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HIPPOCAMPUS MORPHOMETRY STUDY ON PATHOLOGY- CONFIRMED ALZHEIMER'S DISEASE PATIENTS WITH SURFACE MULTIVARIATE MORPHOMETRY STATISTICS

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Abstract

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases in elderly and the incidence of this disease is increasing with older ages. One of the hallmarks of AD is the accumulation of beta-amyloid plaques ($A\beta$) in human brains. Most of prior brain imaging researchers used the clinical symptom based diagnosis without the confirmation of imaging or fluid $A\beta$ information. In this work, we study hippocampus morphometry on a cohort consisting of $A\beta$ positive AD ($N = 151$) and matched $A\beta$ negative cognitively unimpaired subjects ($N = 271$) with $A\beta$ positivity determined via florbetapir PET. The brain images are obtained from publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI). We compute our surface multivariate morphometry statistics from segmented hippocampus structure in structural MR images. With these features, we find statistically significant difference by using Hotelling's T^2 tests. Meanwhile, we apply a patch-based analysis of sparse coding system for binary group classification and achieve an accuracy rate of 90.48%. Our results demonstrate that our surface multivariate morphometry statistics (MMS) perform better than traditional hippocampal volume measures in classification and it may be applied as a potential biomarker for distinguishing dementia due to AD from age matched normal aging individuals.

Index Terms

Alzheimer's disease; Hippocampus; Surface Multivariate Morphometry Statistics (MMS)

1. INTRODUCTION

With the population living longer than ever before, Alzheimer's disease (AD) is now a major public health concern with the number of affected patients expected to triple, reaching 13.8 million by the year 2050 in the U.S. alone. One of the hallmarks of AD is the accumulation of beta-amyloid plaques ($A\beta$) in human brains and a positive $A\beta$ reading is now accepted as 'dementia due to AD' together with the presence of clinical symptoms. Moreover, preclinical AD is now viewed as a gradual process before the onset of the clinical symptoms

and yet with the $A\beta$ positivity which is viewed as precursor of anatomical abnormality such as atrophy and functional changes such as hypometabolism/hypoperfusion. Current therapeutic failures in patients with dementia due to AD might reflect intervention that is too late, or targets that are secondary effects and less relevant to disease initiation and early progression [1].

It is commonly agreed that an effective presymptomatic diagnosis and treatment of AD could have enormous public health benefits. Brain imaging has the potential to provide valid diagnostic biomarkers of preclinical stage as well as symptomatic AD. Owing to its close relationship between neurodegeneration and cognition, atrophy measured by structural magnetic resonance imaging (sMRI) has been shown to detect and track characteristic and progressive measurements of hippocampal, regional gray matter, and whole brain atrophy in clinical and late preclinical stages of AD. While a variety of research has been devoted to studies on the group difference or personal diagnosis with sMRI analysis, limited research has been conducted on those $A\beta$ positive AD patients and $A\beta$ negative cognitively unimpaired subjects. The knowledge gained from this type of research will enrich our understanding on the relationship between brain atrophy and AD pathology and thus benefit assessing disease burden, progression and effects of treatments.

In this paper, we propose to apply surface-based subcortical morphometry analysis to a cohort consisting of patients with dementia due to AD (defined $A\beta$ positive and the presence of clinical symptoms) and $A\beta$ negative cognitively unimpaired subjects (not individuals at preclinical stage of AD). Most of the researchers, who work on subcortical morphometric studies, used volume as the measurement of atrophy [2, 3] but recent research shows that the surface of the subcortical structure may provide more valuable information than the volume [4, 5]. There are many surface morphometry measures, such as radial distances (RD, distance between each surface points to its medical center) [4], local area differences [6], spherical harmonic analysis [7] and Gaussian random fields [8]. Surface tensor-based morphometry (TBM) [9] is an intrinsic surfacer statistic that examines spatial derivatives of the deformation maps that register brains to a common template and construct morphological tensor maps. We recently proposed a multivariate TBM (mTBM) [10] and later further combined RD and mTBM into surface multivariate morphometry statistics (MMS) [11].

In this context, we adopt surface MMS of hippocampi as imaging biomarkers and design two different experiments for validation. The first experiment is to calculate the group difference between $A\beta+$ AD and $A\beta-$ NL and the second experiment to classify these two groups. We hypothesize that our work may provide improved statistical power than traditional hippocampal volume or surface area measures. We achieve satisfying results that support MMS may be used as a valid biomarker of pathology-confirmed AD patients.

2. METHODS

Fig. 1 is the diagram of the system pipeline. We detail our system design in the following subsections.

2.1. Hippocampus Segment

We segmented the hippocampus from MRI scans by using FSL package [12]. Firstly, all the images were registered to a standard space (MNI152). Then, we used FIRST to extract subcortical structures and generate a binary image with different labels for each structure [13].

With the binary image, we could acquire the hippocampus structures and then constructed triangular meshes by marching cubes algorithm [14, 15]. To overcome the noise caused by the image scanning and the effects of partial volume, we built a smoothing method with two steps, “progressive meshed” and Loop subdivision, which can also preserve the features. Fig. 2 shows that the smoothed meshes have better-restored shape.

2.2. Surface Multivariate Morphometry Statistics

Surface multivariate morphometry statistics (MMS) consists of two different features, multivariate tensor-based morphometry (mTBM) and radial distance (RD). To calculate the surface MMS, we need to finish the following two steps. First of all, a nonlinear surface registration method, fluid registration, was used to map the individual hippocampal surface to a standard template surface. After that, we computed the local surface deformation to get mTBM as well as RD.

We proposed a surface registration method, surface fluid registration, by combining conformal mapping and image fluid registration. We treated the hippocampal surface as a cylinder, of which both the top and bottom have a hole and we cut one boundary across the surface that links the two holes [11]. This allowed us to map the hippocampal surface to a 2D rectangular surface. Finally, the hippocampal surface was registered to a standard surface by constrained harmonic maps. For two surfaces, S_1 and S_2 , their harmonic mapping ξ is like following:

$$\xi \circ \xi_1(S_1) = \xi_2(S_2), \xi \circ \xi_1(\partial S_1) = \xi_2(\partial S_2), \delta_\xi = 0. \quad (1)$$

ξ_1 and ξ_2 are conformal parameterizations, which map S_1 and S_2 to the rectangular surface, $\mathbb{R}^2$. We can accordingly obtain a map τ from surface S_1 to S_2 , $\tau = \xi_1 \circ \xi \circ \xi_2^{-1}$.

After registration, we computed the multivariate morphometry statistics. The first feature is called multivariate tensor-based morphometry (mTBM), which is a 3×1 feature vector, a “Log-Euclidean metric” [16] on the set of deformation tensors S . The deformation tensor is defined as $S = (J^T J)^{1/2}$, where J is the Jacobian matrix. Suppose $\tau = S_1 \Rightarrow S_2$ is a map from surface S_1 to S_2 and x and y are two faces isometrically embedded on plane $\mathbb{R}^2$. We can approximate the derivative map $d\tau$ from the face on surface S_1 , $[x_1, x_2, x_3]$, to the one on S_2 , $[y_1, y_2, y_3]$, where x_i and y_i are the planar coordinates of vertices. Then we calculated the Jacobian matrix for derivative map as $J = d\tau = [x_3 - x_1, x_2 - x_1][y_3 - y_1, y_2 - y_1]^{-1}$. The second feature is the radial distance [4, 17], which is represented as the shortest distance from each surface vertex to the medial axis of a tube-shape surface.

2.3. Group Difference Study

We calculated the group difference between the two groups of subjects by using Hotelling's T^2 test. Statistical results were corrected for multiple comparisons using the permutation test [10]. Firstly, with two groups of 4-dimensional vectors, $P_i, i = 1, \dots, m$ and $N_j, j = 1, \dots, n$, we computed their Mahalanobis distance,

$$M = (\bar{P} - \bar{N})\Sigma^{-1}(\bar{P} - \bar{N}), \quad (2)$$

where $\bar{P}$ and $\bar{N}$ are the mean and Σ is the combined covariance matrix of two groups. Secondly, we randomly divided the subjects into two different groups, of which the true group has the same number of subjects, and recomputed the group difference on each point on the surface. The procedure was repeated for 10,000 times and got 10,000 permutation values on each vertex. Then the uncorrected p value on each surface was calculated by the ratio of the number of permutation values greater than the true group t value to the total permutation times. To show the result, we built a form, p -map. By giving a pre-defined statistical threshold, $p < 0.05$, we could define a new feature which is the number of the surface vertex with an uncorrected p value lower than the threshold. We could treat the feature as the real effect in the true experiment. By comparing the features derived from the random groupings, we acquired a ratio stood for the fraction of the time an effect of similar magnitude to the real effect occurs in the random assignments. This ratio provided the map a global-level significance, which is also a corrected significance.

2.4. Classification study

Since the feature dimension is much larger than the number of subjects during a classification algorithm based on 3D images or surface-based features, in this paper, we used dictionary learning and sparse coding to reduce the dimension before prediction. dictionary learning has been widely used in processing image as it can construct the natural image patches accurately [5]. Stochastic Coordinate Coding (SCC) [18] was adopted when constructing the dictionary since it can accelerate the computation speed.

With a finite training set of signals, $P = (p_1, p_2, \dots, p_m)$, in $\mathbf{R}^{x \times m}$ image patches, where each patches $p_i \in \mathbf{R}^x, i = 1, 2, \dots, m$ and x is the dimension of image patch, we tried to optimize the empirical cost function,

$$f_m(D) \triangleq \frac{1}{m} \sum_{i=1}^m l(p_i, D). \quad (3)$$

$D \in \mathbf{R}^{x \times m}$ is the dictionary, of which each column represents a basis vector, and $l(p_i, D)$ is the loss function that measures whether D could represent the signal p well.

Supposed we have n atoms, $d_j \in \mathbf{R}^p, j = 1, 2, \dots, n$, where n is much smaller than m but larger than p and p_i could be represented as $p_i = \sum_{j=1}^n q_{i,j} d_j$. Then, we converted the p -dimensional vector p_i to an n -dimensional vector $q_i = (q_{i,1}, \dots, q_{i,n})$, which means the learned feature vector q_i is a sparse vector. Therefore, we applied the idea of sparse patch features into the optimization problem for each patch p_i .

$$\min_{f_i} (D, q - i) = \frac{1}{2} \|Dq_i - p_i\|_2^2 + \sigma \|q_i\|_1, \quad (4)$$

where σ is the regularization parameter, $\|\cdot\|$ is the standard Euclidean norm and $\|q_i\|_1 = \sum_{j=1}^n |z_{i,j}|$. $D = (d_1, \dots, d_n) \in \mathbf{R}^{p \times n}$ is the dictionary. The first part of the equation measures the degree of the image patches' goodness and the second is the sparsity of the learned feature q_i . The columns d_j is constrained by

$$C \triangleq \{D \in \mathbf{R}^{p \times n} \text{ s.t. } \forall j = 1, \dots, n, d_j^T d_j \leq 1\}, \quad (5)$$

Then we can rewrite the dictionary learning problem as a matrix factorization problem as

$$\min_{D \in C, Q \in m \times n} \frac{1}{2} \|P - DQ\|_2^2 + \sigma \|Q\|. \quad (6)$$

Here, D is the dictionary and Q is the sparse code. When neither D or Q is fixed, it will require a lot of time to solve the other one. Thus, we choose the SCC algorithm, which can dramatically reduce the computational cost of the sparse coding while keeping a comparable performance.

3. EXPERIMENTAL RESULTS

3.1. Data Description

The data we used in the experiment were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) project [2]. From the given form, we get 422 subjects (Table 1), which includes 151 $A\beta$ positive AD subjects and 271 $A\beta$ negative normal (NL) ones. The $A\beta$ positivity was determined using mean-cortical SUVR (standard uptake value ratio) with cerebellum as reference region. The threshold of 1.18 was determined by comparing the mean-cortical SUVR of neuropathologically confirmed $A\beta$ positive AD patients with age matched cognitively unimpaired individuals. All the high-resolution MRI scans were acquired from ADNI 1, ADNI GO and ANDI 2. In the following text, we use the terms *AD*, *$A\beta$ + AD* and *$A\beta$ positive AD*, or *NL*, *$A\beta$ - NL*, and *$A\beta$ negative NL*, interchangeably.

3.2. Morphometric Difference between AD and NL

Initially, we made use of FSL to segment hippocampus structures. They were then converted to meshes and further smoothed by a feature-preserved method. We registered hippocampal surface with surface fluid registration and computed a set of the multivariate statistics (MMS), i.e., mTBM (3×1 vector) and RD (1×1 vector), on each mesh vertex.

With MMS, we computed Mahalanobis distance to measure the group difference. The p -map (bottom row in Fig. 3), shows the group difference computed by the Hotelling's T^2 test and corrected by the multiple comparisons with a 10000-time permutation test. We set the threshold as $p < 0.05$ and the global differences, of which the p -values are less than 0.0001, are significant on both sides of the hippocampi. We also made permutation test on left hippocampal volume and hippocampal surface area measures. The top row in Fig. 3 shows their distributions and their p -values are also lower than 0.0001, which means the features of hippocampal volume and area are equally effective with MMS for group difference study.

3.3. Classification Result

We also processed a classification method to prove the significant difference between AD and NL. After we generated the feature mesh that contains a (4×1 vector) on each vertex, we extracted the surface feature by randomly collecting small image patches on hippocampal surfaces. These image patches are 10 windows that overlapped to each other. As for the vertices that located the overlapped area, we averaged their counterparts from the centered patches. We can consider the procedure as applying a high-pass filter to the hippocampus mesh, which leads to the result that the geometrical structures are kept in the centered mesh and some low frequencies are eliminated. In this way, we convert the features of the whole mesh into 1008 patches. Then the dictionary was initialized by selection random patches. We learned the dictionary and sparse codes by SCC and use a batch size of 1 to train the model for 10 epochs. Finally, max-pooling method [19] was applied to reduce the features to a reasonable size.

With these dimension-reduced MMS features, we adopted a weak classifier, Adaboost, to discriminate subjects into two groups, AD and NL. In order to estimate classification accuracy, we employed 10-fold leave-one-out cross validation method. To indicate the number of correct class labels, we built a contingency table, of which the rows are the true classes and the columns represent assigned classes. And then, we could represent the

combination of ground truth and predicted result as $\begin{pmatrix} Z_{11} & Z_{12} \\ Z_{21} & Z_{22} \end{pmatrix}$ and compute the following

four performance measures, $Sensitivity = Z_{11} / (Z_{11} + Z_{12})$, $Specificity = Z_{22} / (Z_{21} + Z_{22})$, $Positive Predictive Value = Z_{11} / (Z_{11} + Z_{21})$ and $Negative Predictive Value = Z_{22} / (Z_{12} + Z_{22})$.

We also compared our work with two other features, hippocampal volume and surface area. Each of them is a 2×1 vector per subject, which were both classified by SVM classifier [20] with a linear kernel. Fig. 4 shows the result comparison. It shows that the classification accuracy of our features, MMS, reached 90.48%, which is better than the ones on volume (80.09%) and area (78.44%). Our work achieved relatively good sensitivity (91.67%), specificity (88.89%), and negative predictive value (88.89%). Finally, we compared the

results with the ground truth and computed the receiver operation characteristic (ROC) curves (Fig. 5). It shows that the area under the curve (AUC) of our work is 0.9213, which is also higher than those of volume (0.8927) and area (0.8742). Although more studies are warranted, our results show MMS achieved superior results than hippocampal volume/area measures in the pathology-confirmed AD classification research.

4. CONCLUSION AND FUTURE WORK

We employed a surface-based subcortical morphometry analysis on a cohort consisting of $A\beta+$ AD and $A\beta-$ cognitively unimpaired subjects and the two aforementioned experiment results demonstrated our surface MMS can be applied as a potential biomarker for pathology-confirmed AD analysis. Our future work will focus on making our morphometry analysis suitable for other brain structure morphometry research.

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References

1. Hyman BT. Amyloid-dependent and amyloid-independent stages of Alzheimer disease. *Arch Neurol.* Aug; 2011 68(8):1062–1064. [PubMed: 21482918]
2. Jack CR, Slomkowski M, Gracon S, Hoover TM, Felmlee JP, Stewart K, Xu Y, Shiung M, O'Brien PC, Cha R, Knopman D, Petersen RC. MRI as a biomarker of disease progression in a therapeutic trial of milameline for AD. *Neurology.* Jan; 2003 60(2):253–260. [PubMed: 12552040]
3. den Heijer T, van der Lijn F, Koudstaal PJ, Hofman A, van der Lugt A, Krestin GP, Niessen WJ, Breteler MM. A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. *Brain.* Apr; 2010 133(Pt 4):1163–1172. [PubMed: 20375138]
4. Thompson PM, Hayashi KM, De Zubicaray GI, Janke AL, Rose SE, Semple J, Hong MS, Herman DH, Gravano D, Doddrell DM, Toga AW. Mapping hippocampal and ventricular change in Alzheimer disease. *Neuroimage.* Aug; 2004 22(4):1754–1766. [PubMed: 15275931]
5. Zhang J, Stonnington CM, Li Q, Shi J, Bauer RJ, Gutman BA, Chen K, Reiman EM, Thompson PM, Ye J, Wang Y. ISBI. IEEE; 2016. Applying sparse coding to surface multivariate Tensor-based morphometry to predict future cognitive decline; 646–650.
6. Woods RP. Characterizing volume and surface deformations in an atlas framework: theory, applications, and implementation. *Neuroimage.* Mar; 2003 18(3):769–788. [PubMed: 12667854]
7. Styner M, Lieberman JA, McClure RK, Weinberger DR, Jones DW, Gerig G. Morphometric analysis of lateral ventricles in schizophrenia and healthy controls regarding genetic and disease-specific factors. *Proc Natl Acad Sci USA.* Mar; 2005 102(13):4872–4877. [PubMed: 15772166]
8. Bansal R, Staib LH, Xu D, Zhu H, Peterson BS. Statistical analyses of brain surfaces using Gaussian random fields on 2-D manifolds. *IEEE Trans Med Imaging.* Jan; 2007 26(1):46–57. [PubMed: 17243583]
9. Chung MK, Dalton KM, Davidson RJ. Tensor-based cortical surface morphometry via weighted spherical harmonic representation. *IEEE Trans Med Imaging.* Aug; 2008 27(8):1143–1151. [PubMed: 18672431]
10. Wang Y, Zhang J, Gutman B, Chan TF, Becker JT, Aizenstein HJ, Lopez OL, Tamburo RJ, Toga AW, Thompson PM. Multivariate tensor-based morphometry on surfaces: application to mapping ventricular abnormalities in HIV/AIDS. *Neuroimage.* Feb; 2010 49(3):2141–2157. [PubMed: 19900560]

11. Wang Y, Song Y, Rajagopalan P, An T, Liu K, Chou YY, Gutman B, Toga AW, Thompson PM. Surface-based TBM boosts power to detect disease effects on the brain: an N=804 ADNI study. *Neuroimage*. Jun; 2011 56(4):1993–2010. [PubMed: 21440071]
12. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. *Neuroimage*. Aug; 2012 62(2):782–790. [PubMed: 21979382]
13. Shi J, Thompson PM, Gutman B, Wang Y. Surface fluid registration of conformal representation: application to detect disease burden and genetic influence on hippocampus. *Neuroimage*. Sep.2013 78:111–134. [PubMed: 23587689]
14. Han X, Xu C, Prince JL. A topology preserving level set method for geometric deformable models. *Pattern Analysis and Machine Intelligence, IEEE Transactions on*. Jun; 2003 25(6):755–768.
15. Lorensen WE, Harvey EC. Marching cubes: A high resolution 3d surface construction algorithm. *SIGGRAPH '87; Proceedings of the 14th Annual Conference on Computer Graphics and Interactive Techniques*; New York, NY, USA. ACM; 1987. 163–169.
16. Arsigny V, Fillard P, Pennec X, Ayache N. Log-Euclidean metrics for fast and simple calculus on diffusion tensors. *Magn Reson Med*. Aug; 2006 56(2):411–421. [PubMed: 16788917]
17. Pizer SM, Fritsch DS, Yushkevich PA, Johnson VE, Chaney EL. Segmentation, registration, and measurement of shape variation via image object shape. *IEEE Trans Med Imaging*. Oct; 1999 18(10):851–865. [PubMed: 10628945]
18. Lin B, Li Q, Sun Q, Lai M, Ian D, Wei F, Ye J. Stochastic coordinate coding and its application for drosophila gene expression pattern annotation. *CoRR*. 2014; abs/1407.8147
19. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature*. May; 2015 521(7553):436–444. [PubMed: 26017442]
20. Cortes Corinna Vapnik Vladimir. Support-vector networks. *Mach Learn*. Sep; 1995 20(3):273–297.

Fig. 1.

System pipeline. The first part in the blue bar shows the hippocampus segment. The second part in the orange bar represents MMS on each surface point. The last part in the green bar is the study of group difference and classification.

Fig. 2. Hippocampus Segmentation Pipeline. A is the hippocampal image segmented from MRI scan. B is the hippocampal surface generated by using marching cube. C is smoothed surface.

Fig. 3.

The box plots show the distribution of hippocampal mesh volume and area. The bottom bar is the statistical result of group difference and the range of p value is indicated by the color bar. L represents the two sides of left hippocampus and R represents the right one.

Fig. 4.
Classification results with hippocampal area, volume and RD+mTBM features.

Fig. 5. The Receiver operation characteristic (ROC) curves for classification experiments with three hippocampal measures.

Table 1

Demographic information of subjects in this study

$A\beta$	#	Gender(M/F)	Age	MMSE
Positive	151	79/72	74.5 ± 7.9	22.6 ± 3.1
Negative	271	132/139	76.3 ± 6.7	29.0 ± 1.3