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Detecting Hippocampal Shape Changes in Alzheimer's Disease using Statistical Shape Models

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Abstract

The hippocampus is affected at an early stage in the development of Alzheimer's disease (AD). Using brain Magnetic Resonance (MR) images, we can investigate the effect of AD on the morphology of the hippocampus. Statistical shape models (SSM) are usually used to describe and model the hippocampal shape variations among the population. We use the shape variation from SSM as features to classify AD from normal control cases (NC). Conventional SSM uses principal component analysis (PCA) to compute the modes of variations among the population. Although these modes are representative of variations within the training data, they are not necessarily discriminant on labelled data. In this study, a Hotelling's T^2 test is used to qualify the landmarks which can be used for PCA. The resulting variation modes are used as predictors of AD from NC. The discrimination ability of these predictors is evaluated in terms of their classification performances using support vector machines (SVM). Using only landmarks statistically discriminant between AD and NC in SSM showed a better separation between AD and NC.

1. Description of purpose

Early detection and diagnosis of Alzheimer's disease (AD) is a challenging task. Since the hippocampus is affected by atrophy in the earliest stage of disease, which may result in the reduction of volume and the change in the shape of hippocampus. Hippocampal volume has been previously used to classify AD from normal control (NC) subjects, as well as cases with mild cognitive impairment (MCI) [1]. Shape information in the form of spherical harmonics (SH) has been used as features in the support vector machine (SVM) classification [2,3]. Statistical Shape Models (SSMs) have been used to model the variability in the hippocampal shapes among the population (e.g. [4]). They usually rely on principal component analysis (PCA) to determine a lower dimensional subspace that accounts for the most variations. However, these modes of variations are not necessarily discriminant.

In this study, we aim to improve the discrimination between AD and NC using shape information characterized by SSM. We use SSM to search for variations on the surface regions that are significantly discriminant between the two groups. The discriminant regions may be due to both volume and shape changes. We propose to use the morphological variation on these surface regions as variables to distinguish AD from NC cases. These variations are also correlated with the cognitive decline in AD.

2. Methods

2.1 Materials

The hippocampus segmentations used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI), which provides the hippocampal volumes segmented semi-automatically by SNT. The hippocampal volumes were divided into a training set and a testing set. The training set consists of 60 AD subjects with average age 75.2(6.7) years old and 60 NC subjects with average age 77.0(4.8) years old. The testing set consists of 117 subjects, 39 AD with average age 77.8(7.3) years old and 78 NC with average age 76.3(5.2) years old.

2.2 SSMs on discriminant points

An SSM is built upon a set of shape examples, in which each shape is represented by its n_P landmark points. In this study, the hippocampal volumes in the training set were first registered and aligned via rigid transformations, followed by a groupwise optimization and fluid regularization on the shape image [6] to establish the correspondence across the training set. Once the correspondence across the training set is established, the shapes can be aligned by using Procrustes analysis, either through rigid or similarity transformations. The volume information is preserved in rigid transformations. In this case, the variation in the training data will be partly driven by the volumetric change of hippocampus due to tissue loss. If the shape surfaces are aligned via similarity transformations, the shapes are rescaled to normalize the hippocampal volume. This enables the SSM to be more specific to the change in the shape *per se* rather than the variation in the size of hippocampus.
Given a training set $\{\mathbf{x}_i : i=1,2, \dots , n_S\}$ of n_S shapes, in which the correspondence is established and the shapes are aligned rigidly or via similarity transformations, each of its shape containing n_P landmarks can be represented as a $3n_P$-vector

$$\mathbf{x}_i = \left(x_i^{(1)}, y_i^{(1)}, z_i^{(1)}, x_i^{(2)}, y_i^{(2)}, z_i^{(2)}, \cdots , x_i^{(n_P)}, y_i^{(n_P)}, z_i^{(n_P)}\right)^T$$

where $\mathbf{p}_i^{(k)}=(x_i^{(k)}, y_i^{(k)}, z_i^{(k)})$ is the position of the kth landmark point on the ith shape surface. For the kth landmark $\{\mathbf{p}_i^{(k)} : i=1, 2, \dots , n_S\}$ in the SSM, a Hotelling's T^2 test can be performed [6] in order to assess its statistical significance in discriminating the NC group from the AD group. Selecting only the $m(<n_P)$ landmarks that are significantly discriminant on the labelled data, i.e. those landmarks with p-value below a threshold, the shape is represented by the subset of landmarks

$$P(\mathbf{x}_i) = \widetilde{\mathbf{x}}_i = \left(\tilde{x}_i^{(1)}, \tilde{y}_i^{(1)}, \tilde{z}_i^{(1)}, \tilde{x}_i^{(2)}, \tilde{y}_i^{(2)}, \tilde{z}_i^{(2)}, \cdots , \tilde{x}_i^{(m)}, \tilde{y}_i^{(m)}, \tilde{z}_i^{(m)}\right)^T,$$

which is a projection mapping to the regions more relevant to the pathology. A SSM can thus be built concerning only the regions identified by the statistical test. For shape vector $\mathbf{x}$, the coefficients of variation modes on discriminant regions can be calculated as

$$\widetilde{\mathbf{b}} = \widetilde{\mathbf{W}}^T (P(\mathbf{x}) - \bar{\widetilde{\mathbf{x}}})$$

where $\widetilde{\mathbf{W}}$ is the matrix of eigenvectors describing the variation modes from the PCA performed on only significantly discriminant landmarks.
Thus, we have four choices of building SSM on the given training set with established correspondence:

- M_{RA} using all the hippocampal landmarks, with shapes aligned via rigid transformation,
- M_{SA} using all the hippocampal landmarks, with shapes aligned via similarity transformation,
- M_{RD} using hippocampal landmarks significant against AD, with shapes aligned via rigid transformation,
- M_{SD} using hippocampal landmarks significant against AD, with shapes aligned via similarity transformation.

2.3 Representation of the test data

For a given shape not in the training set, the correspondence between the SSM landmarks and the shape surface points needs first to be established, so that the given shape can be represented in the same vector space as the training data. The SSM is deformed to fit the smoothed target surface, minimizing L_1 distance metric between the SSM generated surface and the target. Without the assumption of correspondences between two shape vectors **x** and **y**, the L_1 distance d_S between their surfaces $S(\mathbf{x})$ and $S(\mathbf{y})$ can be defined as the sum of the Euclidean distance from each point in **x** to its closest point on **y** and from each point **y** to **x**. Thus we can fit the SSM to the target surface $S(\mathbf{y})$ by the optimization of parameters using Powell's algorithm

$$(\mathcal{T}_{\mathbf{y}}, \mathbf{b}_{\mathbf{y}}) = \underset{(\mathcal{T},\mathbf{b})}{\arg\min}\, d_S(\mathcal{S}(\mathcal{T}(\bar{\mathbf{x}} + \mathbf{W}\mathbf{b})), \mathcal{S}(\mathbf{y}))$$

where T is a similarity transformation with 7 degrees of freedom, and **b** parameterizes the deformation of the SSM. For the each landmark generated by SSM, we can find the closest point on the target surface as the corresponding landmark point. By aligning the shape vector of correspondences to the shapes in the SSM through Procrustes analysis, we have the n_P-D shape vector representing the surface $S(\mathbf{y})$ in the same space as the shapes in the SSM, ready for further analysis.

2.4 Classification method

The shape descriptors from SSM are evaluated in terms of their performance when being used as features in classification algorithms. SVMs are widely used in solving the classification problem. It usually maps the feature space to higher dimension via a kernel function, and finds the optimal hyperplane with the largest margin separating the classes. We use the classifier trained by the SVM to test the discrimination ability of the features. In this study, the radial basis function was used as the kernel of SVM. The features of each shape **x** for classification are the coefficient variation modes. In order to avoid modelling noise, less significant components produced by PCA are not included in the feature set. A subset of features is selected using random forest by minimizing the out-of-bag (OOB) error [7].

3. Results

In the experiment, hippocampi on both the right and left sides of 60 NC and 60 AD subjects from ADNI data were used as a training set to built the SSM. Hotelling's T^2 test was performed on each SSM between the AD and NC groups, with the resulting significance maps shown in Fig. 1.

Table 1. Results of SVM accuracy on a test set of 117 cases (%).

	With Volumety

	Rigid	Similarity	Rigid	Similarity
All landmarks	77.8	72.6	83.8	85.5
Landmarks with $p < 0.05$	63.2	77.8	84.6	**87.2**
Landmarks with $p < 0.01$	68.4	79.5	84.6	85.5

A PCA was performed on the landmarks with $p < 0.05$ and $p < 0.01$. For the purpose of comparison, conventional PCA on all the landmarks was also performed.
The first 15 principal components in each of the SSM were used for feature selection. These components explained approximately 90% of variations in the training set. In addition to the shape variations, the hippocampal volume normalized by TIV was also used as independent features.
The resulting SSMs were evaluated on a testing set of 117 subjects (39 AD and 78 NC), also from ADNI. The results of the accuracy on the testing set are shown in Table 1.
When using all the points to perform the PCA, the features extracted from the SSM built using a rigid transform reflect largely the volume differences between the hippocampi, whereas the ones extracted from the SSM built using a similarity transform are a better reflection of local shape variations. This is effect results in the M_{RA} yielding better classification results than M_{SA} (77.8% vs 72.6%) as volume alone is a good discriminant (83.8%). Adding volume to the features extracted using M_{RA} and M_{SA} increased both of their accuracy, but to a much less extent for M_{RA} (+6.0%) compared to M_{SA} (+12.8%).
Restricting the PCA to discriminant points on shapes aligned via similarity transformation produced better discrimination between NC and AD than using all the points. Using the shape variation on discriminant points extracted from M_{SD} yielded better accuracy than the global variation incorporating both shape and volume characterised by M_{RA}. The best classification results were obtained when volume was added as an additional feature to the shape features obtained using the SSM built using a similarity transform on the discriminant points (M_{SD}).

4. New and breakthrough work to be presented

- Model the shape variation between the AD and NC population of hippocampus on the regions affected by atrophy identified by statistical tests;
- Improving the disease classification performance by using the shape descriptors extracted from atrophy affected areas on the hippocampal surface.

5. Conclusions

The shape of the hippocampus can provide valuable information for the diagnosis of AD. The variation modes of the hippocampus among the population as modelled by the SSM can be used to classify AD against NC. The conventional PCA in SSM is performed on all the landmark points on the shape which is a good representation of the original shape data in a lower dimensional subspace, while it might be not discriminant between two groups. By applying a statistical test on the landmark points in the SSM, we can identify the regions on the hippocampal surface which are more discriminant between AD and NC groups. The PCA performed on this subset produced variation modes which were used as features for the classification between these two groups.

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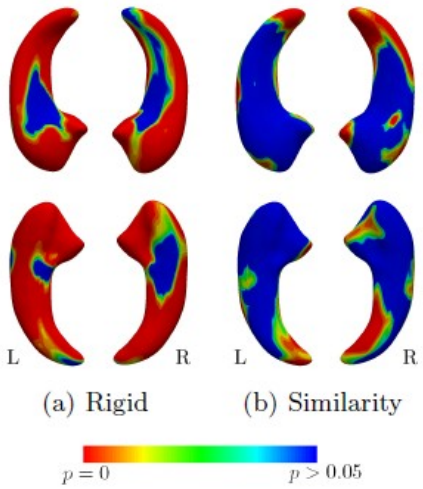

Fig. 1: Signicance map by Hotelling's T^2 test, performed on rigid and similarity aligned SSMs. Top: superior view; bottom: inferior view.