MAPPING MORPHOLOGICAL CHANGES OF THE HIPPOCAMPUS IN ALZHEIMER'S DISEASE AND NORMAL AGING

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Abstract - Histological studies have suggested differing involvement of the hippocampus morphological changes in ageing and in Alzheimer's disease (AD). The aim of this study was to assess in vivo local hippocampus changes in Alzheimer's disease and ageing Alzheimer's disease based on 1.5 Tesla brain magnetic resonance images (MRI). MRI is an important imaging biomarker in AD as the cerebral atrophy has been shown to strongly associate with cognitive symptoms. The decrease of volume estimates in different structures of the medial temporal lobe related to memory correlates with the decline of cognitive functions in neurodegenerative diseases. Special effort has been dedicated to separate AD and mild cognitive impairment (MCI) related modifications from normal aging for the purpose of early detection and prediction. We analyzed baseline MR imaging data from 48 subjects from the Alzheimer's Disease Neuroimaging Initiative-1 (ADNI-1) T1- weighted images were acquired 12 with Alzheimer disease, 12 with mild cognitive impairment, 12 with normal aging and 12 young healthy controls. We analyzed the effect of normal ageing and in Alzheimer's disease on hippocampus based on radial distance mapping.

Index Terms - Alzheimer's disease, mild cognitive impairment, magnetic resonance images, hippocampus, neurodegenerative diseases

I. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that is the most common type of dementia in elderly is characterized by progressive cognitive and functional decline, the main symptom of which is associated with memory losses and unable to create new memories. During the past decades several methods have been developed for quantifying the disease related atrophy of hippocampus from MRI. AD is a progressive disease, it is unclear how AD will progress, and the clinical symptoms appear later than the disease onset, which makes early diagnosis and intervention difficult. In its early stages, memory loss is mild, but with late-stage AD, individuals lose the ability to carry on a conversation and respond to their environment. The hippocampus is one of the first brain regions to show the effects of AD pathology and, consequently, atrophy of the hippocampus structures is the most established neurodegenerative imaging biomarker of AD [1]. Reductions in hippocampus and entorhinal cortex volumes become apparent in the early stages of memory decline and may anticipate progression to MCI and AD [2]. An earlier diagnosis could help to reduce cognitive deterioration and/or treatment costs. It is also important to understand the disease progression when performing clinical trials. In most imaging studies the average hippocampus volume, which can be relatively easily extracted from MRI data, is compared between study groups. Morphological features can detect more subtle alterations in the hippocampus that may provide even more sensitive detection of early changes in hippocampus [3],[4]. Shape-based morphometry has often been used for analyzing structural changes in subcortical structures in the brain, including in the hippocampus. Researchers have previously used quantitative features analysis such as volume and surface area for assessing hippocampus atrophy as a marker for the progression of AD. However, changes in volume in certain regions can be compensated for by atrophy or dilation in other locations, which may obscure changes in the total volume and surface area. This indicates that volumetric analyses may not reveal the true association between local deformations and the disease or risk factors. Additionally, volumetric analyses do not give information about the morphological changes that characterize the appearance and progression of neurodegenerative diseases. A precise analysis of these changes could provide useful early diagnostic information and help to identify individuals at risk [5].

Recently, neuroimaging techniques have allowed for 3D modeling of hippocampus changes and have been valuable for the longitudinal study of neuropathological changes in AD. The present study uses a computational anatomy shape-based method called hippocampus radial distance in order to compare cross-sectional 3D hippocampus maps of subjects diagnosed with AD and normal controls. This technique allows for detection of subtler hippocampus shape changes in AD.

The hippocampus radial distance approach relies on manual or automated hippocampus segmentations, which are converted into 3D anatomical models for each subject. The distance from a center core of the 3D structure to each surface point known as radial distance, is computed and plotted onto the surface [6].

As the disease progresses and the hippocampus atrophies, the radial distance shrinks. Compared to the conventional region of interest (ROI) technique, which extracts hippocampus volumes - a single summary metric - from each hippocampus, our technique allows for visualization of differences between diagnostic groups in cross-sectional studies, or changes over time in longitudinal studies. The results presented here provide further validation of the radial distance mapping technique.

In the present study, we proposed a novel approach to identify the pattern of local morphological changes of the hippocampus in Alzheimer's disease and normal aging. The overall aim of this study was to identify the pattern and color mapping of morphometric and microstructure changes in sub-regions of the hippocampus in AD and MCI.

II. MATERIALS AND METHODS

A. Subjects

ADNI is an ongoing, longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers for the early detection and tracking of Alzheimer's disease (AD). The ADNI study began in 2004 and included 400 subjects diagnosed with mild cognitive impairment (MCI), 200 subjects with early AD and 200 elderly control subjects. The goals of ADNI are to determine relationships among clinical, cognitive, imaging, genetic, and biochemical biomarkers as AD evolves from normal aging to MCI to dementia, to discover biomarkers sensitive to early diagnosis, to establish standardized methods for imaging/biomarker collection, and to conduct research on methodologies that could lower the costs of clinical trials.

Our sample consisted of the 48 subjects in ADNI-1 comprised 12 cognitive normal young (CNY) subjects, 12 cognitive normal elderly (CNE) subjects (aged 70-85), 12 MCI subjects (aged 70-85) and 12 AD subjects (aged 70-85), who underwent 1.5T MR imaging. 1.5T baseline MR images and their associated clinical data were downloaded from the ADNI public data base (http://adni.loni.usc.edu).

B. Imaging Data Collection, Image Preprocessing, and Analysis

We acquired 1.5T scans analyzed in this study from 48 ADNI-1 sites on scanners from 3 MR imaging vendors (GE Healthcare, Philips Healthcare or Siemens) with a standardized protocol developed to evaluate 3D T1-weighted sequences for morphometric analyses (http://adni.loni.usc.edu/methods/documents/mri-protocols/). The 28 of the 48 (58.3%) subjects were scanned on GE Healthcare, 12 (25%) on a Phillips Healthcare, and 8 (16.6%) subjects on Siemens 1.5T scanners. The 1.5T scanning protocols used a 3D sagittal volumetric sequence. The typical 1.5T acquisition parameters were TR 2400ms, minimum full TE, TI 1000 ms, flip angle 8°, and FOV 24 cm, with a 256 x 256 x 170 acquisition matrix in the x, y, and z-dimensions, yielding a voxel size of $1.25x1.25x1.2mm^3$.

Cognitive Status	Numbers	Age	Sex(f/m)
AD	12	77.4 ± 5.3	6/6
MCI	12	77.9 ± 5.2	6/6
ENC	12	77.2 ± 5.1	6/6
YNC	12	27.4 ± 4.3	6/6

Table I. Summary of the experimental subjects

(The data are presented in the format mean ± standard deviation. AD = Alzheimer's disease patients, MCI = mild cognitive impairments, ENC = elderly normal controls, YNC= young normal controls)

C. Image Registration, Hippocampus Segmentation

In this section, we describe the protocol for image registration and manually segmenting the hippocampus. Image registration is the process of combining two or more images for providing more information. Medical image fusion refers to the fusion of medical images obtained from different modalities. Medical image fusion helps in medical diagnosis by way of improving the quality of the images. Fig. 1 shows a sample manual trace of representative sagittal slices of the hippocampus. The manual tracing task was completed by expert rater, who had each performed more than 300 hippocampus traces. We used a custom-built software system to trace the hippocampus. The tracing was performed on contiguous sagittal slices, proceeding in the spatial domain from the most posterior to most anterior slice.

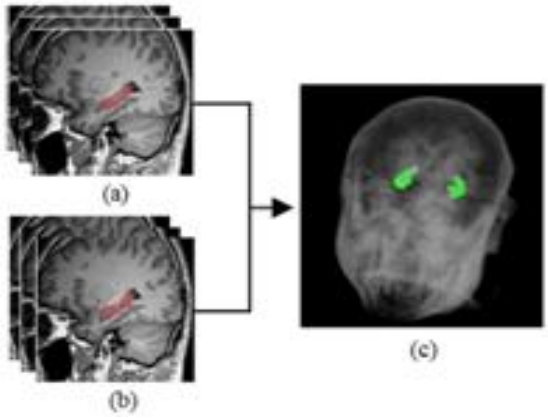


Fig. 1 - A selection of manually segmented hippocampal sagittal slices of a representative subject; (a) left side of a subject, (b) right side of subject with NC, (c) 3D visualization of hippocampus.

D. Hippocampus Shape Normalization

We use data from each segmented hippocampus images to make four different models which represent AD, MCI, ENC and YNC. The shape of hippocampus

was represented by a set of n points. These points were represented by a vector $\bar{X}_i$ in (1), where $\bar{X}_i$ is the number of markers and i is the number of sample images

$$\bar{X}_i = (x_{i1}, y_{i1}, x_{i2}, y_{i2}, x_{i3}, y_{i3}, \ldots . x_{in}, y_{in}) \qquad (1)$$

The variation of hippocampus position on each sample images results in different location of the marker's coordinate. Therefore, it is necessary to align all shapes acquired from segmented datasets. There are several methods of shape alignment; one of them is Generalized Procrustes Analysis (GPA) which is used to align a set of object [7], [8]. In our work, we moved every shape to the base of the image coordinate before applying any transformation. It was done by updating the value of each coordinate in a shape by the mean value of all coordinates in that shape (translation offset). Variation of object orientation can be removed using the direction of each point in a shape. We compute the mean direction of the shape (rotation offset) and uses it to update the direction of each point. The last step of this alignment is to make new points with updated directions that will be used for further computation. After aligning all shapes in the training set, computed the mean shape of the hippocampus set by (2), where $\vec{X}_i$ the vector of is all coordinate in a shape and n is the number of slices used.

$$\bar{X} = \frac{1}{n}\sum_{i=1}^{n} \vec{X}_i \qquad (2)$$

E. Radial distance maps

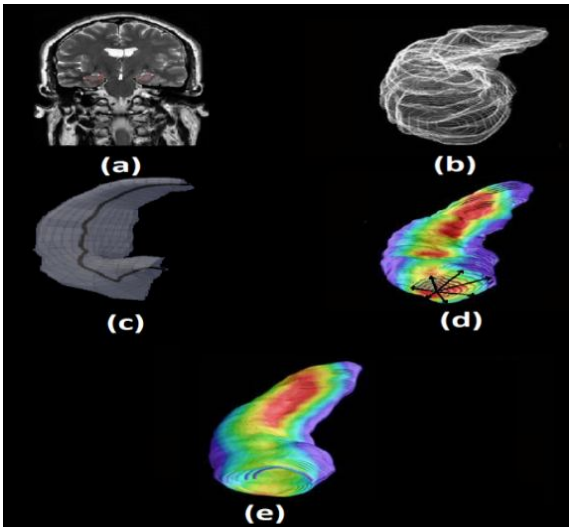


Fig. 2 - Radial distance calculation and color mapping technique; (a) Hippocampus segmentation from MR images, (b) 3D modeling of hippocampus contours, (c) Medial axis calculation, (d) Radial distance calculation and color mapping, (e) Group averaging of hippocampal data.

Radial distance maps were used for analyses of hippocampus surface changes with segmented hippocampus data (see Fig. 2). We calculated the distance from medial axis to surface points and used color labels to represent the distance.

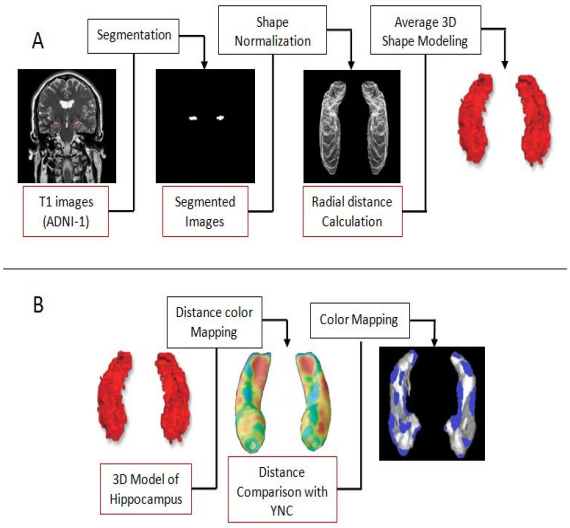


Fig. 3 – Overall scheme of the analysis

III. RESULTS

Hippocampus morphological changes revealed significant atrophy in bilateral CA1 regions and the right ventral subiculum in MCI compared to ECN and in bilateral CA1 and CA2–CA4 regions and the subiculum in AD. Direct comparison of MCI and AD revealed that atrophy in the left ventral subiculum part of the hippocampus was more significant in AD (Fig. 5). Hippocampal atrophy was higher in MCI than in ECN in the bilateral CA2–CA4 and subiculum regions, higher in AD than in ECN in most hippocampal regions, and higher in AD than in MCI in the left hippocampal CA1 region. Direct comparison of ENC and AD revealed that the atrophy was higher in the left hippocampal CA1 region in AD (Fig.5). Direct comparison of MCI and ENC revealed that atrophy was higher in the left hippocampal CA1 region in AD. Atrophy was higher in MCI than in ECN in the bilateral CA2–CA4 regions, higher in LMCI than in CN in the bilateral CA2–CA4 and subiculum regions, higher in AD than in ECN in most hippocampal regions, and higher in AD than in MCI in the left hippocampal CA1 region.

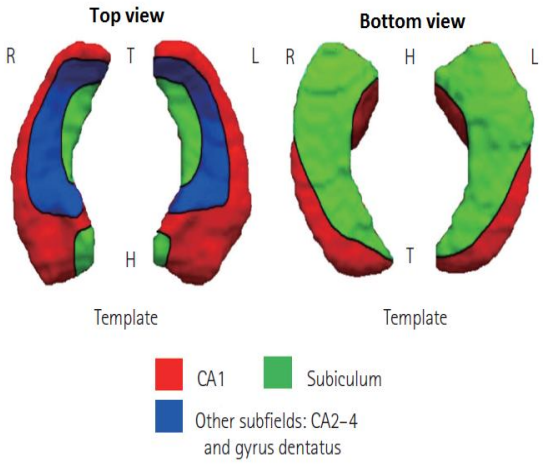


Fig. 4 - Hippocampus sub-regions

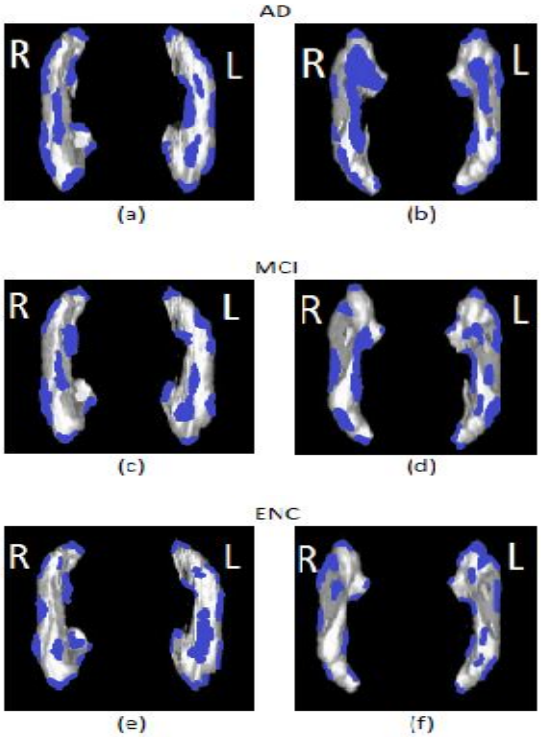


Fig. 5 – Hippocampus atrophy in sub-regions compare with YNC group; (a) top view of hippocampus in AD average group, (b) bottom view of hippocampus in AD average group, (c) top view of hippocampus in MCI average group, (c) bottom view of hippocampus in MCI average group, (e) top view of hippocampus in ENC average group, (f) bottom view of hippocampus in ENC average group.

DISCUSSION

This study aimed to identify the atrophy patterns in sub-regions of hippocampus in AD, MCI and ENC subjects in terms of hippocampal morphology and microstructural changes. As described in the Introduction, we addressed the earlier detection of AD and MCI from normal aging with respect to structural changes in the hippocampus. While several studies have examined changes in AD and MCI, significant AD, MCI and normal aging-related anomalies are not well documented. Moreover, the present study is the first to reveal comparison of AD, MCI and ENC groups with YNC group microstructural changes in the hippocampus sub-regions. The findings of this study provide additional knowledge about earlier AD, MCI and ENC-related changes in the structure of the hippocampus. The adoption of YNC template based comparison made it possible to identify the changes in ENC that were not detected by conventional volumetric analysis. Atrophy in AD was present in the hippocampal CA1 region, the left ventral subiculum and CA2-CA4 regions. Atrophy in EMCI was present in the hippocampal CA1 region and the right ventral subiculum. AD was characterized by a volume decrease in the left hippocampus but additional atrophy relative to MCI in the right hippocampus (Figs.5). Previous studies have found left-less-than-right asymmetry of the hippocampal atrophy as a characteristic change in AD. However, one study [9] found that right hippocampus changes can occur up to 10 years before the clinical onset of AD. Although that study employed a volumetric analysis, its findings suggest that damage to the right hippocampus characterizes a transition from healthy aging to MCI.

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