Title: Assessment the Changes of Cortical Thickness in Alzheimer’s Disease in MR Images Using Freesurfer Software

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Abstract

Purpose: In this study, the main goal was to determine the correlation between the thickness of cerebral cortex and the severity of cognitive disorder in Alzheimer's disease

Materials and method: Twenty patients diagnosed with Alzheimer’s disease with mean age of 72.95 year (14 women and 6 men) and Ten Cognitively normal (CN) subjects with mean age of 70.50 year (7 women and 3 men) were included to the study. Of the AD patient and CN subjects, 70% were female and 30% were male. All individual underwent 1.5 T MRI. The MR scanning protocol included 3D MPRAGE (3D-T1W) sequence. All images were analyzed using Freesurfer v5.3 and then calculated the brain cortical thickness in 7 cortex (Inferior temporal, Middle temporal, Superior temporal, parahippocamp, parstriangularis, rostralmiddle frontal, Superior frontal).

Result: The Analysis of covariance (ANCOVA) was conducted to compare the means of each region between the patient whilst control group. There was a significant difference in mean of cortical thickness in all regions. In all cases the mean of cortical thickness in CN subjects were greater than AD patients. However, the mean of Parstriangularis left hand in CN subjects was not significantly greater than the one in AD patients. The receiver operating characteristic system (ROC) was designed to evaluate the predictive power of the patient and the healthy person. We have selected a thousand cut-off points from 1.5 to 3.5mm for cortical thickness.

When the cut-off points were interval (2.276878, 2.299680) millimeter in left hemisphere, the Youden’s index was maximized. The sensitivity and specificity in this case were 80%. Also when the cut-off points were within the range (2.263278, 2.282278) mm in right hemisphere, the sensitivity and specificity were 90% and 80%, respectively.

Conclusion: This study demonstrates the importance of quantify the cortical thickness changes in early diagnosis of Alzheimer’s disease. In addition, examining the pattern of changes and the quantifying the reduction in the thickness of the cortex is an important tool for displaying the local and global atrophy of the brain. Also, this pattern can be used as an alternative marker for the diagnosis of dementia. Finally, to the best of our knowledge, our study is the first one to report finding on the range of cortical thickness that would help clinician to have better differential diagnose and also in this study have checked the possibility of early diagnosis of the disease.

Keywords: Alzheimer’s disease, Cortical thickness, MRI, Freesurfer software
Introduction

The neurodegenerative disorder Alzheimer’s disease is a fast growing epidemic in ageing populations worldwide. AD is the most prevalence type of dementia in people over the age of 65(1). In 2017, one new case of AD developed every 66 seconds but by 2050, this time is estimated to accelerate to every 33 seconds(2). So the diagnosis of AD in early stage has a considerable effect on decreasing progress of dementia and identification of accurate treatment approach (3).

In order to, the highly folded pattern of cerebral cortex of human brain, the characterization of cortical brain structure changes is important in both normal ageing as well as neurodegenerative disorders (4). The cortical thickness measured by structural neuroimaging has received significant surrogate biomarker that could provide powerful tools for early diagnosing of AD (5).

Gray matter atrophy that extends to the medial temporal lobe, parietal lobe and prefrontal cortices is morphometric feature of neurodegenerative changes (6).

Structural neuroimaging such as MRI and CT offer important advantages for identification of brain atrophy patterns. MRI has no ionizing radiation and provide higher resolution images of gray-white matter boundary. MRI is also reflecting its value in assessment of temporal lobe region because it has no beam hardening artifacts. So, because of all these criteria the sensitivity and specificity of MRI( sensitivity, 80% to 94%; specificity 60% to 100%) is higher than CT( sensitivity, 63% to 88%; specificity, 81%) for AD diagnosis (7).

Functional neuroimaging including brain glucose metabolism and beta amyloid imaging with PET and SPECT might be better in early detection of dementia because of the higher sensitivity(PET: 94%; SPECT: 70% to 89%) (5, 7).

Moreover, clinical examination and functional neuroimaging are affected by cognitive reserve. Therefore, structural neuroimaging had given promising results while being less affected by this factor than other modalities in detection of early onset of dementia (5).

Today, measuring brain cortical thickness and making surface brain models in MRI are used to better distinguish subtle changes of brain cortical structure. Furthermore, quantitative
measurement is sensitive to millimeter changes in neurodegenerative diseases (6). The utility of manual cortical thickness measurement methods are time consuming and require experienced anatomist compared with automated methods (8).

Freesurfer(https://surfer.nmr.mgh.harvard.edu/) is a freely available software and it can provide information for quantifying the functional and structural features of the brain. Freesurfer is fully automated corticometry method. On the other hand, creating surface brain models and the ability to inflate brain cortex lead to superior efficiency of this method in comparison of other software (9).

Ultimately, assessment of brain cortical properties and white matter atrophy has given complementary information about AD process (6). In this study we emphasized on the role of corticometry in early detection of Alzheimer’s disease and hypothesized that measurement of cortical thickness would increase the power of differential diagnosis of AD from normal brain ageing changes.

**Material and Method:**

Twenty patients with Alzheimer’s disease with mean age of 72.95(14 women and 6 men) and ten healthy individuals as control group with mean age of 70.50( 7 women and 3 men) were included in our study. All AD patient was examined by neurologist and all control subjects had normal MRI and no intracranial pathology. All individual gave written informed consent and then underwent MRI. Participant from all group who had a history of neurologic or psychiatric disease were excluded from the study.

**MR examination protocols:**

All MR studies were collected on a 1.5 Tesla GE explorer 360 MRI scanner. The MR scanning protocol included 3D MPRAGE( 3D-T1W) sequence( TR=9.7 ms, TE=3.7 ms, flip angle=12°, NEX=1, Matrix size=256×256, FOV=25.6).

Finally, the expert radiologist checked the quality and probable artifacts of all images.

**Image analysis:**
All images were analyzed using Freesurfer v5.3 and then calculated the brain cortical thickness in 7 cortex frome 3 region of brain(Inferior temporal, Middle temporal, Superior temporal, parahippocamp, parstriangularis, rostralmiddle frontal, Superior frontal).

At first, DICOM images converted to nft format. Then images process steps included: Skull stripping (removes skull and other structures from brain tissue); Intensity normalization (normalize the white matter intensity values all around 110); White matter segmentation (the segmentation of whit matter from other structures); Surface atlas registration (inflation of brain hemisphere and creates a map of brain sulcus); Surface extraction (separating brain hemisphere and creating surface brain model). Finally, thickness measures were mapped on the inflated surface map.

**Statistical Analysis**

Statistical analysis of data considering special characteristic (cortical thickness) was performed in SPSS version 23.

The Analysis of covariance (ANCOVA) was performed based on a vertex-by-vertex procedure to determine if there is a significant difference between regional cortical thickness variations of patients with Alzheimer diseases (AD) and cognitively normal (CN) subject, adjusting to age and gender. The homogeneity of gender and age between groups was test with chi-square independence test and independent T-test, respectively. The significance was defined as p<0.05. Two Receiver operating characteristic (ROC) curves were plotted to compare sensitivity versus specificity across a range of cortical thickness values for the ability to predict a dichotomous outcome (AD and CN).

**Results**

Ten Cognitively normal (CN) subjects and twenty patients diagnosed with Alzheimer’s disease (AD) from Athari medical imaging center were included to the study between December 2016 And May 2017. The mean age of CN subject and patients with AD were 70.50 and 72.95, respectively. Of the AD patient and CN subjects, 70% were female and 30% were male (table1). Mean cortical thickness (+/- s.e.) for each hemisphere and region are presented in table 2.
A one-way ANCOVA was conducted to compare the means of each region between the groups whilst controlling for age and gender as covariate. Leven’s test and normality checks were carried out and the assumptions met. There was a significant difference in mean of cortical thickness in regions such as inferior temporal Left hand (p<0.001), inferior Temporal Right hand (p<0.001), middle temporal left hand (p=0.006), middle temporal right hand (p=0.001), superior temporal left hand (p=0.006), superior temporal right hand (p<0.001), Parahippocampal left hand (p=0.026), Parahippocampal right hand (p=0.049), Parstriangularis right hand (p=0.041), Rostral middle Frontal left hand (p=0.003), Rostral middle Frontal right hand (p=0.003), Superior Frontal left hand (p=0.023) and Superior Frontal right hand (p=0.008) between the group (CN subjects V.S AD patients). In all cases the mean of cortical thickness in CN subjects were greater than AD patients. However, the mean of Parstriangularis left hand in CN subjects was not significantly greater than the one in AD patients (table3).

Table 1. Demographic Statistics

<table>
<thead>
<tr>
<th></th>
<th>CN Subjects</th>
<th>Alzheimer’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number(F/M)</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>3 (30%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>7 (70%)</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>75.50 ± 5.74</td>
<td>72.95 ± 6.87</td>
</tr>
</tbody>
</table>

Table 2. Mean Cortical Thickness (+/− s.e.) for Each Hemisphere and Region

<table>
<thead>
<tr>
<th>Region</th>
<th>CN Subjects</th>
<th>Alzheimer’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left thickness</td>
<td>Right thickness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>Group</td>
<td>Mean Difference ($\mu_{CN} - \mu_{AD}$)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Inferior Temporal. LH</td>
<td>CN</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Inferior Temporal. RH</td>
<td>CN</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Middle Temporal. LH</td>
<td>CN</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Middle Temporal. RH</td>
<td>CN</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Superior Temporal. LH</td>
<td>CN</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Superior Temporal. RH</td>
<td>CN</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>AD</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Result and Comparison of mean cortical thickness for each hemisphere and region between groups.
<table>
<thead>
<tr>
<th>Region</th>
<th>CN</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parahippocampal. LH</td>
<td>0.45</td>
<td>0.026</td>
</tr>
<tr>
<td>Parahippocampal. RH</td>
<td>0.30</td>
<td>0.049</td>
</tr>
<tr>
<td>Parstriangularis. LH</td>
<td>0.08</td>
<td>0.290</td>
</tr>
<tr>
<td>Parstriangularis. RH</td>
<td>0.28</td>
<td>0.041</td>
</tr>
<tr>
<td>Rostral middle Frontal. LH</td>
<td>0.17</td>
<td>0.003</td>
</tr>
<tr>
<td>Rostral middle Frontal. RH</td>
<td>0.21</td>
<td>0.003</td>
</tr>
<tr>
<td>Superior Frontal. LH</td>
<td>0.17</td>
<td>0.023</td>
</tr>
<tr>
<td>Superior Frontal. RH</td>
<td>0.19</td>
<td>0.008</td>
</tr>
</tbody>
</table>

In current study, Sensitivity (“positivity in health”) refers to the proportion of subjects who have the target condition (CN subjects) and give positive test results. Specificity (“negativity in health”) is the proportion of subjects without the target condition and give negative test results.
We have selected a thousand cut-off points from 1.5 to 3.5, then depending on the cut-off selected, the sensitivity and specificity of test were changed. When cortical thickness of a sample was less than the cut-off, we have considered it as a negativity in health (AD patients).

![ROC curve](image)

Fig.1 ROC curve for various cut-off levels, (A) of left hemisphere regions, (B) of right hemisphere regions.

Sensitivity and specificity were varied with the cut-off chosen. When the cut-off points were interval (2.276878, 2.299680) in left hemisphere, the Youden’s index was maximized. The sensitivity and specificity in this case were 80% (see figure 1.a). Also when the cut-off points were within the range (2.263278, 2.282278) in right hemisphere, the sensitivity and specificity were 90% and 80%, respectively (see figure 2.b).

Discussion
According to the fast growing rate of dementia especially Alzheimer’s disease all over the world, the promotion of diagnostic approaches at an earlier stage of disease has an important role (3). The measurement of brain cortical thickness can demonstrate the subtle changes of cortex thinning.

In this study, the main goal was to determine the correlation between the thickness of cerebral cortex and the severity of cognitive disorder in Alzheimer’s disease. So, the amount of cerebral cortex thickness was measured using Freesurfer software.

These changes can be revealed quantitatively by measuring the thickness of the cortex and studying the pattern of its changes. Moreover, it is possible to provide additional information about the process of the Alzheimer's disease.

Hence, the ability of diagnosing in early stages of Alzheimer’s disease increases in line with the differential diagnostic power between patients with mild Alzheimer’s and healthy people. Its progress can be eradicated with the early diagnosis of the disease.

Due to the structural nature of the cerebral cortex, which is twisted in several layers, manual methods for determining the thickness of the cortex is problematic due to being time-consuming and it requires a trained anatomist (4). That’s why automatic Freesurfer software in measuring the thickness of the cortex and quantifying structural properties has the advantage of inflating brain hemispheres and building a Surface Model (SBM) from the cerebral cortex which makes it possible to get sensitive and measure the cortex thickness in millimeters in neurodegenerative diseases.

Data achieved from Freesurfer software were studied for statistical analysis. The results of our study were in agreement with the results of studies by Salat et al(10), Ridway et al (11) and Jing Ming and colleagues (6). Reducing the thickness of the cerebral cortex was observed in all studies.

The results of the study showed changes in the thickness of the cortex with the severity of Alzheimer's disease that in all the seven cortexes studies, the mean cortical thickness of the brain in Alzheimer's patients was significantly lower than of the control group except parstriangularis cortex in the left hemisphere of the brain. The difference between the mean cortex thickness in healthy subjects and Alzheimer’s patients was very small and this was not statistically significant.
That is the only difference between our study and others. This slight difference in the thickness of the parstriangularis cortex can be due to the low volume of specimen. In order to investigate the possibility of early diagnosis of Alzheimer's disease, there was no significant difference in the mean brain cortex in three patients in the control group with patients. In these three people, the thickness of the cortex has been reduced so much which is close to the thickness of the cortex in people with Alzheimer's. It can be concluded that this reduction in thickness is due to the normal process of changing in the thickness of the cerebral cortex due to the normal ageing. Then, if they had symptoms of Alzheimer's disease in clinical trials, they must be considered as a susceptible person to disease which must undergo more clinical examination.

The receiver operating characteristic system (ROC) was designed to evaluate the predictive power of the patient and the healthy person. According to the ROC curve, if the thickness of the left hemisphere cortex is less than 2.27-2.22 mm, with a sensitivity of 80%, we can say that the person has Alzheimer. The specificity is also 80%. Sensitivity and specificity were 90% and 80%, respectively, when the average thickness of cortex was about 2.28-2.26 mm in the right hemisphere of the brain. In most studies done before, the sensitivity and specificity based on the thickness of the cortex for predicting a healthy or AD person has not been calculated. Unlike our study, which, in addition to determining the thickness of the cortex to determine the patient's person between healthy one, the sensitivity and specificity are also calculated.

There are several restrictions in this study, the first is the insufficient collaboration of the patients with Alzheimer's during the imaging and also 3D-T1w images collection, which may subsequently affect the software analysis. Although, images with motion artifacts were excluded from the study. The second limitation is the software errors. Because Freesurfer software is automatic, there may be errors during the analysis which we have done the three-step quality check as far as possible to optimize the software analysis stage. Thirdly, there were fewer patients.

According to the study taken, it is suggested that future studies be carried out in a wide range of samples to obtain better and more accurate results. Also, considering that this study was performed on 7 cortex of brain. So, it is recommended that subsequent studies be performed on all cortex. In further studies, patients in the MCI stage with a high sample volume could be
considered. Using three Tesla MRI devices makes it easier to measure few changes in the thickness of the cerebral cortex especially in patients with MCI.

**Conclusion**

In conclusion, to the best of our knowledge, our study is the first one to report finding on the range of cortical thickness that would help clinician to have better differential diagnose and also this study have checked the possibility of early diagnosis of the disease.

This study demonstrates the importance of quantify the cortical thickness changes in early diagnosis of Alzheimer’s disease.

In addition, examining the pattern of changes and the quantifying the reduction in the thickness of the cortex is an important tool for displaying the local and global atrophy of the brain. Also, this pattern can be used as an alternative marker for the diagnosis of dementia (12).

**References:**