Minimal Atrophy of the Entorhinal Cortex and Hippocampus: Progression of Cognitive Impairment

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Key Words

Alzheimer disease • Brain MRI • Cognitive and functional impairment • Dementia • Entorhinal and hippocampal atrophy • Progression • Visual rating

Abstract

Background: In Alzheimer's disease, neurodegenerative atrophy progresses from the entorhinal cortex (ERC) to the hippocampus (HP), limbic system and neocortex. The significance of very mild atrophy of the ERC and HP on MRI scans among elderly subjects is unknown. **Methods:** A validated visual rating system on coronal MRI scans was used to identify no atrophy of the HP or ERC (HP₀; ERC₀), or minimal atrophy of the HP or ERC (HP_{ma}; ERC_{ma}), among 414 participants. Subjects fell into the following groups: (1) ERC₀/HP₀, (2) ERC_{ma}/HP₀, (3) ERC₀/HP_{ma}, and (4) ERC_{ma}/HP_{ma}. HP volume was independently measured using volumetric methods. **Results:** In comparison to ERC₀/HP₀ subjects, those with ERC₀/HP_{ma} had impairment on 1 memory test, ERC_{ma}/HP₀ subjects had impairment on 2 memory tests and the Mini

Mental State Examination (MMSE), while ERC_{ma}/HP_{ma} subjects had impairment on 3 memory tests, the MMSE and Clinical Dementia Rating. Progression rates of cognitive and functional impairment were significantly greater among subjects with ERC_{ma}. **Conclusion:** Minimal atrophy of the ERC results in greater impairment than minimal atrophy of the HP, and the combination is additive when measured by cognitive and functional tests. Rates of progression to greater impairment were higher among ERC_{ma} subjects.

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Introduction

Very early diagnosis and intervention has been proposed as the most promising approach for the successful treatment of Alzheimer's disease (AD), which may have two phases prior to the development of a dementia syn-

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drome [1]. These prodromal phases of AD include: (1) a presymptomatic stage [1], marked primarily by amyloid deposition, as reflected by elevated levels of cerebrospinal fluid A β -42 levels [2, 3] and amyloid PET tracer retention [4] but little or no neurodegenerative changes; (2) a prodromal stage characterized not only by amyloid deposition, but also by subtle cognitive deficits associated with synaptic dysfunction, cell death and atrophy [5], especially of the entorhinal cortex and the hippocampus (particularly the anterior aspects of the CA1 sector and the subiculum), and eventually the entire limbic system and neocortex [6]. Measurement of atrophy in the entorhinal cortex (ERC) and subregions of the hippocampus (HP) is therefore likely to be an early biological marker of the neurodegenerative phase of AD.

While moderate-to-severe medial temporal atrophy may support the diagnosis of AD, the significance of isolated minimal or mild atrophy of the ERC and/or the HP, especially among individuals with subjective memory complaints or subtle cognitive deficits, is unknown. Automated methods have been developed to provide quantitative volumetry of the ERC and the subregions of the HP [7, 8]; however, these methods are labor intensive, require a high level of technical expertise, are invalidated by common technical deficiencies in image acquisition, and are not easily adaptable for routine clinical or research use.

We have refined a semiquantitative visual rating system for assessing medial temporal atrophy (VRS-MTA), initially developed by Scheltens et al. [9], so as to produce reliable, valid and independent assessments of atrophy in the anterior aspects of the ERC, HP (including the subiculum and CA1 regions) and perirhinal cortex. We have shown that VRS-MTA provides better discrimination between subjects with amnesic MCI (aMCI) and no cognitive impairment, as well as higher correlations with tests of episodic memory among subjects with aMCI, than standard volumetric methods of assessing HP volumes [10]. Furthermore, assessments of ERC and HP atrophy by VRS-MTA or volumetric methods have been shown to predict future cognitive decline and conversion to AD among healthy elderly individuals and those with MCI [10–14].

In the current study, the effect of minimal atrophy of the ERC and the anterior HP on cognitive test performance, functional abilities and progression to more impaired states was assessed. Given that ERC atrophy precedes HP atrophy in AD, and that HP atrophy appears to be a non-specific finding in many conditions, we hypothesized that minimal ERC atrophy (even in the absence of

HP atrophy) would be best correlated to subtle cognitive impairment in the elderly, especially among those individuals who are in the early stages of AD.

Methods

Subject Recruitment

In this study, we included 414 male and female participants from the Florida Alzheimer's Disease Research Center Clinical Core in Miami Beach and Tampa. Subjects were between 50 and 88 years of age, with 71% being English- and 29% Spanish-speakers. The study was approved by the Institutional Review Boards at Mount Sinai Medical Center, Miami Beach, University of Miami, Miami, and the University of South Florida, Tampa. All subjects or a legal representative provided informed consent.

Evaluations

The following were completed on all subjects: (1) full clinical history, obtained from a reliable informant; (2) neurological evaluation; (3) psychiatric evaluation, including administration of the Geriatric Depression Scale [15] and the Neuropsychiatric Inventory [16]; (4) Clinical Disease Rating Scale (sum of boxes; CDR-sb) [17]; (5) Mini-Mental State Examination (MMSE) [18]; (6) a neuropsychological test battery, as outlined in the National Alzheimer's Coordinating Center [19] protocol, as well as additional tests, which included the Three Trial Fuld Object Memory Evaluation [20] and the Hopkins Verbal Learning Test (delayed recall) [21]; (7) Unified Parkinson Disease Rating Scale (motor section) [22].

Diagnostic Procedures

Physician's Cognitive Diagnosis

The physician assigned a cognitive diagnosis of no cognitive impairment, MCI or dementia, as described previously [23]. Briefly, the physician's cognitive diagnosis was based on the subject's entire clinical history and functional status, which was derived from the history itself, CDR rating, functional activity questionnaire, and MMSE score and subscores – taking into account the subject's educational and cultural background, sensory (especially visual and hearing) and motor deficits, language and speech disorders, medical and psychiatric conditions, and the perceived reliability of the informant. The presence of subtle cognitive and personality deficits – such as repetitiveness, impaired logical reasoning, difficulty understanding or following implicit and even explicit instructions, executive dysfunction, perseverative behaviors and mental rigidity – were also taken into consideration [24].

Neuropsychological Diagnosis

All neuropsychological tests were administered in the subjects' native language (English or Spanish), and compared to age- and education-adjusted normative data, as described previously [25, 26]. Memory measures were: the 3-trial Fuld Object Memory Evaluation [20], Delayed Visual Reproduction of the Wechsler Memory Scale-R [27] and the Hopkins Verbal Learning Test (delayed recall) [21]. Non-memory tests included: category fluency [28], letter fluency (language) [29], block design WAIS-III (visuospatial) [30], trails B (executive) [29] and similarities WAIS-R (executive) [31]. Neuropsychological classifications [25, 26] were made as follows: (1) a test score of ≥ 1.5 SD below expected nor-

Fig. 1. VRS-MTA. Images depicting 4 degrees of atrophy in HP and ERC. 0 = No atrophy; 1 = minimal atrophy; 2 = mild atrophy; 3 = moderate atrophy; 4 = severe atrophy.

mative values on any single test for MCI syndromes; (2) ≥ 2.0 SD below expected normative values in 1 memory and 1 non-memory test for dementia (corresponding to NINCDS-ADRDA criteria) [32]. Nomenclature used for neuropsychological diagnosis was: normal, non-amnesic MCI (naMCI; single or multi-domain), amnesic MCI (aMCI; single or multi-domain) and dementia.

Consensus Cognitive Diagnoses

To ensure that the consensus diagnosis was made systematically across sites and longitudinally in the same individual, an algorithmic approach to combining the physician's cognitive diagnosis with the neuropsychological diagnosis was used, as described previously [23]. Patients diagnosed with aMCI met all of the formal criteria of Petersen et al. [33] for MCI.

MRI scans were acquired on a 1.5-T machine (Siemen's Symphony, Iselin, N.J., USA, or General Electric, HDX, Milwaukee, Wisc., USA) using a proprietary 3D-magnetization-prepared rapid-acquisition gradient echo or 3D spoiled gradient echo sequences. MRI scans were acquired in the coronal plane, and contiguous slices with thickness of ≤ 1.5 mm were reconstructed.

Visual Rating System for Assessing Medial Temporal Atrophy

Using this validated computer-assisted VRS, coronal images on a single coronal MRI slice (at the level of the mamillary bodies) were semiquantitatively assessed so as to grade atrophy of the HP and ERC according to the following scale: 0 = no atrophy; 1 = minimal atrophy; 2 = mild atrophy; 3 = moderate atrophy; 4 = severe atrophy (fig. 1). The VRS-MTA program provides a library of drop-down images, depicting images showing each grade of atrophy for the ERC, HP and perirhinal cortex, as well as the anatomical boundaries of these structures. We have previously reported that excellent inter-rater reliability for individual medial temporal lobe structures has been obtained with κ -values among 2 raters ranging between 0.75 and 0.94 for inter-rater reliability 0.87 and 0.93 for intra-rater reliability [34]. Furthermore inter-rater reliabilities for scores 0, 1 or 2 were performed on a new data set of patients by two of the authors on this paper (D.V. and E.P.).

The inter-rater reliabilities obtained were: left HP 0.705 (SE = 0.16), right HP 0.835 (SE = 0.11), left ERC 0.744 (SE = 0.13) and right ERC 0.794 (SE = 0.14).

Specifically for this study, we included only those subjects who had no atrophy of the HP (HP₀) or ERC (ERC₀) on both right and left sides or minimal atrophy of the HP (HP_{ma}) or the ERC (ERC_{ma}), on either the left, right or both sides – thus providing subjects with 4 possible combinations of HP and ERC atrophy: (1) ERC₀/HP₀; (2) ERC_{ma}/HP₀; (3) ERC₀/HP_{ma}; (4) ERC_{ma}/HP_{ma}.

Volumetric Measures

Volumetric analysis of brain MRIs utilized the modified International Brain Atlases using Statistical Parametric Mapping (IBASPM) [35].

ApoE Genotype

ApoE genotype was determined using standard methods [34], and ApoE- $\epsilon 4$ frequencies were subsequently calculated for each diagnostic group. ApoE genotypes were available for 296 subjects.

Longitudinal Evaluation Procedures

A total of 305 subjects had a 1-year follow-up evaluation, including neurological, psychiatric and neuropsychological evaluations, all clinical scales and re-diagnosis by the diagnostic algorithm.

Statistical Analysis

Group comparisons of demographic variables across the 4 atrophy groups were analyzed using ANOVA or χ^2 tests, as appropriate. Comparisons of clinical variables (e.g. MMSE score) across 4 atrophy groups were analyzed using a general linear model from SAS for Windows version 9.1 (SAS Institute, Inc, Cary, N.C., USA), with age as a covariate, or with a χ^2 test. The Scheffe post hoc procedure was used to examine differences between means of demographic variables. The GT2 post-hoc option in the general linear model of SAS, which is more conservative than the Tukey-Kramer option, was used to examine differences between age-adjusted means of clinical variables. Differences in progression rates between groups were assessed using χ^2 procedures.

Table 1. Demographics, diagnosis and ApoE allele

	ERC ₀ /HP ₀ (n = 163)	ERC ₀ /HP _{ma} (n = 148)	ERC _{ma} /HP ₀ (n = 39)	ERC _{ma} /HPC _{ma} (n = 64)	p value (for F or χ^2)
Age (mean), years	68.9 $\pm$ 5.7 ^a	71.7 $\pm$ 6.3 ^b	70.3 $\pm$ 6.2 ^{a, b}	74.8 $\pm$ 7.5 ^c	<0.0001
Race, n					
White	128	128	33	52	n.s.
Non-White	35	20	6	12	
Hispanic, n					
Yes	42	43	12	21	n.s.
No	120	103	27	43	
Education, years	14.0 $\pm$ 3.2	13.9 $\pm$ 3.1	13.8 $\pm$ 4.3	13.5 $\pm$ 3.8	n.s.
ApoE- ϵ 4 allele frequency, %	13.4	15.1	20.4	13.5	n.s.
Subjects genotyped, n	116	116	27	37	
Consensus cognitive diagnosis, n	158	141	36	60	0.03
Normal or Pre-MCI	131 (83)	106 (24)	24 (66)	34 (57)	
naMCI	8 (5)	13 (9)	3 (8)	8 (13)	
aMCI	13 (8)	16 (11)	5 (14)	13 (22)	
Dementia	6 (4)	6 (4)	4 (11)	5 (8)	

Figures in parentheses are percentages.

^{a-c} Different letters indicate significantly different values (post hoc Scheffe tests).

Results

Demographics and ApoE

The subjects differed with respect to age [$F(3, 410) = 14.7$; $p < 0.0001$]. Post hoc tests indicated that the ERC₀/HP_{ma} group was older than the ERC₀/HP₀ group by nearly 3 years, and the ERC_{ma}/HP_{ma} group was significantly older than the other 3 groups by as much as 6 years. There were no significant differences among the groups in terms of years of education, race or ApoE- ϵ 4 allele frequency (table 1). Among subjects diagnosed with no cognitive impairment, the largest percentage belonged to the ERC₀/HP₀ group, and the lowest percentage belonged to the ERC_{ma}/HP_{ma} group ($\chi^2 = 26.5$; $p = <0.03$). Among subjects diagnosed with naMCI, aMCI or dementia, the largest percentage belonged to the ERC_{ma}/HP_{ma} group, whereas the lowest percentage belonged to the ERC₀/HP₀ group of subjects ($\chi^2 = 26.5$; $p = <0.003$) (table 1).

Clinical Data and Volumetric Hippocampal Measures

Analyses of ordinal measures were adjusted for age, since there were significant age differences between atrophy groups. Subjects in the ERC₀/HP₀ group had the highest scores on the cognitive tests – MMSE, Logical Memory (delayed recall), Fuld Object Memory Evaluation and the Hopkins Verbal Learning Test (delayed recall) – and the lowest (least impaired) scores on the func-

tional tests – CDR-sb. Those in the ERC_{ma}/HP_{ma} group had the lowest scores on the cognitive tests and the highest scores on the CDR-sb group, with the ERC₀/HP_{ma} and ERC_{ma}/HP₀ groups being intermediate on all test scores (table 2). The percentage of subjects with global CDR scores of ≥ 0.5 was lowest among ERC₀/HP₀ (38%) and greatest among the ERC_{ma}/HP_{ma} group (80%), with the other 2 groups being intermediate [$\chi^2(3) = 32.4$, $p < 0.0001$].

The right HP volume was higher for the ERC₀/HP₀ than for the ERC₀/HP_{ma}, ERC_{ma}/HP₀ and ERC_{ma}/HP_{ma} groups, while the left HP volume was significantly higher in the ERC₀/HP₀ group than for the ERC_{ma}/HP₀ and the ERC_{ma}/HP_{ma} groups, but not higher than for the ERC₀/HP_{ma} group. There were no differences between the ERC_{ma}/HP₀, ERC₀/HP_{ma} and ERC_{ma}/HP_{ma} groups with regards to HP volumes on either side (table 2).

Clinical Diagnoses (table 3)

Subjects with ERC_{ma} (isolated or co-occurring with HP_{ma}) were more likely to be cognitively impaired (naMCI, aMCI and dementia) (56 vs. 27%), and were more likely to have global CDR scores of ≥ 0.5 (69%) than subjects with no ERC atrophy, with or without minimal HP atrophy (45%) (fig. 2). The frequency of progression from a global CDR score of 0 to 0.5 was significantly greater among those with ERC_{ma}/HP₀ or ERC_{ma}/HP_{ma} as com-

Table 2. Cognitive/functional scores and HP volumes among subjects with and without ERC_{ma} or HP_{ma}

	ERC ₀ /HP ₀ (n = 163)	ERC ₀ /HP _{ma} (n = 148)	ERC _{ma} /HP ₀ (n = 39)	ERC _{ma} /HPC _{ma} (n = 64)	F or χ^2	p value
<i>Clinical data</i>						
MMSE	28.3 (2.5) ^a	28.0 (2.0) ^{a, b}	27.2 (2.6) ^b	27.2 (2.4) ^b	4.86	0.002
Logical Memory (delayed recall)	10.1 (4.2) ^a	9.1 (4.2) ^a	9.4 (4.8) ^a	7.2 (4.5) ^b	7.02	<0.0001
Fuld Object Memory Test	24.5 (3.2) ^a	23.7 (4.1) ^{a, b}	22.4 (5.2) ^{b, c}	21.2 (5.1) ^c	8.8	<0.0001
Hopkins Verbal Retention Test (delayed recall)	8.4 (2.7) ^a	6.9 (3.1) ^b	6.8 (3.5) ^b	4.9 (3.6) ^c	17.0	<0.0001
CDR-sb	0.6 (1.2) ^a	0.8 (1.0) ^{a, b}	0.9 (1.3) ^{a, b}	1.4 (1.5) ^b	5.4	0.0004
Global CDR scores ≥ 0.5 , %	38	53	52	80	32.4	<0.0001
<i>Volumetric hippocampal measures</i>						
Right HP/whole brain	0.00195 ^a (n = 143)	0.00180 ^b (n = 132)	0.00176 ^b (n = 34)	0.00169 ^b (n = 50)	16.4	<0.0001
Left HP/whole brain	0.00208 ^a	0.00196 ^{a, b}	0.00194 ^b	0.00184 ^b	11.3	<0.0001

F statistics are adjusted for age.

^{a-c} Means with different letters are significantly different (post hoc Tukey-Kramer).

Table 3. Clinical diagnosis, CDR global score and progression (or improvement) in subjects with and without ERC_{ma}

	No ERC atrophy (ERC ₀ /HP ₀ or ERC ₀ /HP _{ma} ; n = 311), %	Minimal ERC atrophy (ERC _{ma} /HP ₀ or ERC _{ma} / HP _{ma} ; n = 103), %	χ^2	p value
Subjects with cognitive impairment, %	27	56	18.6	<0.0001
CDR scores of ≥ 0.5 , %	45	69	17.6	<0.0001
Progression from CDR of 0 to ≥ 0.5 , %	11 (13/122)	27 (7/26)	4.9	0.03
Progression from CDR of 0.5 to ≥ 1 , %	4 (4/113)	5 (2/44)	0.9	n.s.
Improvement from CDR of 0.5 to 0.0, %	21 (24/113)	9 (4/44)	3.2	0.07

Cognitive impairment defined as a National Alzheimer's Coordinating Center diagnosis of naMCI, aMCI or dementia [19].

pared to those who with ERC₀/HP₀ or ERC₀/HP_{ma} (27 vs. 11%). There was no difference in the distribution of atrophy among those who progressed from a CDR of 0.5 to 1.

Discussion

This study demonstrates that among mildly impaired subjects (mean MMSE score = 27.8), isolated minimal atrophy of the HP was associated with deficits in 1 of 3 episodic memory tests (i.e. the Hopkins Verbal Learning Test delayed recall), while isolated minimal atrophy of the ERC was associated with more widespread cognitive deficits on memory tests and the MMSE. The combination of HP_{ma} and ERC_{ma} was associated with even more ac-

centuated cognitive deficits, along with functional deficits (i.e. elevated scores on the CDR-sb). The presence of minimal atrophy of the ERC was also more likely to be associated with a cognitively impaired diagnosis than if there was no atrophy of the ERC. Regardless of the presence of HP_{ma}, subjects with ERC_{ma} more frequently than not (56 vs. 27%) were diagnosed with naMCI, aMCI or dementia or a CDR score of 0.5 or 1 (69 vs. 45%) (table 3), suggesting that minimal atrophy of the ERC is a clinically significant finding.

In this study, ApoE- ϵ 4 carriers were no more likely to have minimal atrophy of the ERC or HP than non-carriers. ApoE- ϵ 4 frequencies were not different across patient groups categorized by the presence or absence of minimal atrophy in the HP, ERC or HP+ERC. This lack

of influence of the ApoE- ϵ 4 genotype on the likelihood of having ERC or HP atrophy is consistent with the already known mechanism of action of the ApoE- ϵ 4 genotype, which mediates its risk for AD solely via increasing amyloid deposition, but not by enhancing risk of neurodegeneration and resulting selective atrophy of medial temporal structures [5]. As shown by data obtained from the Alzheimer's Disease Neuroimaging Initiative patients [1], atrophy of the hippocampus (and presumably of the ERC) becomes detectable only after a substantial delay following detectable deposition of A β protein in the brain, suggesting that degenerative changes – presumably mediated by amyloid deposition and measured by HP and ERC atrophy – will be relatively insensitive to the rate or amount of amyloid deposition in the brain mediated by the ApoE genotype.

The rate of progression from a CDR score of 0 to 0.5 was significantly greater among those with minimal ERC atrophy, as compared to those without ERC atrophy. There was also a trend towards improvement ($p = 0.07$) in CDR scores from 0.5 to 0 among those without ERC atrophy compared to those with minimal ERC atrophy. These findings point to the importance of even minimal atrophy of the ERC as a marker of neurodegenerative disease in very early stages.

While minimal atrophy of the HP is also indicative of neurodegenerative disease – as suggested by the cognitive impairment associated with isolated minimal HP atrophy – it appears clear from the results of this study that minimal atrophy of the ERC has a greater impact than minimal atrophy of the HP on cognition, as well as on functional abilities, as reflected in elevated CDR-sb scores. An apparent 'dose effect' is also suggested in tables 2 and 3, such that the combination of minimal atrophy of the ERC with minimal atrophy of the HP has greater cognitive and functional consequences than isolated minimal ERC atrophy.

In each group in which minimal atrophy of either the HP, ERC or HP+ERC was present (as measured by the VRS), HP volumes were also reduced (table 2). Even though the reduction in HP volumes appeared to be severest among those with combined ERC and HP minimal atrophy, there was no significant difference found in HP volumes between the 3 groups with minimal atrophy measured by VRS. Reduction of HP volumes appears to be a relatively non-specific event that occurs in response to various degenerative and non-degenerative insults to the brain. Mild degrees of HP atrophy have been associated with neocortical amyloid deposition [37]. Conditions, such as Lewy body disease, depression, stress-relat-

Fig. 2. Frequency of cognitive impairment, defined by clinical diagnosis and CDR scores, for minimal ERC versus HPC atrophy. * $p < 0.05$, ERC = 1 vs. ERC = 0 for both definitions of cognitive impairment (χ^2 test).

ed disorders, steroid treatment, seizures, multiple sclerosis, stroke and brain trauma have all been associated with mild HP atrophy [38]. Many of these conditions are often not associated with cognitive or functional deficits, which by itself results in very subtle, if any, cognitive deficits. Atrophy of the ERC may be more specific to early degenerative diseases, such as AD and frontotemporal lobar dementias.

The anterior aspects of the ERC and the HP, especially the subiculum and CA1 sector of the HP – which is the focus of atrophy measurement by VRS-MTA at the coronal slice intersecting the mamillary bodies – may be especially vulnerable to the pathological changes in early AD [6, 39]. A close correlation between whole HP volume measures and VRS-MTA measures of minimal atrophy of HP on a single slice intersecting the anterior aspect of the HP was not expected. Reduction in HP volumes (5.8–7.7%) was found among those with HP_{ma}, but there was no significant further reduction in HP volume among those with isolated ERC_{ma} or the combination of ERC_{ma} and HP_{ma} (10.6–13.3%). Even though subjects with ERC_{ma}/HP_{ma} clearly had more cognitive and functional impairment than subjects with isolated HP_{ma}, or isolated ERC_{ma}, HP volumes did not distinguish between these subject groups.

Quantitative assessment of the volume of the ERC can be achieved by a technique involving manual outlining of the boundaries of the ERC in contiguous MRI slices. This method – which is labor-intensive and requires rigorous

attention to detail to ensure reliability – has shown that among patients with MCI and early AD, ERC volume is reduced well before HP volume [40], and may be superior to HP volume reduction in predicting conversion from MCI to AD [14, 41–43]. These findings suggest that in a typical clinical setting, visual rating of ERC atrophy – in addition to rating of HP atrophy – can be a practical and reliable biomarker of early AD pathology [32] for confirming the diagnosis of early predementia stages of AD.

A limitation of this study is that we measured atrophy of the ERC and HP on a single coronal slice, which may not always be representative of the anatomy and severity of atrophy of the entire medial temporal lobe. The advantage gained by using a single standard slice is that it considerably increases inter-rater and intra-rater reliability of measurement. However, VRS-MTA measurements can be limited by the ability of the raters, the quality of the images and the slice thickness (slice thickness of <2 mm is required to avoid partial volume artifacts from neighboring structures).

Currently used criteria for the diagnosis of AD have been found to have high sensitivity (range 0.81–0.98), but relatively low specificity (range 0.41–0.84), when assessed against a histopathological diagnosis of AD [44]. The results of this study demonstrate that the presence of a degenerative disease, such as AD, is implied by even minimal atrophy of the ERC, because it is associated with progressive cognitive and functional impairment. This

suggests that the accuracy of a diagnosis of early AD (in the MCI or pre-MCI stage) could be improved by using even minimal atrophy of the ERC and HP as biomarkers to support the diagnosis. These findings may be of particular importance among subjects with MCI, very mild dementia, or those with confounding factors such as ongoing psychiatric illness, low education and cultural deprivation. Structural MRI is ordered routinely for the assessment of patients with cognitive impairment and dementia so as to exclude the presence of structural abnormalities, such as stroke, brain tumors and hydrocephalus as causative factors. The results of this study suggest that the use of visual rating of the ERC on appropriately ordered sequences and slice thicknesses of structural MRI scans could be a highly cost effective method of confirming the diagnosis of early forms of AD, thereby often avoiding the expense of additional methods.

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Disclosure Statement

The authors report no conflicts of interest.

References

- 1 Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ: Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010;9:119–128.
- 2 Riemenschneider M, Lautenschlager N, Wagenpfeil S, Diehl J, Drzezga A, Kurz A: Cerebrospinal fluid tau and beta-amyloid 42 proteins identify Alzheimer disease in subjects with mild cognitive impairment. *Arch Neurol* 2002;59:1729–1734.
- 3 Mattsson N, Zetterberg H, Hansson O, Andreassen N, Parnetti L, Jonsson M, Herukka SK, van der Flier WM, Blankenstein MA, Ewers M, Rich K, Kaiser E, Verbeek M, Tsolaki M, Mulugeta E, Rosén E, Aarsland D, Visser PJ, Schröder J, Marcussen J, de Leon M, Hampel H, Scheltens P, Pirttilä T, Wallin A, Jönköping ME, Minthon L, Winblad B, Blennow K: CSF Biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA* 2009;302:385–393.
- 4 Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergström M, Savitcheva I, Huang GF, Estrada S, Ausén B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Långström B: Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* 2004;55:306–319.
- 5 Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA: APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol* 2010;67:122–131.
- 6 Braak H, Braak E: Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 1991;82:239–259.
- 7 Konrad C, Ukas T, Nebel C, Arolt V, Toga AW, Narr KL: Defining the human hippocampus in cerebral magnetic resonance images – an overview of current segmentation protocols. *Neuroimage* 2009;47:1185–1195.
- 8 Price CC, Wood MF, Leonard CM, Towler S, Ward J, Montijo H, Kellison I, Bowers D, Monk T, Newcomer JC, Schmalfluss I: Entorhinal cortex volume in older adults: reliability and validity considerations for three published measurement protocols. *J Int Neuropsychol Soc* 2010;16:846–855.
- 9 Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool: Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *J Neurol* 1995;242:557–560.
- 10 Duara R, Loewenstein DA, Potter E, Appel J, Greig MT, Urs R, Shen Q, Raj A, Small B, Barker W, Schofield E, Wu Y, Potter H: Medial temporal lobe atrophy on MRI scans and the diagnosis of Alzheimer disease. *Neurology* 2008;71:1986–1992.
- 11 Jack CR, Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, Kokmen E: Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment. *Neurology* 1999;52:1397–1403.

- 12 Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Tangalos EG, Kokmen E: Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology* 2000;55:484–489.
- 13 Rusinek H, Endo Y, De Santi S, Frid D, Tsui WH, Segal S, Convit A, de Leon MJ: Atrophy rate in medial temporal lobe during progression of Alzheimer disease. *Neurology* 2004; 63:2354–2359.
- 14 Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, Rusinek H, Pelton GH, Honig LS, Mayeux R, Stern Y, Tabert MH, de Leon MJ: Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. *Neurology* 2007; 68:828–836.
- 15 Sheikh JJ, Yesavage JA: Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version; in Brink TL (ed): *Clinical Gerontology: A Guide to Assessment and Interventions*. New York, Haworth Press, 1986, pp 165–173.
- 16 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J: The Neuropsychiatric Inventory: comprehensive assessment of neuropathology in dementia. *Neurology* 1994;44:2308–2314.
- 17 Morris JC: The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* 1993;43:2412–2414.
- 18 Folstein M, Folstein S, McHugh P: "Mini-Mental State": a practical method for grading the clinician. *J Psychiatr Res* 1975;12:129–138.
- 19 Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, Cummings J, DeCarli C, Foster NL, Galasko D, Peskind E, Dietrich W, Beekly DL, Kukull WA, Morris JC: The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. *Alzheimer Dis Assoc Disord* 2009;23:91–101.
- 20 Fuld PA: Fuld Object-Memory Evaluation. Wood Dale, Stoelting, 1981.
- 21 Brant J, Benedict R: Hopkins Verbal Learning Test—Revised. Odessa, Psychological Assessment Resources, 2001.
- 22 Fahn S, Elton R: Unified Parkinson's disease rating scale; in Fahn S, Marsden D, Calne D (eds): *Recent Developments in Parkinson Diseases*. London, Macmillan, 1987, pp 153–163.
- 23 Duara R, Loewenstein DA, Greig M, Acevedo A, Potter E, Appel J, Raj A, Schinka J, Schofield E, Barker W, Wu Y, Potter H: Reliability and validity of an algorithm for the diagnosis of normal cognition, mild cognitive impairment, and dementia: implications for multi-center research studies. *Am J Geriatr Psychiatry* 2010;18:363–370.
- 24 Storandt M, Grant EA, Miller JP, Morris JC: Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. *Neurology* 2006;67:467–473.
- 25 Loewenstein DA, Acevedo A, Ownby R, Agron J, Barker WW, Isaacson R, Strauman S, Duara R: Using different memory cut-offs to assess mild cognitive impairment. *Am J Geriatric Psych* 2006;14:911–919.
- 26 Loewenstein DA, Acevedo A, Agron J, Martinez G, Duara R: The use of amnesic and nonamnesic composite measures at different thresholds in the neuropsychological diagnosis of MCI. *J Clin Exp Neuropsychol* 2007;29:300–307.
- 27 Wechsler D: *The Wechsler Adult Intelligence-Revised*. New York, Psychological Corporation, 1981.
- 28 Acevedo A, Loewenstein DA, Barker WW, Harwood DG, Luis C, Bravo M, Hurwitz DA, Aguero H, Greenfield L, Duara R: Category fluency test: normative data for English- and Spanish-speaking elderly. *J Int Neuropsychol Soc* 2000;6:760–769.
- 29 Spreen O, Strauss E: *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*, ed 2. New York, Oxford University Press, 1998.
- 30 Wechsler D: *The Wechsler Adult Intelligence-Revised*. New York, Psychological Corporation, 1981.
- 31 Wechsler D: *The Wechsler Adult Intelligence Scale*, ed 3. San Antonio, Psychological Corporation, 1997.
- 32 McKhann G, Drachman DA, Folstein MF, Katzman R, Price DL, Stadlan E: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–944.
- 33 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–308.
- 34 Urs R, Potter E, Barker W, Appel J, Loewenstein DA, Zhao W, Duara D: Visual rating system (VRS) for assessing magnetic resonance images (MRIs): a tool in the diagnosis of MCI and Alzheimer's disease. *J Comput Assist Tomogr* 2009;33:73–78.
- 35 Alemán-Gómez Y, Melie-García L, Valdés-Hernández P: IBASPM: Toolbox for automatic parcellation of brain structures. Presentation, 12th Ann Meet Organ Human Brain Mapping, June 11–15, 2006, Florence. Available on CD-ROM NeuroImage 2005; 27(1).
- 36 Wenham PR, Price WH, Blandell G: Apolipoprotein E genotyping by one-stage PCR. *Lancet* 1991;337:1158–1159.
- 37 Chételat G, Villemagne VL, Bourgeat P, Pike KE, Jones G, Ames D, Ellis KA, Szoeke C, Martins RN, O'Keefe GJ, Salvado O, Masters CL, Rowe C, Australian Imaging Biomarkers and Lifestyle Research Group: Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. *Ann Neurol* 2010; 67:317–324.
- 38 Geuze E, Vermetten E, Bremner JD: MR-based in vivo hippocampal volumetrics. 2. Findings in neuropsychiatric disorders. *Mol Psychiatry* 2005;10:160–184.
- 39 Braak H, Alafuzoff I, Arzberger T, Kretschmar H, Del Tredici K: Acta staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Neuropathology* 2006; 112:389–404.
- 40 Killiany RJ, Hyman BT, Gomez-Isla T, Moss MB, Kikinis R, Jolesz F, Tanzi R, Jones K, Albert MS: MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology* 2002;58:1188–1196.
- 41 Jauhiainen AM, Pihlajamäki M, Tervo S, Niskanen E, Tanila H, Hänninen T, Vanninen RL, Soironen H: Discriminating accuracy of medial temporal lobe volumetry and fMRI in mild cognitive impairment. *Hippocampus* 2009;19:166–175.
- 42 Desikan RS, Cabral HJ, Fischl B, Guttman CR, Blacker D, Hyman BT, Albert MS, Killiany RJ: Temporoparietal MR imaging measures of atrophy in subjects with mild cognitive impairment that predict subsequent diagnosis of Alzheimer disease. *AJNR Am J Neuroradiol* 2009;30:532–538.
- 43 Desikan RS, Fischl B, Cabral HJ, Kemper TL, Guttman CR, Blacker D, Hyman BT, Albert MS, Killiany RJ: MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD. *Neurology* 2008;71:819–825.
- 44 Nagy Z, Esiri MM, Hindley NJ, et al: Accuracy of clinical operational diagnostic criteria for Alzheimer's disease in relation to different pathological diagnostic protocols. *Dement Geriatr Cogn Disord* 1998;9:219–226.