# Cortical and Subcortical Structural Segmentation in Alzheimer's Disease

**Jafar Zamani [1], Ali Sadr [1, *], Amir-Homayoun Javadi [2,3,4]**

[1] School of Electrical Engineering, Iran University of Science and Technology, Tehran, Iran

[2] School of Psychology, Keynes College, University of Kent, Canterbury, Kent, CT2 7NP, UK

[3] Institute of Behavioural Neuroscience, University College of London, London, UK

[4] School of Rehabilitation, Tehran University of Medical Sciences, Tehran, Iran

## Abstract

**Purpose:** Alzheimer's disease is a neurodegenerative disease that begins before clinical symptoms emerge. Amyloid-beta plaques and tau neurofibrillary tangles are the hallmark lesions of Alzheimer's Disease (AD). Amyloid-beta plaques deposition is associated with increased hippocampal volume loss. The tissue volume measures reflect multiple underlying pathologies contributing to neurodegeneration, of which are the most characteristics of AD. Anatomical atrophy, as evidenced using Magnetic Resonance Imaging (MRI), is one of the most validated, easily accessible and widely used biomarkers of AD. Measurements of whole brain and hippocampal atrophy rates from serial structural MRI are potential markers of the underlying neuroaxonal damage and disease progression in AD. In this study, we extract automatically subcortical brain structures in AD and control subjects.

**Materials and Methods:** In this study we used 20 images (10 AD patients and 10 controls) taken from the Minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD) dataset. We obtained volumes of Cerebrospinal Fluid (CSF), White Matter (WM), Grey Matter (GM), brain hemispheres, cerebellum and brainstem using volBrain pipeline. Subcortical brain structure segments and related volumes and label maps information were extracted. We compared left and right sides of some of the important brain area in AD for obtaining a biomarker with brain atrophy. Amygdala, caudate and hippocampus have shown to be undergone atrophy in AD.

**Results:** We provided volume information of some intracranial areas such as brain hemispheres, cerebellum and brainstem.

**Conclusion:** The results showed smaller hippocampal volume in AD patients compared to the controls. In addition to hippocampus, similar atrophy is also observable in amygdala and caudate.

## 1. Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease that begins before clinical symptoms emerge [1]. Amyloid-beta plaques and tau neurofibrillary tangles are the hallmark lesions of AD. Amyloid-beta plaques deposition is associated with increased hippocampal volume loss. The tissue volume measures reflect multiple underlying pathologies contributing to neurodegeneration, of which are the most characteristic of AD. Anatomical atrophy, as evidenced using Magnetic Resonance Imaging (MRI), is one of the most validated, easily accessible and widely used biomarkers of AD.

***Corresponding Author:***
*Ali Sadr, PhD*
*School of Electrical Engineering, Iran University of Science and Technology, Tehran, Iran*
*Tel: (+44) 2177240401*
*Email: sadr@iust.ac.ir*

Measurements of whole brain and hippocampal atrophy rates from serial structural MRI are potential markers of the underlying neuroaxonal damage and disease progression in AD [2-3]. AD involves significant impairments in many cognitive domains; failure of recent memory is usually the most prominent feature in the early stages of the disease. The primacy and prominence of memory impairment in AD is consistent with findings suggesting that neuropathological changes in the hippocampus and entorhinal cortex are the first and most severe to occur [4]. Involvement of these areas in AD leads to decrements in learning and memory during a pre-clinical phase of AD [5]. Hippocampal atrophy at the medial temporal lobe is therefore a site of early changes in AD. This can be visualised with high quality Magnetic Resonance (MR) Imaging. Hence, there is a role for volumetric measurement of the hippocampus in the earlier diagnosis of AD [6]. Quantification of the rate of global and regional brain volume loss from serially acquired MRI is increasingly used both to understand the progression of the disease and as an outcome measure for clinical trials [7]. In order to diagnose AD, we applied MRI volumetry approach for the hippocampus and cerebrum in an attempt to detect the changes of AD. The analysis of different brain structures separately is very useful in AD. Segmentation of structures such us cerebrum, cerebellum, brainstem, and brain hemispheres is of interest to assess brain asymmetry in AD subjects. The volumes of the hippocampi and the lateral ventricles have been shown to act as early biomarkers of AD. Hippocampus is involved in many brain functions such as memory and spatial reasoning. The study of the hippocampus volume is of great interest as it is a valuable tool for follow-up and treatment adjustment in AD. The analysis of the whole hippocampus is a consented approach to study AD [8].

In this study, we extract automatically subcortical structure segmentation of AD and control subjects.

The rest of this paper is organised as follows: Section II is about subject recruitment, data acquisition and exploited method for brain volume segmentation, Section III describes the implementation and results, and Section IV concludes the delineates and summarises the future works.

## 2. Materials and Methods

### 2.1. Subjects

In this study we used 20 images (10 AD patients and 10 controls) taken from the Minimal Interval Resonance Imaging in Alzheimer's Disease (MIRIAD) dataset. MIRIAD is a series of longitudinal volumetric T1 MRI scans of AD patients and controls. All seen at the Dementia Research Centre, Institute of Neurology, UCL, and 23 nondemented control subjects, typically the patient's spouse or carer. Inclusion criteria included age over 55 years old and a Mini-Mental State Examination (MMSE) [9] score between 12/30 and 23/30 according to database. Controls had MMSE scores >26/30, and no history of cognitive impairment, head injury, major psychiatric disease or stroke. Exclusion criteria included any neurodegenerative disease (apart from AD for the patients), or inability to tolerate undergoing MRI.

### 2.2. MR Imaging

All subjects underwent MRI scanning on a 1.5 T Signa scanner (GE Medical Systems, Milwaukee, WI, USA) at baseline and at approximately 6 months and 12 months (mean[SD] intervals 180[6] days; and 365[10] days). T1-weighted volumetric images were obtained using an inversion recovery prepared fast spoiled gradient echo sequence with acquisition parameters time to repetition = 15 ms, time to echo =5.4 ms, flip angle =15°, TI =650 ms, a 24-cm field of view and a $256 \times 256$ matrix, to provide 124 contiguous 1.5-mm thick slices in the coronal plane (voxels 0.9735 mm×0.9735 mm×1.5 mm) [11].

### 2.3. Methods

We obtained volumes of Cerebrospinal Fluid (CSF), White Matter (WM), Grey Matter (GM), brain hemispheres, cerebellum and brainstem using volBrain pipeline, Figure 1. [12]. This method is based on an advanced pipeline providing automatic segmentation of different brain structures from T1w MRI. The preprocessing is based on: (1) a denoising step with an adaptive non-local mean filter, (2) an affine registration in the Montreal Neurological Institute (MNI) space, (3) a correction of the image inhomogeneities, and (4) an intensity normalisation. Afterwards, MRI images were

segmented in the MNI space using non-local patch-based multi-atlas method subcortical structure segments and related volumes and label maps information extracted. We compared left and right side of some of the important brain area in AD for obtaining a biomarker with brain atrophy.

The global GM, WM and CSF atrophy in AD are useful markers of disease progression in clinical trials. A method for quantifying GM, WM and CSF atrophy is segmentation and subtraction of serial GM, WM and CSF volumes. Images were corrected for intensity inhomogeneity using the N4 algorithm [13], and the images were segmented into brain/nonbrain using a semi-automated technique (MIDAS). The non-local means filter [14] was used for each pixel in the image by computing a weighted average of surrounding pixels using a robust similarity measure that takes into account the neighbouring pixels surrounding the pixel being compared. Our segmentation method was based on the idea of non-local patch-based label fusion technique where patches of the subject to be segmented are compared with those of the training library [15-16].
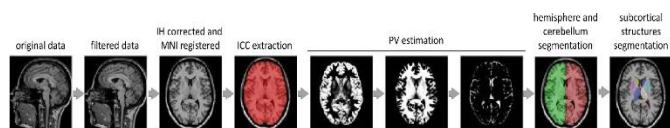


**Figure 1.** Processing pipeline. Preprocessing steps. Subsequently the tissue estimation of Grey Matter (GM), White Matter (WM) and Cerebrospinal Fluid (CSF) were performed. Finally, macrostructures and subcortical structures segmentation are extracted. Adapted from [5] under the terms of the Creative Commons Attribution License (CC BY)

## 3. Results

We provided volume information of some macroscopic areas such as brain hemispheres, cerebellum and brainstem, Table 1. Automatic subcortical structure segmentation is performed and related volumes and label maps were provided, Figure 2; also, segmented Cerebellum, white matter and lobules in T1 MRI, Figure 3. Volumetry values were calculated through the hippocampus subfield segmentation and their asymmetries in MNI space, Figure 4.

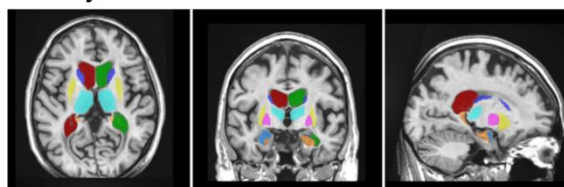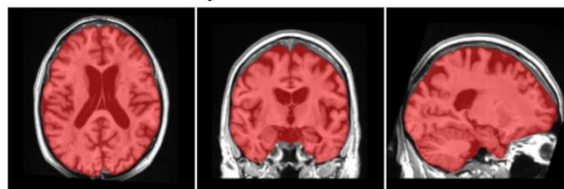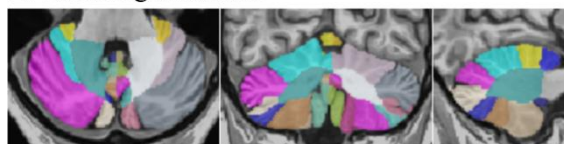Alzheimer's disease patient



Healthy control



**Figure 1.** Subcortical structures in an AD patient and a healthy control participant, highlighting the volumetric difference between segments of hippocampus shown in green
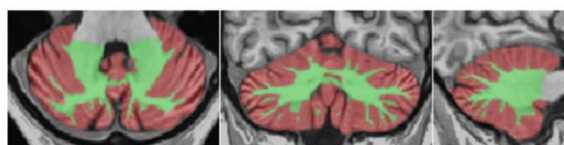
Intracranial cavity extraction



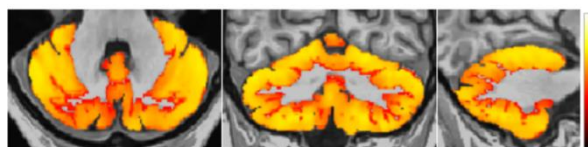Lobules segmentation



Tissue classification



Cortical tichness



**Figure 2.** Cerebellum MRI brain segmentation of a sample case AD

**Table 1.** Summary of the average of numerical brain segment volume for Alzheimer's Disease patients (AD) and healthy Controls (CN) in Native space. The values (%) represent size and percentage of the brain volume

|  | WM | GM | CSF | Brainstem | Hippocampus | Amygdala | Caudate |
|---|---|---|---|---|---|---|---|
| AD | 475.74 (29.45%) | 774.45 (47.00%) | 366 (22.52%) | 27.42 (1.7%) | 8.35 (0.51%) | 1.18 (0.07%) | 6.03 (0.37%) |
| CN | 455.48 (33.19%) | 688.45 (48.82%) | 258.38 (18.84%) | 20.88 (1.51%) | 7.83 (0.57%) | 1.74 (0.13%) | 4.15 (0.52%) |

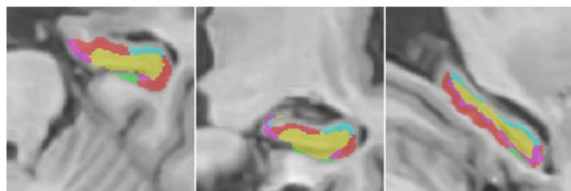Left hippocampus
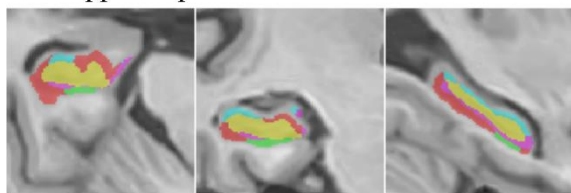


Right hippocampus



**Figure 3.** Right and left hippocampus subfield segmentation

## 4. Discussion

In our results, automated methods have shown better accuracy of brain segmentation can be used in classification of T1w MRI images into AD and HC. Out of the segmented brain areas, amygdala and caudate showed the greatest percentage difference between the two groups. The caudate volume 52% of whole brain in normal subjects changes into 37% in AD subjects that shown significant difference between two groups.

The volume of hippocampus is now considered as an important biomarker for AD. It has been shown that the hippocampal atrophy estimated on anatomical T1w MRI can help in classifying the different stages of AD [16].

In this study, we proposed a method that combines a range of volumetric measurements, cortical thickness measurements, cerebellum, and hippocampal shape, to obtain a combination biomarker with main IntraCranial Cavity (ICC) tissues and hippocampus subfields that

Future research should investigate methods that are more robust and targeted to find brain areas that are indicative of different levels of cognitive impairments as measured by standardised methods such as MMSE. Furthermore, predictive methods should be devised to anticipate progress of the disease given MRI images taken in different time-points.

## References

1- Nestor, P.J., Scheltens, P. and Hodges, J.R., "Advances in the early detection of Alzheimer's disease". *Nature Medicine*, Vol.10 (7s), p.S34, 2004.

2- Henneman, W.J., Sluimer, J.D., Barnes, J., van der Flier, W.M., Sluimer, I.C., Fox, N.C., Scheltens, P., Vrenken, H., Barkhof, F., "Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures". *Neurology*, Vol. 72, pp.999–1007, 2009.

3- Fox, N.C., Black, R.S., Gilman, S., Rossor, M.N., Griffith, S.G., Jenkins, L., Koller, M., "Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease". *Neurology*, Vol. 64, pp.1563–1572, 2005.

4- Braak, Heiko, and Eva Braak. "Neuropathological staging of Alzheimer-related changes." *Acta Neuropathologica* ,Vol 82, no. 4 ,pp.239-259,1991.

5- Ahmed, M.N., Yamany, S.M., Mohamed, N., Farag, A.A. and Moriarty, T., "A modified fuzzy c-means algorithm for bias field estimation and segmentation of MRI data". *IEEE Transactions on Medical Imaging*, Vol. 21(3), pp.193-199, 2002.

6- Buades, A., Coll, B., and Morel, J. M, "A nonlocal algorithm for image denoising, "in IEEE International Conference on Computer Vision and Pattern Recognition, CVPR ,Vol. 2 (San Diego, CA), pp.60–65,2005.

7- Fox, N.C., Schott, J.M., "Imaging cerebral atrophy: normal ageing to Alzheimer's disease." *Lancet*, Vol. 363, pp.392–394, 2004.

8- Pipitone, J., Park, M.T.M., Winterburn, J., Lett, T.A., Lerch, J.P., Pruessner, J.C., Lepage, M.,Voineskos A.N., Chakravarty, M.M., " the Alzheimer's Disease Neuroimaging Initiative, Multiatlas segmentation of the whole hippocampus and subfields using multiple automatically generated templates". *NeuroImage*, Vol.101, PP.494 – 512, 2014.

9- Folstein, M.F., Folstein, S.E., McHugh, P.R., "Mini-mental state: a practical method for grading the cognitive state of patients for the clinician." *Journal of Psychiatric Research*, Vol.12, pp.189–198, 1975.

10- Romero, J.E., Coupé, P. and Manjón, J.V., "HIPS: A new hippocampus subfield segmentation method." *NeuroImage*, Vol.163, pp.286-295, 2017.

11- Malone, Ian B., David Cash, Gerard R. Ridgway, David G. MacManus, Sebastien Ourselin, Nick C. Fox, and Jonathan M. Schott, "MIRIAD—Public release of a multiple time point Alzheimer's MR imaging dataset." *NeuroImage*, Vol 70,pp.33-36,2013.

12- Manjón, José V., and Pierrick Coupé, "volBrain: an online MRI brain volumetry system." *Frontiers in Neuroinformatics*, Vol.10, pp. 30, 2016.

13- NJ Tustison, BB Avants, PA Cook, Y Zheng, A Egan, PA Yushkevich,"N4ITK: improved N3 bias correction"., *IEEE Transactions on Medical Imaging*, Vol.29 (6), PP.1310-1320,2010.

14- Manjón, José V., Pierrick Coupé, Luis Martí-Bonmatí, D. Louis Collins, and Montserrat Robles, "Adaptive non-local means denoising of MR images with spatially varying noise levels". *Journal of Magnetic Resonance Imaging*, Vol. 31, pp.192-203, 2010.

15- Pierrick Coupé, Jose V. Manjón, Vladimir Fonov, Jens Pruessner, Montserrat Robles, D. Louis Collins, "Patch-based Segmentation using Expert Priors: Application to Hippocampus and Ventricle Segmentation". *NeuroImage*, Vol.54 (2), pp.940-954, 2011.

16- Romero, J.E., Manjón, J.V., Tohka, J., Coupé, P. and Robles, M, "NABS: non-local automatic brain hemisphere segmentation". *Journal of Magnetic Resonance Imaging*, Vol.33 (4), pp.474-484, 2015.