDC subjects. Within AD subjects, ERC volumes correlated significantly with baseline MMSE ($p<0.01$, $r^2=0.3$), ADAS-cog ($p<0.01$, $r^2=0.3$), and CDR scores ($p<0.001$, $r^2=0.3$) and with hippocampal volume ($p=0.04$, $r^2=0.2$). Within the MCI group, there were no significant correlations between MMSE and brain volumes.

Brain region and longitudinal changes in cognition

We did not identify any deviation from a linear cognitive decline model by including the TIME squared variable in the model (non-significant coefficient) and all the models therefore assumed a linear cognitive decline.

Association of baseline ERC thickness with cognitive decline in AD subjects

Mixed effects models indicated a significant interaction between follow-up time measured with the

| Table 1 | Demographics and brain volumes between subjects with Alzheimer’s disease (AD), mild cognitive impairment (MCI), and non-demented controls (NDC). |
|---|---|---|---|---|---|---|
| Gender (Female %) | 54 | 49 | 53 | NS\textsuperscript{c} | a |
| Age in years | 74.62 (6.21) | 74.00 (5.64) | 74.56 (5.16) | NS\textsuperscript{a} | b |
| Education | 7.91 (4.01) | 9.03 (4.18) | 10.67 (4.89) | b\textsuperscript{c} | a, c |
| APOE4 (%) | 56 | 38 | 28 | NS\textsuperscript{a} | a |
| MMSE | 20.83 (4.83) | 27.21 (6.44) | 28.96 (1.24) | a, b, c\textsuperscript{c} |
| % reduction to NDC | 1.95 (0.37) | 2.27 (0.35) | 2.67 (0.27) | a, b, c\textsuperscript{c} |
| Hippocampus (cm\textsuperscript{3}) | 27 | 15 | 27 | a, b, c\textsuperscript{c} |
| % reduction to NDC | 0.82 (0.04) | 0.85 (0.03) | 0.85 (0.03) | a, b\textsuperscript{c} |
| Whole brain volume | 0.82 (0.04) | 0.85 (0.03) | 0.85 (0.03) | a, b\textsuperscript{c} |

Mean (SD); \textsuperscript{c} chi-square; \textsuperscript{a} t-test; MMSE, Mini-Mental State Examination; APOE4, presence of at least one e4 allele. **Multiple comparisons abbreviated as: (a) AD subjects differ from subjects with MCI, (b) AD subjects differ from NDC subjects, (c) MCI subjects differ from NDC subjects.
Table 2
Mixed effects regression for subjects with Alzheimer’s disease (AD), non-demented control (NDC), and mild cognitive impairment (MCI) over one year, adjusted for age, gender, center, education, APOE e4, and cholinesterase inhibitor therapy in AD group

<table>
<thead>
<tr>
<th>Baseline brain area</th>
<th>Variable</th>
<th>AD (n=120)</th>
<th>ADAS-cog</th>
<th>NDC (n=99)</th>
<th>MCI (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MMSE</td>
<td>MMSE</td>
<td>MMSE</td>
<td>MMSE</td>
</tr>
<tr>
<td></td>
<td>Beta</td>
<td>SE</td>
<td>p</td>
<td>Beta</td>
<td>SE</td>
</tr>
<tr>
<td>Entorhinal cortex</td>
<td>Time (years)</td>
<td>–1.333</td>
<td>0.334</td>
<td>&lt;0.001</td>
<td>2.675</td>
</tr>
<tr>
<td></td>
<td>Entorhinal cortex thickness</td>
<td>2.661</td>
<td>0.755</td>
<td>&lt;0.001</td>
<td>–5.083</td>
</tr>
<tr>
<td></td>
<td>Time (years) × ERC thickness</td>
<td>1.705</td>
<td>0.648</td>
<td>0.009</td>
<td>–5.737</td>
</tr>
<tr>
<td>Whole brain volume</td>
<td>Time (years)</td>
<td>–1.300</td>
<td>0.531</td>
<td>0.000</td>
<td>2.505</td>
</tr>
<tr>
<td></td>
<td>Whole brain volume</td>
<td>0.029</td>
<td>0.012</td>
<td>0.016</td>
<td>–0.065</td>
</tr>
<tr>
<td></td>
<td>Time (years) × WB volume</td>
<td>0.018</td>
<td>0.009</td>
<td>0.049</td>
<td>–0.052</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Time (years)</td>
<td>–1.322</td>
<td>0.336</td>
<td>&lt;0.001</td>
<td>2.574</td>
</tr>
<tr>
<td></td>
<td>Hippocampal volume</td>
<td>2.471</td>
<td>1.105</td>
<td>0.025</td>
<td>–2.471</td>
</tr>
<tr>
<td></td>
<td>Time (years) × Hipp volume</td>
<td>0.219</td>
<td>0.906</td>
<td>0.809</td>
<td>–2.509</td>
</tr>
</tbody>
</table>

Coefficients of the interaction terms (brain measure × time) represented the influence of baseline brain measures on rates of change. Time (years) represents the association of follow-up time with cognitive decline for mean brain measures, and the respective brain measure coefficients represent the association of baseline measures with cognitive decline at baseline. MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer disease assessment scale-Cognitive.
MMSE and ADAS-Cog and baseline ERC thickness \( p = 0.009 \) and \( p < 0.001 \), respectively) which indicated that baseline ERC thickness was related to the rate of cognitive decline measured with these two cognitive scales (Table 2).

Higher baseline ERC thickness was associated with slower cognitive decline measured with MMSE and ADAS-cog. In more detail, after adjusting for covariates, higher baseline ERC thickness in AD cases were associated with both higher baseline cognition measured with the MMSE and ADAS-cog measures (beta = 2.661 (0.755), \( p < 0.001 \)) and with a slower cognitive decline, measured with MMSE (beta = 1.705 (0.648), \( p = 0.009 \)) and ADAS-cog (beta = −5.737 (1.282), \( p < 0.001 \)). To aid the interpretation, Fig. 1A displays the predicted MMSE and ADAS-cog slopes for the four baseline ERC thickness quartiles, highlighting the differences both in baseline cognitive scores but also in the rate of cognitive decline between different ERC quartiles, especially, for patients in the 4th quartile. For example, the expected average MMSE decline for patients in the lower ERC quartile was −2.34 per year (\( p = 0.001 \)), whereas there was no
significant decline for patients in the upper ERC quartile \( (\beta = 0.372, \ p = 0.557) \). The same effect was observed for ADAS-Cog.

**Association of baseline WBV with cognitive decline in AD subjects**

As in the case of ERC, mixed effect models indicated that baseline WBV was associated with higher baseline cognitive scores (MMSE \( \beta = 0.028 \) (0.012), \( p = 0.016 \); ADAS-cog \( \beta = -0.065 \) (0.024), \( p = 0.006 \)) and also appeared to modify the rate of cognitive decline measured with MMSE and ADAS-cog, although the effect on MMSE measured decline was only marginal (Table 2). In more detail, baseline WBV appeared to have a strong influence on the rate of cognitive decline measured with ADAS-cog \( (\beta = -0.052 \) (0.019), \( p = 0.007 \)\) and showed a modest effect on MMSE assessed decline \( (\beta = 0.018 \) (0.009), \( p = 0.049 \)\). Lower baseline WBV predicted cognitive decline when assessed with the ADAS-cog and also to an extent with the MMSE (Fig. 1B, Table 2).

**Association of baseline hippocampal volume with cognitive decline in AD subjects**

Finally, mixed effects models indicated that the baseline volume of the hippocampus was associated with baseline MMSE \( (\beta = 2.473 \) (1.105), \( p = 0.025 \)), i.e., patients with larger hippocampus volumes had higher MMSE (Table 2), but was not associated with baseline ADAS-cog scores, neither did it seem to modify the rate of cognitive decline assessed by the two cognitive tools (Fig. 1C, Table 2).

**Discussion**

The main findings of the study were: (A) patients with mild to moderate AD had thinner ERC, smaller hippocampal volume, and WBV compared to subjects with MCI and NDC. Within the AD group, (B) baseline ERC and WBV were significantly associated with baseline cognition measured by MMSE and ADAS-cog and also with stage of dementia as measured by CDR sum of boxes scores. (C) Baseline ERC thickness but not hippocampal volume was associated with longitudinal changes in cognition over one year and could predict the degree of decline slopes as measured by MMSE and ADAS-cog. (D) Baseline WBV was also associated with greater subsequent cognitive decline measured with ADAS-cog, although the association with the MMSE was marginal. The models were controlled for age at baseline, education years, gender, cholinesterase inhibitors, center, and APOE genotype.

Reductions in the hippocampal and entorhinal regions between the AD and NDC in our study were similar to previous studies [4, 46]. The differences in these regions between MCI and NDC were also
and AD [57]. Within the ERC, there is subregional promotion of early susceptibility of this cell type to aging features of layer II neurons in the ERC interact to developmental, morphological, functional, and molecular neurons and then spread to the ERC proper [5]. Development of brains appears first in the prealpha transentorhinal the spread of neurofibrillary tangles in postmortem [5]. Pathologically, Braak and Braak demonstrated that progression through subiculum to the hippocampus proper primarily begins in ERC, followed by immediate pro-
declarative (conscious) memory [56]. AD pathology parts of the medial temporal lobe system that supports the first functions to be affected in disease progres-
sion [51]. Both ERC and hippocampus are essential
elements of the medial temporal lobe system that supports declarative (conscious) memory [56]. AD pathology primarily begins in ERC, followed by immediate pro-
gression through subiculum to the hippocampus proper
[5]. Pathologically, Braak and Braak demonstrated that the spread of neurofibrillary tangles in postmortem brains appear first in the prealpha transentorhinal neurons and then spread to the ERC proper [5]. Develop-
ment, morphological, functional, and molecular features of layer II neurons in the ERC interact to promote early susceptibility of this cell type to aging and AD [57]. Within the ERC, there is subregional specificity for molecular alterations that may initiate cognitive decline and with a potential to directly con-
tribute to downstream cascades in its primary afferent regions, the hippocampus [57].

Previous clinical stud-
ies demonstrated that the rates of cognitive decline accelerated with time in AD [58, 59], suggesting accel-
erated neurodegeneration in AD. Both cross-sectional and serial MRI studies on patients with AD have consistently found volume losses in both ERC and hippocampus [48, 51, 60–64]. Taken together, these findings suggest that AD is associated with progressive atrophy of both ERC and hippocampus, providing potential surrogate markers for this disease. Assuming that degenerative processes proceed at similar rates in the ERC and hippocampus, one might therefore expect to find higher atrophy rates in the structure where neu-
rodegeneration began earlier. Our results substantiate this hypothesis, which is consistent with the view of earlier involvement of AD pathology in the ERC than the hippocampus [65].

Mungas and colleagues previously reported that hippocampal atro-
phy predicted decline in AD but only in those subjects without lacunes [12].

WBV correlated with baseline clinical measures and predicted future cognitive decline, which probably reflects the correspondence between these measures of overall cerebral loss and global cognitive measures in the moderate stages of AD as reported earlier [52, 55].

Structures within the temporal lobe have long been associated with AD decline because of their critical role in the formation of long-term memory, one of the first functions to be affected in disease progress-
sion [51]. Both ERC and hippocampus are essential parts of the medial temporal lobe system that supports declarative (conscious) memory [56]. AD pathology primarily begins in ERC, followed by immediate pro-
gression through subiculum to the hippocampus proper
[5]. Pathologically, Braak and Braak demonstrated that the spread of neurofibrillary tangles in postmortem brains appear first in the prealpha transentorhinal neurons and then spread to the ERC proper [5]. Develop-
ment, morphological, functional, and molecular features of layer II neurons in the ERC interact to promote early susceptibility of this cell type to aging and AD [57]. Within the ERC, there is subregional
better predictor of future clinical decline than cerebrospinal fluid biomarkers [69, 70]. Neuroimaging biomarkers that predict decline would have a great potential for increasing the efficacy of early intervention [71]. By focusing structural analyses on regions known to be first affected in AD, we may better identify those individuals at greatest risk for future memory decline, valuable in determining the course of future care needed by these individuals, requiring more substantial care at an earlier time point.

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