Shape analysis of brain ventricles for improved classification of Alzheimer's patients.

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SHAPE ANALYSIS OF BRAIN VENTRICLES FOR IMPROVED CLASSIFICATION OF ALZHEIMER’S PATIENTS

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ABSTRACT
One of the hallmarks of Alzheimer’s disease (AD) is the loss of neurons in the brain. In many cases, the medical experts use MR (magnetic resonance) images to qualitatively measure the neuronal loss by the shrinkage (atrophy) of the structures-of-interest, or sometimes more easily by the enlargement of the fluid-filled structures, such as the ventricles. For quantitative analysis, volume is the common choice. Volume, or area in 2D, is a gross measure and it cannot capture shape differences that can improve the diagnostic accuracy. Because most existing methods use complex and difficult-to-reproduce shape descriptors, the experts prefer more easily and robustly extractable area and volume in their diagnosis. In this paper, we introduce several novel and easily-extractable 2D shape descriptors for brain ventricle, and show that they and some of the well-known simple shape descriptors, such as perimeter, are better descriptors in the classification of AD patients and healthy controls.

Index Terms— shape descriptors, brain ventricle, Alzheimer’s disease, correlation with cognitive tests, MMSE, classification, unpaired t-test.

1. INTRODUCTION
Alzheimer’s Disease (AD) is the most common dementia and it accounts for 50 to 70 percent of the cases [1]. AD afflicts an estimated 5 million people in the US, and 12 million worldwide. Because age is the primary risk factor, the demographic trend of aging population will double these numbers by 2025. Although there is currently no drug that can stop or prevent the disease, there are various symptomatic drugs that relieve the symptoms and in some cases, slow down the progress. Most of these drugs are effective only in early or mid-stages of the disease making early detection essential.

Currently, the primary tests for AD diagnosis are cognitive tests. Depending on the design, these tests measure various cognitive functions, such as memory, attention, orientation, language, and learning. The main appeal of these tests, such as mini-mental state examination (MMSE) [2], is their ease of administration, but the results can be subjective and affected by patient’s mental and physical state at the time of the test. In the diagnosis of AD, although cognitive test scores are powerful, imaging is useful and required for various clinical purposes [3]: 1) To eliminate other possible causes, such as tumor, for the low cognitive score. 2) To confirm that the patient does not have other forms of dementia, such as vascular and fronto-temporal. 3) Because some patients, especially of higher education and intelligence, are able to hide cognitive deficits in the tests for a long time, image-based analysis can detect AD earlier by quantifying the structural brain changes.

One of the structural changes occurring in the brain due to aging and AD is the enlargement of ventricles [4]. The ventricles are filled with cerebro-spinal fluid (CSF), a watery solution that provides physical and nutritional support to the brain. They enlarge at the expense of atrophy resulting from neuronal loss. In Figure 1, ventricles are visible as central hyper-intense regions for a healthy control and an AD patient. In clinics, the volume of ventricles is used qualitatively or quantitatively in the diagnosis of AD. Although shape of several brain structures, including ventricles, have been shown to provide more information than volume [5, 6, 7], the proposed shape descriptors for ventricle require advanced processing with very controlled parameters that hampers their widespread clinical usage. In contrast, this paper investigates simple, easy-to-extract 2D shape descriptors. In addition to known ones, such as perimeter and shape signature, we propose novel ventricle shape descriptors that should be even more easily extractable than area or volume. We compare these descriptors with area in two tasks: 1) Correlation with cognitive scores, and more importantly, 2) Classification of AD patients and healthy controls. For the latter, our results indicate that some of the simple shape descriptors provide superior results to area. In the next Section, we explain the commonly used and the proposed novel shape descriptors. To extract the proposed descriptors, 2D slices should be selected from 3D data. We describe that process in Section 3. In Section 4, we provide results in correlation and classification tasks, and finally, in Section 5, we draw conclusions.

2. SHAPE DESCRIPTORS
In this section, we first define the simple 2D shape descriptors that we use, such as perimeter, circularity, and eccentricity, and introduce several novel descriptors particularly tailored to brain ventricles. All descriptors are extracted from a binary ventricle map that is computed in the pre-processing stage, which is not the focus of this paper. Figure 5 shows the key-steps of the extraction. Given any MR data, we first register it to a common coordinate system, and then, extract the CSF region by using a clustering-based segmentation algorithm with \( k = 3 \) clusters (background, CSF, and combined white and gray matter). From the CSF map, we extract the 3D ventricle map by using spatial (brain atlas) and morphological constraints. In the following, we first start with area-derived descriptors.
Fig. 2. Extraction of 3D ventricle map: an axial MR T2 slice (left), the corresponding CSF segmentation map (middle), the ventricle segmentation map extracted from the CSF segmentation map by using some spatial and morphological constraints (right).

- Area: Area is the simplest and the most natural property of a binary image. It is equal to the number of object pixels. We first calculate the area of each object as a whole. Further we divide the object into four major parts (top left, top right, bottom left, bottom right) along the horizontal and vertical directions with the centroid as the center and do the calculations respectively.

- Perimeter: Perimeter is calculated from the number of boundary pixels of the closed binary image.

- Circularity: Circularity represents how closely-packed the shape is. This feature is calculated with Eq. 1 [8]. The most compact shape is circle ($4\pi$). All other shapes have a compactness larger than $4\pi$.

$$\text{Circularity} = \frac{\text{Perimeter}^2}{\text{Area}} (1)$$

- Eccentricity: There are several ways to define eccentricity. Here we use the ratio of the length of the longest chord of the shape to the longest chord perpendicular to it.

- Elongation: The ratio of the height and the width of a rotated minimal bounding box. In other words, rotate a rectangle so that it is the smallest rectangle in which the shape fits. Then compare its height to its width.

- Rectangularity: Rectangularity shows how much the shape fills its minimal bounding box. It is defined as the ratio of the area of an image object and the area of the minimum bounding rectangle (MBR) [9] as in Eq. 2. The maximum value is one and is achieved by a solid rectangle.

$$\text{Rectangularity} = \frac{\text{Area}_{\text{image}}}{\text{Area}_{\text{MBR}}} (2)$$

- Axis Shape Descriptors: Here we propose our novel shape descriptors. There are four important corner points on the brain ventricle shape (Figure 3, left), that is the top left point (point A), top right point (point B), bottom right point (point C) and bottom left point (point D). By connecting opposite pairs of the corner points, we create two axes. We name $d(A, C)$, that is the distance between A and C, and $d(B, D)$ as wing spans. We also calculate corner to center distances, that is $d(A, G)$, $d(B, G)$, $d(C, G)$ and $d(D, G)$ respectively. Another axis shape descriptor is the minimum thickness. Let (AD) be the set of points on the shortest contour between corner A and corner D (the contour not passing B and C) and (BC) be the point set on the shortest contour between corner B and corner C (the contour not passing A and D). Then the minimum thickness can be defined as follows:

$$\text{Minimum Thickness} = \min(d(P_1, P_2))$$

where $\forall P_1 \in (AD), \forall P_2 \in (BC)$

- Mean Signature Value: A signature is a 1-D functional representation of a boundary and may be generated in various ways [9]. In our case, we plot the function $z(i)$ as the distance from each boundary pixel to the centroid, where $i$ stands for the $i$th boundary pixel starting with the corner point A and follows clockwise direction (Figure 3). Based on this, we then take the mean value for each object.

$$\text{Boundary Moments: Assuming the shape boundary has been represented as a shape signature } z(i), \text{ the } r \text{th moment } m_r \text{, and central moment } \mu_r \text{ can be estimated as } [8]$$

$$\begin{align*}
    m_r &= \frac{1}{N} \sum_{i=1}^{N} [z(i)]^r \\
    \mu_r &= \frac{1}{N} \sum_{i=1}^{N} [z(i) - m_1]^r, (3)
\end{align*}$$

where $N$ is the number of boundary points. Less noise-sensitive shape descriptors can be obtained using the following representations:

$$\begin{align*}
    F_1 &= (\mu_2)^{1/2}/m_1 \\
    F_2 &= (\mu_3)/(\mu_2)^{3/2} \\
    F_3 &= (\mu_4)/(\mu_2)^2
\end{align*}$$

3. SLICE SELECTION

The shape descriptors defined in Section 2 are extracted from 2D ventricle segmentation maps. Brain MR scans are acquired in 3D; hence, the selection of the 2D slice(s) for processing is an important step and is discussed in this section. In the slice selection, we consider two issues: 1) Whether the ventricle area computed from a selected slice is highly correlated to volume for a large number of patients and 2) If our assumptions, explained below, about the shape descriptors hold for the selected slice and whether we can accurately extract the descriptor.

To measure the effect of area in slice selection, we have analyzed ventricle segmentation maps from 128 patients registered to a common coordinate system. For each slice, we have computed the correlation between the area and volume, which has been calculated as the sum of the brain ventricle area of all slices for the corresponding
In each slice, we have 128 \((area, volume)\) pairs, one pair for each patient. We have expected that if area descriptor is reliable to use, then, it should have high correlation between area and volume for the selected patient population. Figure 4 shows the sample slices with visible ventricle. In all slices showing ventricle, the minimum correlation value has been computed to be greater than 0.98, as shown in Figure 5. We conclude that area computed from most of the slices showing ventricle can replace the ventricle volume.

For the computation of shape descriptors, the assumptions for at least one of the descriptors are: 1) the ventricle forms one connected region, and 2) the four corners should be identifiable. These assumptions eliminate some of the slices from consideration. The two slices from the top-left and the two slices to the bottom-right do not satisfy the two assumptions. Except for these four slices, any other slice can be used for shape descriptor extraction.

Fig. 4. Axial slices where lateral ventricle appears. The direction from top-left to bottom-right indicates the direction from the bottom of the head to the top. Area has high correlation with volume for all slices. For shape descriptors, any slice except for the two slices from both top-left and bottom-right can be used.

Fig. 5. Correlation values between area and volume for the central eight selected slices in Figure 4.

4. RESULTS

In this section, we compare the performance of all the other shape descriptors with area descriptor in two tasks: 1) Correlation with cognitive test score, and 2) Classification of AD patients. Our first dataset consists of T2 MR scans of 128 subjects (the same set that we use for the area-volume correlation experiment in Section 3), which are acquired on a Philips Intera 1.5T whole body scanner at Leiden Univ. Medical Center with parameters (TR/TE: 3000/120 ms, FLIP: 90, 220mm FOV, 3mm slice thickness, no slice gap and 256x256 matrix), with MMSE scores (mean 22.5, standard deviation 5.87) but without AD diagnosis. Figure 6 shows several samples of the first data set. Our second set includes MR data of 10 patients (age: 70-80) with moderate AD diagnosis and 10 age-matched healthy controls. We use the first set for correlation analysis, and the second for classification.

Fig. 6. Sample slices of the first dataset

4.1. Correlation with Cognitive Test Scores

The performance of each shape descriptor is evaluated by the correlation value \(r\) between the feature extracted and the corresponding MMSE scores. The correlation coefficient indicates the strength and the direction of a linear relationship between two sets of variables. The performance results are presented in Table 1. The results show that, although there are some slight fluctuations in different regions, area descriptors generate higher correlation values than most shape descriptors. A notable exception is our novel minimum thickness descriptor, which resulted in slightly higher correlation value than that of area. Among the shape descriptors, mean signature value and perimeter have also resulted in close correlation values to those of area descriptors. Regarding the axis shape descriptors, they give good correlation results except for the corner to center DG which shows an unusual low correlation value.

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>(r)</th>
<th>Descriptor</th>
<th>(r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum Thickness</td>
<td>-0.37</td>
<td>Eccentricity</td>
<td>-0.20</td>
</tr>
<tr>
<td>Whole Area</td>
<td>-0.34</td>
<td>Corner to Center AG</td>
<td>-0.18</td>
</tr>
<tr>
<td>Top Left Area</td>
<td>-0.33</td>
<td>Moment (F_2)</td>
<td>-0.18</td>
</tr>
<tr>
<td>Bottom Left Area</td>
<td>-0.32</td>
<td>Wing Span AC</td>
<td>-0.17</td>
</tr>
<tr>
<td>Bottom Right Area</td>
<td>-0.32</td>
<td>Corner to Center BG</td>
<td>-0.17</td>
</tr>
<tr>
<td>Top Right Area</td>
<td>-0.29</td>
<td>Corner to Center CG</td>
<td>-0.16</td>
</tr>
<tr>
<td>Mean Signature Value</td>
<td>-0.27</td>
<td>Circularity</td>
<td>0.16</td>
</tr>
<tr>
<td>Perimeter</td>
<td>-0.24</td>
<td>Wing Span BD</td>
<td>-0.14</td>
</tr>
<tr>
<td>Moment (F_1)</td>
<td>0.24</td>
<td>Elongation</td>
<td>0.14</td>
</tr>
<tr>
<td>Rectangularity</td>
<td>-0.23</td>
<td>Corner to Center DG</td>
<td>-0.09</td>
</tr>
</tbody>
</table>
4.2. Classification of AD Patients and Controls

We have measured the performance of the shape descriptors in the classification of moderate AD patients and healthy controls. To this end, we have used the second dataset having 10 AD patients and 10 age-matched healthy controls (HC). In this task, we haven’t explicitly designed a classifier, instead, computed the significance of the difference of the means of the AD and HC groups for each descriptor with the unpaired t-test. The unpaired t-test is applicable to groups that are not paired. None of the AD patients is related to the subjects in the HC group. When the test is applied, a significance value, p-value, is computed. The p-value is the probability of obtaining a result at least as extreme as a given data point under the null hypothesis. The lower values of p are desired.

In Table 2, we provide the statistics for several promising shape descriptors, including area, perimeter, mean signature value and axis shape descriptors. Differently from the correlation with cognitive tests, mean signature value gives the best classification ability and axis shape descriptors, bottom left wing length especially, also show good performances. This is in line with our expectations as the posterior lobe of ventricles show more variation than the anterior lobe, whose shape is more consistent across pathologies.

<table>
<thead>
<tr>
<th>Table 2. Classification Testing Results</th>
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<tbody>
<tr>
<td>Descriptor</td>
</tr>
<tr>
<td>Mean Signature Value</td>
</tr>
<tr>
<td>Minimum Thickness</td>
</tr>
<tr>
<td>Corner to Center DG</td>
</tr>
<tr>
<td>Perimeter</td>
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<tr>
<td>Whole Area</td>
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<tr>
<td>Corner to Center CG</td>
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<tr>
<td>Wing Span BD</td>
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<tr>
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<tr>
<td>Corner to Center AG</td>
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5. CONCLUSION

In this paper, we have introduced several novel and easily-computable shape descriptors for brain ventricle as alternative to commonly-used area measure. We have intentionally chosen simple 2D descriptors because more complicated shape descriptors usually require many parameters to be fine-tuned and may not be easily reproducible. That prevents their widespread adoption in clinical usage. To compare the shape descriptors with area, we have measured their performance in correlation with cognitive scores, and classification of AD patients and normal controls. We have also analyzed the effect of slice selection in our results and defined a region-of-interest where we can select the slices to extract the proposed shape descriptors.

Correlation testing results have demonstrated that minimum thickness and area have the highest correlation to cognitive test scores, measured by MMSE. Mean signature value also gives much information about the brain ventricle status since it is derived from the average value of the distance from the centroid to each boundary pixel. To some extent, this definition is in line with that of area.

In the classification task, we have investigated the differences of the means between the two groups by the unpaired t-test. In the classification, shape descriptors have shown more promise. Mean signature value, one of the axis descriptors, minimum thickness and perimeter have shown superior results to area. A result worth mentioning is that the upper part and lower part of the ventricle shape in the axial plane differ greatly in their classification ability. This is in line with our expectations. We have found the lower part (posterior lobe of ventricle) more descriptive of the disease.

With respect to extraction, we have found that only perimeter has a major disadvantage because of its sensitivity to noise. Consequently, the quality of the testing data sets will affect its behaviour greatly.

Based on the testing results, we conclude that mean signature value, axis descriptors (for posterior lobe), minimum thickness, and perimeter can be alternatives to area because of their low computational complexity as well as good ventricle shape representation and classification ability. As a future work, we are planning to confirm this result in a larger dataset.

6. REFERENCES