2018 IEEE EMBS International Conference on Biomedical & Health Informatics (BHI)
4-7 March 2018
Las Vegas, Nevada, USA

Hippocampal and Entorhinal cortex volume changes in Alzheimer's Disease patients and Mild Cognitive Impairment Subjects

S.Leandrou, I. Mamais, S Petroudi, Member IEEE, PA, Kyriacou, Senior Member, IEEE, Constantino Carlos Reyes- Aldasoro, Senior Member, IEEE, C.S. Pattichis, Senior Member, IEEE
for the Alzheimer's Disease Neuroimaging Initiative**

***Abstract*— Hippocampal and entorhinal cortex as scanned in Magnetic Resonance Imaging (MRI), are two of the most commonly used Regions of Interest (ROIs) for the assessment of Alzheimer's disease (AD). Both structures are used for the classification between Normal Controls (NC), Mild Cognitive Impairment (MCI) and AD subjects and for the disease prognosis. The objective of this study was to evaluate how the volume of these two structures changes between the following groups: NC vs AD, NC vs MCI, MCI vs MCI converters (MCIc - subjects who had converted to AD within 48 months), and AD vs MCIc subjects. Both structures were significantly reduced in volume for MCIc and AD subjects compared to NC. For both MCI and MCIc groups, the atrophy rate was correlated for both structures. In AD subjects, entorhinal cortex was more affected by atrophy. In conclusion, structural MRI and volumetric measurements of the hippocampus and entorhinal cortex can be used as early signs for the assessment of AD, and this is in agreement with previous studies.**

***Keywords*-Alzheimer's disease; classification; entorhinal cortex; hippocampus; mild cognitive impairment; prediction**

I. INTRODUCTION

Alzheimer's Disease (AD) represents the most common form of dementia, and one of the major causes of disability in later life. Every 67 seconds someone in the United States develops Alzheimer's and it is the 6th leading cause of death in the United States [1]. According to World Health Organization (WHO) the number of people living with dementia worldwide is currently estimated at 47 million and is projected to increase to 75 million by 2030. It is estimated that by 2050 the number of cases will almost triple.

Even nowadays, the diagnosis of AD is probable and only post-mortem material can confirm the disease. The biopsy reveals deposits of amyloid-β (Aβ) plaque deposition and tau protein (Neurofibrillary Tangles - NFTs) in the brain tissue [2]. Thus, due to brain inaccessibility, the diagnosis is based on clinical and neuropsychological tests, which evaluate memory and language abilities. Mini Mental State examination (MMSE) [3] and Clinical Dementia Rating (CDR) [4] are commonly used in the assessment of AD.

However, structural changes within the brain occur years before the first clinical symptoms appear [5]. As a consequence, when a patient is diagnosed with AD by using only clinical and psychometric assessment the brain tissue will probably undergone widespread and irreversible synaptic loss. Furthermore, the Mild Cognitive Impairment (MCI) stage, which represents the transitional stage between normal ageing and AD, is not easily identified by cognitive tests, because these subjects do not have major memory problems. Therefore, the research community has driven a search for diagnostic imaging markers especially of those derived from quantitative Magnetic Resonance Imaging (MRI). According to the new diagnostic criteria [6] for the assessment of AD, a subject should be positive to one of the following tests: (i) Medial Temporal Lobe (MTL) atrophy as seen in MRI, (ii) Temporoparietal hypometabolism as seen in Positron Emission Tomography (PET), (iii) Positivity on amyloid imaging as seen in PET and (iv) abnormal neuronal Cerebrospinal Fluid (CSF) markers (tau and/or Aβ).

At the very early stage of the disease there is an inevitable progression of atrophy which initially affects the MTL [7] followed by progressive neocortical damage. The entorhinal cortex and hippocampus are two of the most common Regions of Interest (ROIs) used in both *in vivo* and post mortem investigations for the detection of AD. *In vivo* structural MRI studies [8], [9], agree with post mortem studies [10], [11], and indicate that the degenerative process, initiates from the entorhinal cortex, followed by hippocampus, amygdala and parahippocampal gyrus. With the disease progression, atrophy expands in temporal, parietal and frontal neocortices [12], [13] and as a consequent to the rest of the brain.

The objective of this study was to investigate how the hippocampus and entorhinal cortex ROIs, are affected in AD and MCI subjects.

II. MATERIALS AND METHODS

A. Study design and participants

For the fulfilment of this study, data were acquired from the Alzheimer's Disease Neuroimaging Initiative (ADNI)

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

S. Leandrou is with Department of Health Sciences, European University Cyprus, Nicosia, Cyprus and with School of Mathematical Sciences, Computer Science and Engineering, City, University of London, London, United Kingdom. (email: s.leandrou@euc.ac.cy)

C.S. Pattichis is with Department of Computer Science, University of Cyprus, Nicosia, Cyprus (email: pattichi@ucy.ac.cy)

PA. Kyriacou and Constantino Carlos Reyes-Aldasoro are with School of Mathematical Sciences, Computer Science and Engineering, City, University of London, London, United Kingdom (email: p.kyriacou@city.ac.uk and Reyes@city.ac.uk)

(http://adni.loni.usc.edu/). The ADNI is an ongoing longitudinal multicenter effort launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations as a public-private partnership. Subjects across the US and Canada, from over 50 sites have been recruited to test whether serial MRI, Positron Emission Tomography (PET), Cerebrospinal fluid (CSF), and other biological markers with clinical and neuropsychological assessment can be used for the classification of subjects or to predict the progression of MCI and early AD. All the subjects were selected from standardized data collections and specifically the ADNI-1 Complete 2 and 3 year 1.5 Tesla datasets. These subjects had a screening scan and then at 6 months, 1 year, 18 months (MCI only), 2, and 3 year (Normal Controls (NC) and MCI only). According to the ADNI inclusion criteria, enrolled subjects were all between 55 and 90 years of age and spoke either English or Spanish. Each subject was willing, able to perform all test procedures described in the protocol and had a study partner able to provide an independent evaluation of functioning. Inclusion criteria for NC were: MMSE scores between 24 and 30; CDR of zero; absence of depression, MCI and dementia. Inclusion criteria for MCI were: MMSE scores between 24 and 30; CDR of 0.5; objective memory loss, measured by education adjusted scores on Wechsler Memory Scale Logical Memory II [14], absence of significant levels of impairment in other cognitive domains; absence of dementia. Inclusion criteria for AD were: MMSE scores between 20 and 26; CDR of 0.5 or 1.0; NINCDS/ADRDA criteria for probable AD [6], [15]. Detailed description of inclusion/exclusion criteria can be found in the ADNI protocol (http://adni.loni.usc.edu/methods/documents/).

Overall, 218 NC, 349 MCI and 165 AD subjects were included in this study. However, 74 MCI subjects converted within 48 months from their baseline scan to AD thus, MCI converters (MCIc) group was added to the analysis.

B. MRI Acquisition

All the subjects had a standardized protocol on 1.5-T MRI units from Siemens Medical Solutions and General Electric Healthcare. MR protocols included high-resolution (typically $1.2\times1.25\times1.25$ mm^3 voxels) volumetric T1-weighted, inversion recovery prepared, structural images obtained in sagittal plane. The data had undergone gradwarp-corrected for (i) distortion due to gradient non-linearity [16], and (ii) corrected for image intensity non-uniformity using N3 [17], and B1 non-uniformity [18] and (iii) scaling-corrected based on phantom measures.

C. Measurements extraction

T1-weighted volumetric 3D sagittal magnetization prepared rapid gradient-echo (MPRAGE) scans were collected for each subject. Volume measures of the hippocampus and entorhinal cortex were reconstructed using FreeSurfer v5.3 software, Martinos Center for Biomedical Imaging, Harvard-MIT, Boston USA [19]. Freesurfer is based on Surface-based Analysis (SBA) and derives morphometric measures from geometric models of the cortical surface. It uses a probabilistic atlas derived from a manually labeled training set of expert measurements and automatically performs subcortical and cortical segmentation of the brain.

Briefly, the Freesurfer surface-based pipeline stages include: (i) volume registration using MNI305 atlas [20], (ii) voxel intensity allocation and classification as White Matter (WM) or other tissue, (iii) separation of both hemispheres and exclusion of the cerebellum and brain stem, (iv) surface generation (for each hemisphere) by tiling the outside of the WM mass for that hemisphere, (v) this surface is refined to follow the intensity gradients between the WM and Gray Matter (GM) (this is referred to as the white surface) and (vi) white surface is nudged to follow the intensity gradients between the GM and CSF (pial surface) [21].

The Freesurfer subcortical-based pipeline consists of 5 stages which label subcortical tissues and calculates their volumes. These stages are: (i) affine registration with MNI305, (ii) initial volumetric labeling, (iii) intensity variation correction, (iv) dimensional nonlinear volumetric alignment to the MNI305 atlas, and (v) label atlas is built from a training set. For more details of Freesurfer streams, the reader is referred to [19], [22].

III. RESULTS

Table I tabulates the volume differences between the hippocampus and the entorhinal cortex between the 3 groups (from their baseline scan) through ANOVA statistics. STATA V14 was used and the level of significance was $\alpha=0.05$.

Table II illustrates the percentage of volume reduction of hippocampus and entorhinal cortex between the 3 groups from the baseline scans.

TABLE I. VOLUMES (MEAN (SD)) OF ENTORHINAL CORTEX AND HIPPOCAMPUS IN BASELINE SCANS

Group	N	Left ERC (mm^3)	Right ERC (mm^3)	Left Hip. (mm^3)	Right Hip. (mm^3)
NC	218	1944 (367)	1935 (411)	3290 (435)	3323 (458)
MCI	349	1667 (457)*	1689 (455)*	2873 (501)*	2910 (526)*
AD	165	1437 (406)*†	1438 (441)*†	2549 (502)*	2598 (549)*†

Values in parentheses are SD NC=Normal cognition; MCI=mild cognitive impairment; AD=Alzheimer's disease;
* P<0.001 for MCI Vs NC, and AD Vs NC
† P<0.001 for AD Vs MCI

TABLE II. VOLUME REDUCTION (%) OF ENTORHINAL CORTEX AND HIPPOCAMPUS BETWEEN THE 3 GROUPS IN BASELINE SCANS

Group	Left ERC (%)	Right ERC (%)	Left Hip. (%)	Right Hip (%)
AD Vs NC	-26.08*	-25.68*	-22.52*	-21.82*
MCI Vs NC	-14.25*	-12.71*	-12.69*	-12.45*
AD Vs MCI	-13.80*	-14.86*	-11.28*	-10.69*

GLOSSARY: NC=Normal cognition; MCI=mild cognitive impairment; AD=Alzheimer's disease; ERC: Entorhinal cortex; Hip.: Hippocampus.
*p<0.05

Figure 1 shows the percentage changes of the mean volumes for the two regions for all subjects. According to

table 1 the total left entorhinal cortex volume of all NC was 1944 (SD 367) mm^3 and 1936 (SD 411) mm^3 for the right. These values were significantly reduced for the MCI subjects, to 1667 (SD 457) mm^3 and 1689 (SD 455) mm^3 for left and right entorhinal cortex respectively. For the same groups, the hippocampal volumes were reduced from 3290 (SD 435) mm^3 and 3323 (458) mm^3 to 2873 (SD 501) mm^3 and 2910 (SD 526) mm^3 for the left and right hippocampus respectively.

Figure 2 represents the longitudinal volume changes between the two structures for the MCI and MCIc groups.

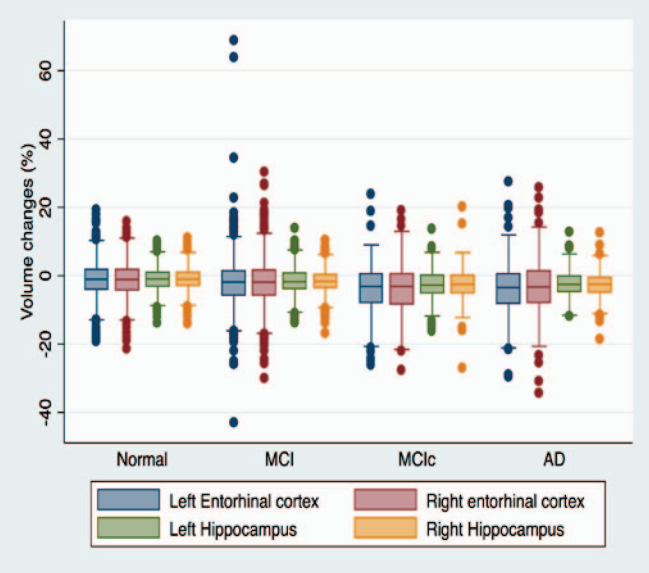

Figure 1: Volume changes for the two structures, between the 4 groups.

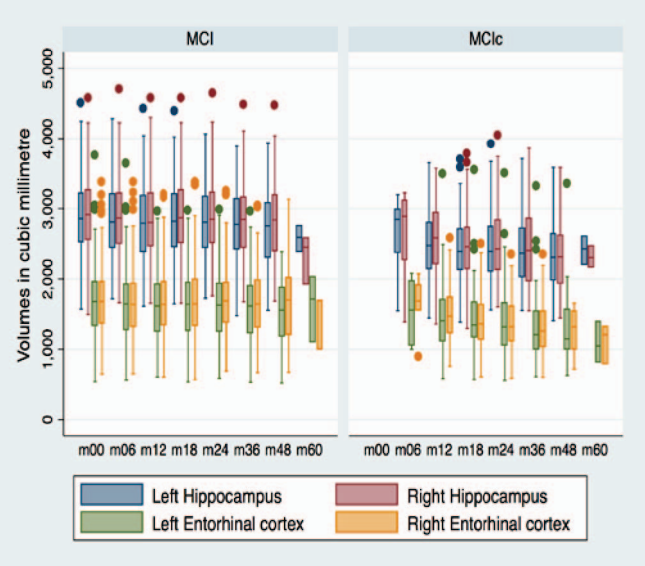

Figure 2: Volume changes between MCI and MCIc.

IV. Discussion

From all the biomarkers used in AD, hippocampal atrophy as assessed on high-resolution T1-weighted MRI images is the best established and validated biomarker [23], [24]. Hippocampal measurements are more feasible due to hippocampus shape which allows easier segmentation and thus, it can be evaluated with more accuracy rather than other MTL structures such as entorhinal, perirhinal and parahippocampal cortices [25]. However, the earlier involvement of the entorhinal cortex was proved by many MR quantitative studies [26]–[28] and this was correlated with our results where entorhinal cortex was more affected by atrophy rather than the hippocampus.

Juottonen *et al*. [29], used volume measurements on both entorhinal cortex and the hippocampus in NC and AD subjects and both regions had similar results on the classification between NC and AD subjects. Both regions appear to have similar pattern of atrophy. Similar to our results, the entorhinal cortex was more affected rather than the hippocampus in AD patients, however, both structures had similar discriminative power.

Pennanen *et al*. [30] noticed that entorhinal cortex in MCI subjects was the region with the more severe volume loss providing an accuracy of 66% for the classification of NC from MCI subjects. On the other hand, the hippocampus appeared to be more affected in AD subjects which was not correlated with our findings were entorhinal cortex was found to be more affected by atrophy. More severe atrophy of the entorhinal cortex was also reported by Du *et al.* [31].

V. Concluding Remarks

The major findings of this study were:

- Both entorhinal cortex and hippocampal volumes were significantly reduced in MCIc group compared to NC subjects.
- Compared to hippocampus, entorhinal cortex seems to be the region with the more severe volume loss in MCI converters and AD subjects.
- The atrophy rate between entorhinal cortex and hippocampus was correlated for both MCI and MCIc groups.
- Entorhinal cortex was more affected in the MCIc group and it should be preferred more for the disease prognosis.

In conclusion, the entorhinal cortex is more affected by atrophy in MCI and AD subjects and it should be preferred for a better diagnosis of AD. Furthermore, the more severe involvement of the entorhinal cortex could provide a more accurate prediction of the disease.

Acknowledgment

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan

Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Furthermore, this study was partially funded by the H2020-WIDESPREAD-04-2017-Teaming Phase 1, Grant Agreement 763781, Integrated Precision Medicine Technologies (IPMT).

REFERENCES

[1] "Facts and Figures | Alzheimer's Association." [Online]. Available: http://www.alz.org/mglc/in_my_community_60862.asp. [Accessed: 23-Dec-2015].

[2] H. Braak and E. Braak, "Frequency of stages of Alzheimer-related lesions in different age categories," *Neurobiol. Aging*, vol. 18, no. 4, pp. 351–357, Aug. 1997.

[3] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician," *J. Psychiatr. Res.*, vol. 12, no. 3, pp. 189–198, Nov. 1975.

[4] J. C. Morris, "The Clinical Dementia Rating (CDR): current version and scoring rules," *Neurology*, vol. 43, no. 11, pp. 2412–2414, Nov. 1993.

[5] H. Braak and E. Braak, "Neuropathological stageing of Alzheimer-related changes," *Acta Neuropathol. (Berl.)*, vol. 82, no. 4, pp. 239–259, 1991.

[6] B. Dubois *et al.*, "Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria," *Lancet Neurol.*, vol. 6, no. 8, pp. 734–746, Aug. 2007.

[7] R. I. Scahill, J. M. Schott, J. M. Stevens, M. N. Rossor, and N. C. Fox, "Mapping the evolution of regional atrophy in Alzheimer's disease: Unbiased analysis of fluid-registered serial MRI," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 99, no. 7, pp. 4703–4707, Apr. 2002.

[8] L. R. Squire, C. E. L. Stark, and R. E. Clark, "The medial temporal lobe," *Annu. Rev. Neurosci.*, vol. 27, pp. 279–306, 2004.

[9] R. J. Killiany *et al.*, "MRI measures of entorhinal cortex vs hippocampus in preclinical AD," *Neurology*, vol. 58, no. 8, pp. 1188–1196, Apr. 2002.

[10] H. Braak and E. Braak, "Staging of Alzheimer-related cortical destruction," *Int. Psychogeriatr. IPA*, vol. 9 Suppl 1, pp. 257-261; discussion 269-272, 1997.

[11] J. H. Kordower *et al.*, "Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment," *Ann. Neurol.*, vol. 49, no. 2, pp. 202–213, Feb. 2001.

[12] C. R. McDonald *et al.*, "Regional rates of neocortical atrophy from normal aging to early Alzheimer disease," *Neurology*, vol. 73, no. 6, pp. 457–465, Aug. 2009.

[13] N. C. Fox, R. I. Scahill, W. R. Crum, and M. N. Rossor, "Correlation between rates of brain atrophy and cognitive decline in AD," *Neurology*, vol. 52, no. 8, pp. 1687–1687, May 1999.

[14] R. W. Elwood, "The Wechsler Memory Scale—Revised: Psychometric characteristics and clinical application," *Neuropsychol. Rev.*, vol. 2, no. 2, pp. 179–201, Jun. 1991.

[15] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, "Clinical diagnosis of Alzheimer's disease Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease," *Neurology*, vol. 34, no. 7, pp. 939–939, Jul. 1984.

[16] J. Jovicich *et al.*, "Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data," *NeuroImage*, vol. 30, no. 2, pp. 436–443, Apr. 2006.

[17] C. R. Jack *et al.*, "The Alzheimer's disease neuroimaging initiative (ADNI): MRI methods," *J. Magn. Reson. Imaging*, vol. 27, no. 4, pp. 685–691, Apr. 2008.

[18] P. A. Narayana, W. W. Brey, M. V. Kulkarni, and C. L. Sievenpiper, "Compensation for surface coil sensitivity variation in magnetic resonance imaging," *Magn. Reson. Imaging*, vol. 6, no. 3, pp. 271–274, Jun. 1988.

[19] B. Fischl *et al.*, "Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain," *Neuron*, vol. 33, no. 3, pp. 341–355, Jan. 2002.

[20] D. L. Collins, P. Neelin, T. M. Peters, and A. C. Evans, "Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space," *J. Comput. Assist. Tomogr.*, vol. 18, no. 2, pp. 192–205, Apr. 1994.

[21] B. Fischl and A. M. Dale, "Measuring the thickness of the human cerebral cortex from magnetic resonance images," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 97, no. 20, pp. 11050–11055, Sep. 2000.

[22] B. Fischl *et al.*, "Automatically parcellating the human cerebral cortex," *Cereb. Cortex N. Y. N 1991*, vol. 14, no. 1, pp. 11–22, Jan. 2004.

[23] C. R. Jack, R. C. Petersen, P. C. O'Brien, and E. G. Tangalos, "MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease," *Neurology*, vol. 42, no. 1, pp. 183–183, Jan. 1992.

[24] R. J. Killiany, M. B. Moss, M. S. Albert, T. Sandor, J. Tieman, and F. Jolesz, "Temporal lobe regions on magnetic resonance imaging identify patients with early Alzheimer's disease," *Arch. Neurol.*, vol. 50, no. 9, pp. 949–954, Sep. 1993.

[25] G. B. Frisoni, N. C. Fox, C. R. Jack, P. Scheltens, and P. M. Thompson, "The clinical use of structural MRI in Alzheimer disease," *Nat. Rev. Neurol.*, vol. 6, no. 2, pp. 67–77, Feb. 2010.

[26] T. Tapiola *et al.*, "MRI of hippocampus and entorhinal cortex in mild cognitive impairment: a follow-up study," *Neurobiol. Aging*, vol. 29, no. 1, pp. 31–38, Jan. 2008.

[27] D. P. Devanand *et al.*, "Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease," *Neurology*, vol. 68, no. 11, pp. 828–836, Mar. 2007.

[28] G. F. Busatto *et al.*, "A voxel-based morphometry study of temporal lobe gray matter reductions in Alzheimer's disease," *Neurobiol. Aging*, vol. 24, no. 2, pp. 221–231, Apr. 2003.

[29] K. Juottonen, M. P. Laakso, K. Partanen, and H. Soininen, "Comparative MR analysis of the entorhinal cortex and hippocampus in diagnosing Alzheimer disease," *AJNR Am. J. Neuroradiol.*, vol. 20, no. 1, pp. 139–144, Jan. 1999.

[30] C. Pennanen *et al.*, "Hippocampus and entorhinal cortex in mild cognitive impairment and early AD," *Neurobiol. Aging*, vol. 25, no. 3, pp. 303–310, Mar. 2004.

[31] T. Du A *et al.*, "Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease," *J. Neurol. Neurosurg. Psychiatry*, vol. 71, no. 4, pp. 441–447, Oct. 2001.