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Correlation studies of Hippocampal Morphometry and Plasma NFL Levels in Cognitively Unimpaired Subjects

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Abstract

Alzheimer's disease(AD) is being the burden of society and family. Applying computing-aided strategies to reveal its pathology is one of the research highlights. Plasma neurofilament light (NFL) is an emerging noninvasive and economic biomarker for AD molecular pathology. It is valuable to reveal the correlations between the plasma NFL levels and neurodegeneration, especially hippcampal deformations at the preclinical stage. The negative correlation between plasma NFL levels and hippocampal volumes has been documented. However, the relationship

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between the plasma NFL levels and the hippocampal morphometry details at the preclinical stage is still elusive. This study seeks to demonstrate the capacity of our proposed surface-based hippocampal morphometry system to discern the plasma NFL positive (NFL+>41.9 pg/L) level and plasma NFL negative (NFL−<41.9pg/L) level and illustrate its superiority to the hippocampal volume measurement by drawing the cohort of 154 CU middle aged and elderly adults. We also apply this morphometry measure and a proposed sparse coding based classification algorithm to classify CU individuals with NFL+ and NFL− levels. Experimental results show that the proposed hippocampal morphometry system offers stronger statistical power to discriminate CU subjects with NFL+ and NFL− levels, comparing with the hippocampal volume measure. Furthermore, this system can discriminate plasma NFL levels in CU individuals (Accuracy=0.86). Both the group level and individual level analysis results indicate that the association between plasma NFL levels and the hippocampal shapes can be mapped at the preclinical stage.

Index Terms—

Alzheimer's disease; Preclinical stage; Plasma NFL; Magnetic resonance imaging (MRI); Hippocampal morphometry; Pattern analysis

I. Introduction

AGING society is coming, neurodegenerative diseases, especially Alzheimer's disease (AD), are being the burden of society and family [1]. Identifying AD biomarkers at the pre-symptomatic stage will help improving the therapeutic effect [2], [3]. Variety of amyloid, blood and neurodegeneration based biomarkers are studied for revealing the neuropathology mechanisms, especially for dementia risk predictions [4], [5], [6], [7]. Molecular pathologies such as cerebral β-amyloid plaques and tau tangles occur decades before Alzheimer's disease (AD) symptom onset [8]. However, current available techniques to detect molecular pathology are either intrusive (lumbar puncture) or highly costly (amyloid positron emission tomography (PET)), which limit the application in clinical [9].

Blood-based biomarkers (BBBs), as the emerging AD molecular pathology measurements, are reliable, sensitive, economic, and less invasive [10], [11], [12]. Low-cost BBBs, such as plasma amyloid beta, plasma neurofilament light protein (NFL), and plasma tau, have close relationships with neurodegeneration biomarkers measured by the expensive neuroimaging equipments [13]. And they offer a promising chance to reduce the quantity of people requiring more expensive examinations, to perform extensive screening for clinical diagnosis, and allow for longitudinally tracking pathological process in clinical trials [13].

Among these BBBs, Plasma NFL has recently been proposed as an early-diagnosis BBB in AD continuum and a potential biomarker related to neuronal injury [14]. To verify the distinguishable effects of the plasma NFL at the pre-clinical stages, it is necessary to reveal its association with AD-related neuropathological biomarkers, such as, cortical thickness reduction, hippocampal atrophy, ventricular enlargement [15], [16], [17]. Zhou et al. [18] show significantly increased plasma NFL levels in dementia groups compared to cognitively unimpaired (CU) group. Studies [19], [20] show that plasma NFL is related to cognitive impairment in AD as well as imaging markers of this disease. According to the study by

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Nyberg et al. [21], clinical AD is characterized by higher blood NFL, which presumably reflects brain white matter changes. Specially, the hippocampus plays a key role in the AD progression analysis [22]. Mattson et al. [19] show that plasma NFL levels have negative association with the hippocampal volume in the AD patients. The study of [23] shows that the plasma NFL is the most sensitive plasma biomarkers for hippocampal subfield alterations in the MCI stage.

However the correlation between plasma NFL levels and the hippocampus at the preclinical stage is still elusive. The study of [18] indicates that plasma NFL levels may not be very applicable as a AD diagnosis biomarker at the preclinical stage. Another study by [24] finds elevated plasma NFL levels at the preclinical stage of familial AD but scarce for sporadic AD. Nyberg et al. [25] suggest that the plasma NFL levels have no significant associations with cognition but are associated with white matter alterations at the preclinical phase.

Structural magnetic resonance imaging (MRI) biomarkers have been widely appiled in the research of AD related brain structures and clinical diagnosis because of the noninvasive and cost-effective properties. MRI based surface multivariate morphometry statistics (MMS) proposed by [26], [27] demonstrate superior performances of encoding Apolipoprotein E4 (APOE4) dose effects on brain structures of nondemented and CU groups [22], [28], [29]. The principle of the MMS is to encode morphometry along the surface tangent direction by the multivariate tensor-based morphometry (mTBM) and encode morphometry along the surface normal direction based on the radial distance (RD). Compared with other structural analysis methods such as using the Jacobian determinant, the maximum and minimum eigenvalues of surface metric, and the pair of eigenvalues of the Jacobian matrix [26], [27], the MMS approach performs optimally in detecting clinically-relevant brain structure differences. In addition, it is also extended to other neuropathology studies [30], [31].

The aim of the study is to characterize the capacity of hippocampal MMS to distinguish CU subjects with two plasma NFL levels at the group and individual levels. We hypothesize that our unique automatic hippocampal surface morphometry system [28], [22] may help reveal the association of plasma NFL levels and hippocampal morphometry. We conduct experiments on structural MRI data of 154 cognitively unimpaired subjects from publicly available Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Group comparison analysis [28], [26], [22] and classification methods [32] are applied to reveal the association between plasma NFL and surface-based hippocampal morphometry in the preclinical stage.

The following are the key contributions of this work.

1. Hippocampal MMS has been proven to be an effective AD biomarker, this work develops MMS-based system to verify plasma NFL levels in the CU subjects, which is useful to verify other emerging biomarkers based on well-studied metrics.
2. The association between hippocampal morphometry and plasma NFL levels is revealed, which is helpful to comprehensively understand the AD pathology progress in the preclinical stage.

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The remaining part of this work is outlined as follows. Section II introduces the proposed methodology and the experimental results are presented in section III detailedly. Section IV is the discussion of the study. And finally, conclusions are presented in Section V.

II. Materials and Methodology

A. Sample Data

The data used in the study is obtained from the ADNI database (https://adni.loni.usc.edu/), which recruited participants from more than 50 locations in the United States and Canada and includes multi-modal neuroimages such as MRI, PET, clinical evaluation biomarker such as MMSE and APOE. ADNI aims to explore the use of clinical and imaging markers in the early diagnosis of AD, to predict progression risk, and to develop novel therapies. From ADNI, we found 154 CU participants who have MRI and plasma NFL recordings. Plasma NFL measures are introduced in [19]. Plasma NFL+ (>41.9pg/L) CU subjects have higher risk to progress to AD stage relative to Plasma NFL− (>41.9pg/L) CU subjects [18], [19].

A one-way analysis of variance was used to compare the ages and education years between plasma NFL+ and NFL-groups, while a chi-squared test was used to analyze the data relevant to the gender [22]. Table I summarizes the statistical findings, revealing that the sex and education years of the two groups are matched. While age differences of the two groups are significant ($p<0.01$).

B. Processing Pipeline

To study the relationship between plasma NFL levels and hippocampal morphometry, this work firstly makes group analysis using our proposed hippocampal surface morphometry system [28], [29], [22], which works effectively for evaluating the APOE-e4 dose effects on the hippocampal deformation of non-demented subjects. Then, the MMS patches in individuals with different plasma NFL levels are refined and classified using the Patch Analysis-based Surface Correntropy-induced Sparse coding and max-pooling (PASCS-MP) and classification system [32].

1) Group Comparison Analysis: As shown in (1)~(4) of Fig. 1, T1 MRI images are linearly registered into MNI152 standard space with the FSL software package to eliminate the influence of brain size [33]. Then hippocampal structures are segmented with FIRST in the FSL [34], [35], and on this basis, surface meshes are constructed with the topology-preserving level set [36] and marching cubes algorithm [37]. The holomorphic flow segmentation approach [26] is used to parameterize each hippocampal surface with refined triangular meshes and the surface fluid registration method is used to register the parameterized surfaces to a common rectangular grid template. After that, there are equal amount of vertices (150*100) illustrating in Fig. 1 (3) on each hippocampal surface. The surface vertices are presented as the intersections of the red and blue curves. To evaluate the shape differences, the hippocampal morphomety are described by vertex-wise MMS encoding morphometry along the surface tagent direction and normal direction [26], [27]. Using Hotelling's T2 test with a permutation test [26], [27], [28], [29], [22], group differences of hippocampal morphometry between plasma NFL levels are analyzed.

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The toolkit for the surface MMS estimation and group analysis is available at https://www.nitrc.org/projects/mtsms_2020/.

2) Individual Classification: Hippocampal MMS performs well to describe the association between hippocampal morphometry and plasma NFL levels at the group level [29], [22]. However it can not be directly used for individual plasma NFL levels classifications. The dimension of the surface MMS feature is substantially larger than the sample size, which is likely to cause high dimension-small problem for individual classification. To validate the association between morphometry and plasma NFL levels at the individual level, PASCS-MP [32] is used to refine the hippocampal shape features, following random forests classifier, as shown in (5)~(6) of Fig. 1. Based on the PASCS algorithm, some patches on the hippocampal surface were randomly selected and a sparse code was generated for each patch. On these sparse codes, a new vector was generated to represent the surface features of each subject applying the max-pooling (MP) operation. Finally, the random forest classifiers are trained to binary classify the sparse codes in individuals with different plasma NFL levels and the 10-fold cross-validation was applied to validate the performance of the classifiers.

$$\min_{D,Z_i} \frac{1}{2}\Sigma_{i=1}^{n}\exp\left(-\frac{\| Dz_i - x_i \|_2^2}{\sigma^2}\right) + \lambda\Sigma_{i=1}^{n} \| z_i \|_1 \quad (1)$$

The regularization parameter for the l_1-norm (λ), the kernel size (σ) in the exponential function (see Eq. 1), the patch size and the dimension of the learned sparse codes are the key hyperparameters for sparse coding optimization and have a significant impact on the PASCS-MP performance [32]. The sparsity of the sparse codes are determined by the parameter λ, which can affect the selection of significant features and reduction of the noise. The correntropy properties are determined by the parameter σ [32], [38]. The correntropy has direct relationship to the probability of similarity between two random variables in the kernel bandwidth-controlled joint space neighborhood. That is, the kernel bandwidth serves as a zoom lens and controls the observation window which evaluates similarity and provides an effective mechanism to eliminate the destructive influence of abnormal values [39]. Since MMS of hippocampal vertices with strong discriminate power are always clustered, patch-selection strategy is suitable for refining these critical regional features. For extracting significant features on each surface and reducing the dimensionality before sparse coding, the square windows are randomly generated producing a set of image patches with various amounts of overlapping. As in the previous studies of AD [40], [41], [42], kinds of patch size settings are tested. The dimension of the learned sparse coding represents individual hippocampal shape features, if it is too low, some significant morphometry information might miss, if it is too large, there will be a lot of redundant information. With the algorithm in Table. II, the learned sparse codes under kinds of hyperparameter candidates are calculated.

These optimal hyperparameters are to be tested by comparing different settings of classification performances which are measured by accuracy (ACC), negative predictive value (NPV), positive predictive value (PPV), sensitivity (SEN), specificity (SPE) and

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balance accuracy (BAC). The dataset is shuffled and splitted into ten groups for the 10-fold cross-validation. One group is taken as the test set and the remaining groups are for training. The key parameters with the best performance measures are selected. For further details of the parameter optimizations, please refer to [32].

III. Results

A. Hippocampal Volume Analysis

Since hippocampal volume is a widely-used AD biomarker, it negatively correlates with plasma NFL levels in AD symptom groups [19], [43]. Firstly, we computed the hippocampal volumetric measures on the CU cohort. Similar to previous AD diagnosis studies using hippocampal volume [44], [45], the volumes were linearly registered to the MNI standard space and then calculated on the processed hippocampal structures [35]. To adjust for post-conception age effects on hippocamby volumes, we applied general linear model on the hippocampal volumes [46]. Then the group differences of the adjusted hippocampal volumes of two plasma NFL groups were estimated using t-test. Table III shows the adjusted hippocampal volume group analysis results. No significant group differences are observed between hippocampal volumes of two Plasma NFL levels at the preclinical stages.

B. Hippocampal Morphometric analysis

This work analyzed the hippocampal morphometry differences using cross-sectional analysis and expected to observe significant differences between 58 plasma NFL+ and 96 NFL-subjects. The point-wise MMS adjusted for age effects were estimated using the general linear model proposed by [46]. The p-maps of group differences on the bilateral hippocampus are showed in the Fig. 2. Vertices in non-blue colors have statistical differences at the nominal 0.05 level, uncorrected for multiple comparisons. We found overall significant morphometric differences on the left hippocampus (p = .01, corrected) and the right hippocampus (p = .03, corrected). These ROIs are mainly at the CA1, CA3 and SUB subfields which are consistent with the findings in the MCI and AD stages [19], [23].

C. Plasma NFL Levels Classification

To further reveal the association between plasma NFL levels and hippocampal MMS at the individual level, the sparse coding and classification framework of our previous study [32] are applied to extract the low dimensional representations of MMS measures and predict plasma NFL levels for each person. With 10-cross validation for classification performances, key hyper-parameters, λ, σ, patch size and sparse code dimension of the framework are optimized separately, Figure 3 shows the ROC curves of the λ, patch size and sparse code dimension candidates for the plasma NFL levels classification. Then we get the optimal hyper-parameters as $\lambda = 0.13$ and the sparse code dimension is 2000. Similarly, we get the optimal $\sigma = 0.48$. Table IV shows under the patch size=20*20, the optimal performances ACC=85.5%, NPV=88.13%, PPV=81.73%, SPE=85.77%, SEN=85.51%, and BAC=85.64%.

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IV. Discussion

Our previous studies [26], [28], [22] show that hippocampal MMS is a robust biomarker for AD pathology study, especially its distinguishable performance at the preclinical stage. It is an accessible way to validate these emerging plasma biomarkers using the hippocampal MMS measure. In this study, we propose a hippocampal surface-based plasma NFL level assessment system which includes hippocampal MMS calculation, group comparison analysis, and individual classification models. This system is applied on 154 CU subjects with two plasma NFL levels. There are two main findings. Firstly, group comparison analysis results show that the hippocampal surface-based MMS effectively encodes a substantial quantity of adjacent intrinsic geometry information related to plasma NFL status at the preclinical stage which otherwise is inaccessible with classical hippocampal volume. Secondly, our proposed sparse coding method, PASCS-MP, can be generalized to the association study of plasma NFL and hippocampal morphometry, high dimensional MMS features are coded as low-dimensional sparse features. And the outstanding classification performances on these sparse features further indicate that there is a close relationship between hippocampal MMS measure and plasma NFL levels at the individual level.

BBBs are economic and convenient, more and more studies [12], [47], [48], [49] expect to find plasma biomarkers for AD risk evaluation. Among them, plasma NFL levels of AD patients are significant higher than CU subjects [50]. Studies have shown that plasma NFL levels rise over time in mild cognitive impairment and AD patients, and have association with AD-related brain deformations, especially hippocampal volume loss [19], [43], [51]. However the association of plasma NFL levels and AD pathology are still elusive at the preclinical stage. The study of [18] indicates that plasma NFL levels may not be applicable as a AD diagnosis biomarker at the preclinical stage. Another study finds elevated plasma NFL levels at the preclinical stage of familial AD but scarce for sporadic AD [24]. Our previous studies show that hippocampal MMS [26], [28], [29], [22], [30] has an outstanding performance for tracking neuropathology continuum from the preclinical stage to dementia, it is accessible to verify the significant hippocampal subregions related to plasma NFL effects at the preclinical stage using the MMS measurement.

This work proposed one pipeline to verify the association between the plasma NFL levels and the neurodegeneration effects at the preclinical stage. The group comparison analysis and the individual classification results indicate that the plasma NFL levels implies a close relationship with hippocampal MMS at the preclinical stage. The significant hippocampal subfields are mainly at the CA1, CA3 and SUB [52], which are consistent with the findings in the AD continuum progress. While these preclinical hippocampal alterations associated with plasma NFL levels cannot be identified with the hippocampal volume analysis. So this proposed pipeline is useful to verify other emerging biomarkers, especially at the preclinical stage.

Despite the promising results of the association between hippocampus MMS and plasma NFL levels are obtained by applying the group and individual analysis strategies at the preclinical stage, there are three critical caveats to note. Firstly, the sample sizes utilized in the study to estimate the hippocampal morphomertry differences between plasma NFL

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levels are limited. In the future work, we will use other public sMRI cohorts to validate our proposed algorithm, such as UK Bioband [53] and Adolescent Brain Cognitive Development (ABCD) study [54]. In addition, we will employ the MMS approach to reveal the association between plasma NFL levels with other well-known AD related nucleus, such as caudate, amygdala, putamen, and thalamus [55], [56]. Secondly, the cross-sectional MMS analysis identifies the abnormal subregions of the plasma NFL positive at the preclinical stage. In future work, we will explore the longitudinal brain subregions related to plasmal NFL progressing, and apply COX model [57] to estimate the AD conversion risk dynamically based on the plasma NFL values. Thirdly, minimally invasive and cost-effective BBBs have the potential to become the preclincal diagnosis tools for AD continuum. Carmen et al. [58] suggest that plasma GFAP and p-tau can identify AD risk individuals at the preclinical stage. In future work, we will verify the associations between more BBBs and neuropathological biomarkers.

V. Conclusion

This work proposes a novel surface-based morphometry analysis framework to reveal the association between plasma NFL levels and hippocampal subfields on a CU cohort. Results show that the hippocampal MMS encodes a great deal of information that may be inaccessible or overlooked by hippocampal volume measures. This work has found significant hippocampal morphometry differences in the CU individuals with plasma NFL+/−. This proposed framework can be applied to verify the associations between other emerging periphery physiological biomarkers and neurodegeneration criterion. The results additionally indicate a potential utility for the integration of plasma NFL and MMS as a noninvasive method to study the association between AD induced molecular and brain structural changes at the preclinical stage. In future, we will study the correlations between longitudinal plasma NFL and hippocampal MMS features in CU subjects. We also plan to extend this association analysis method to more AD-related emerging blood-based biomarkers [13] and brain regions of interest [44], [5], and further integrate these noninvasive measures of BBBs and MMS for tracking AD pathology progress at the preclinical AD stages. It will contribute new insights to a better understanding of the BBB effectiveness as the potential preclinical biomarkers.

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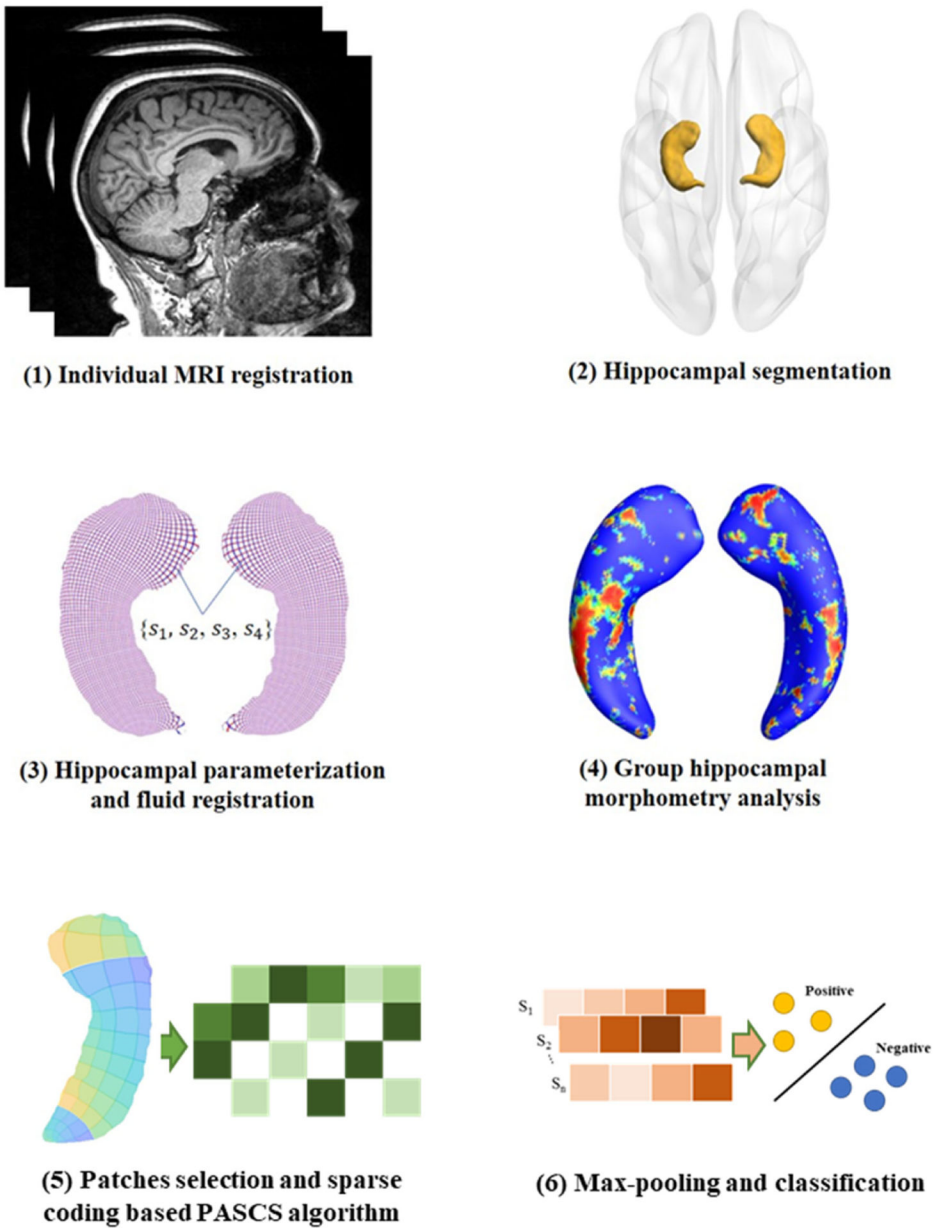

Fig. 1.

Hippocampal morphometry analysis system: (1) Individual MRIs were linearly registered to the brain template; (2) Hippocampal structures were segmented; (3) Hippocampal surfaces were parameterized and then fluid-registered to a standard template to extract the morphometric features; (4) The group differences of hippocampal morphometry were statistically analyzed between two plasma NFL levels. $\{S_1, S_2, S_3, S_4\}$is the multivariate morphometry statistics vector on each surface point; (5) The PASCS algorithm is used on individual hippocampal morphometry features for feature selection and sparse coding; (6) Applying the max-pooling (MP) operation on the learned sparse codes, a new vector was generated to represent each subject(P_1,P_2,…,P_n) and random forest classifiers are used to identify individuals with different NFL levels. NFL: neurofilament light.

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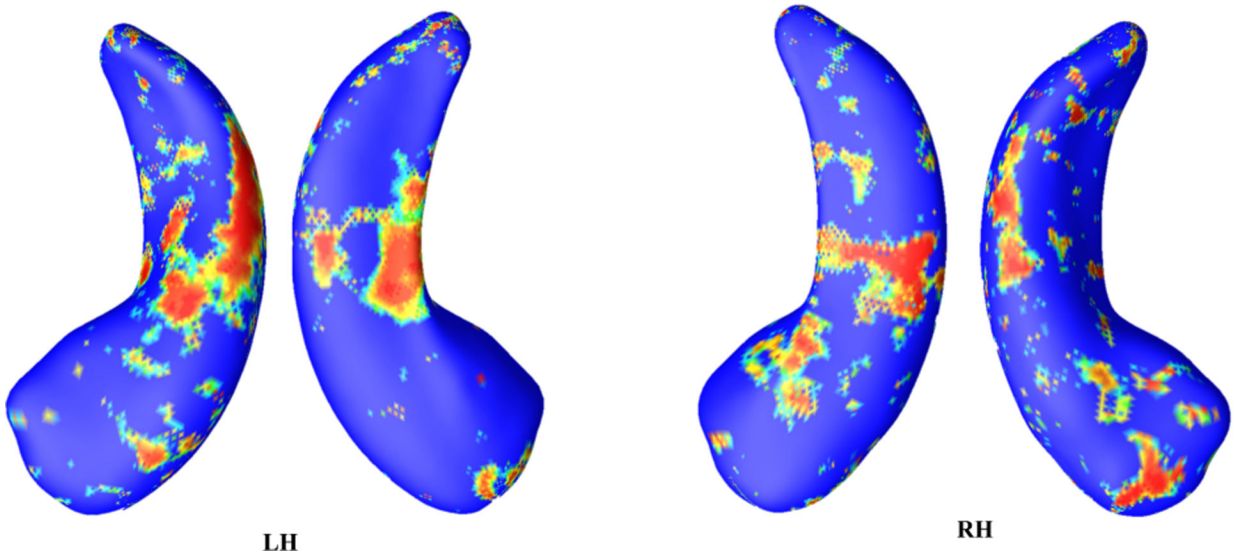

Fig. 2.

Group hippocampal shape differences adjusted for age effects between plasma NFL+(N=58) and NFL−(N=96) in the CU cohort, at the nominal 0.05 level, uncorrected. The overall significance of LH and RH with permutation test were p=0.01 and p=0.03, respectively. LH: left hippocampus; RH: right hippocampus; NFL: neurofilament light.

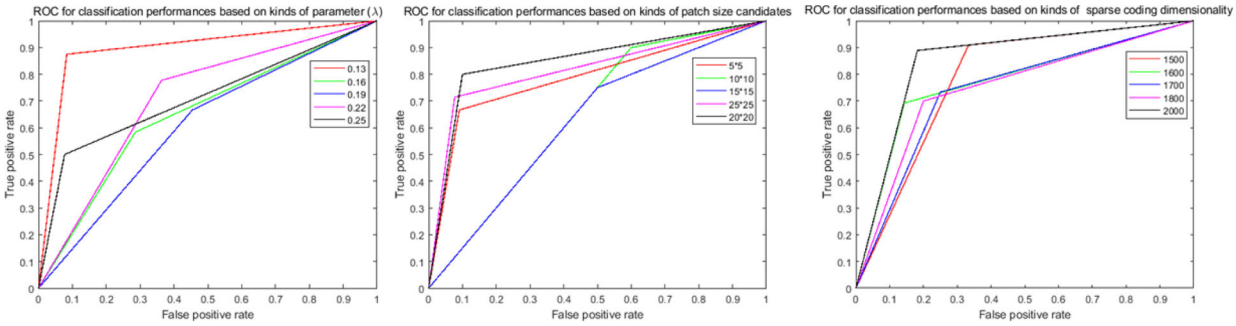

Fig. 3.

ROC curves for classification based on kinds of hyperparameter settings. The left subfigure displays the ROC curves under different λ settings, the midle subfigure displays the ROC curves under different patch size for refining hippocampal morphometry features, the right subfigure displays the ROC curves under different sparse code dimension settings.

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TABLE I

Demographic characteristic statistics between plasma NFL levels on cognitively unimpaired cohort.

	Plasma NFL+ (n=58)	Plasma NFL- (n=96)	Inferential statistics
Sex (M/F)	24/34	51/45	0.21
Age	80.10±5.77	73.56±5.45	<0.01
Education	15.97±2.87	16.69±2.5	0.1

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TABLE II

Algorithm for solving PASCS-MP.

Algorithm 1 PASCS-MP

Require: Hippocampal shape features $X = (x_1, x_2, \ldots, x_n) \in R^{p \times n}$,

patch size x_p, regularization parameter λ, kernel size σ

Ensure: Dictionary D and sparse code Z

Initialize: $D^{1,1}$, x_p, λ_i, σ_i, $i = 1, \ldots, \mathbf{n}$

1: for $t = 1$ to τ do

2: for $i = 1$ to n do

3: Get an image patch x_i from X, and obtain useful surface features via Eg.(1)

4: Update the sparse code by calculating the partial derivative of z_i^t

$$\frac{\partial}{\partial z_l} c\left(D^{i,t}, z_i^t\right) = \frac{\partial}{\partial z_l} \frac{1}{2} h_i \parallel D^{i,t} z_i^t - x_i \parallel_2^2$$

Where $c()$ is coordinate descent:

5: Update the Hessian matrix and the learning rate:

$$M \leftarrow M + z_i^t \left(z_i^t\right)^T, \gamma_{i,l} = 1/m_{ll}.$$

6: Update D through via stochastic gradient descent (SGD)

$$\frac{\partial}{\partial z_l} f\left(D^{i,t}, z_i^t\right) = \frac{\partial}{\partial z_l} c\left(D^{i,t}, z_i^t\right) + \frac{\partial}{\partial z_l} \lambda \parallel z_i^t \parallel_1$$

7: Update auxiliary variable h_i:

8: If $i = n$, Then $D^{1,t+1} = D^{n,t}$.

9: end for

10: end for

Output: $D = D^{n,\tau}$ and $z_j = Z_J^\tau$ for $i = 1_1, \ldots, \mathbf{n}$

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TABLE III

Bilateral hippocampal volumes of two plasma NFL levels on cognitively unimpaired cohort. NFL: neurofilament light.

	Plasma NFL+ (n=58)	Plasma NFL- (n=96)	Inferential statistics
Left HP	3341.08±409.7	3652.59±502.52	0.10
Right HP	3652.59±502.52	3788.08±528.28	0.12

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TABLE IV

Patch size testing with the optimal λ, σ and sparse code dimension

Patch Size	ACC	NPV	PPV	SPE	SEN	BAC
10*10	67.00	65.28	78.42	80.68	56.05	68.37
15*15	78.50	79.05	80.94	83.79	73.21	78.50
25*25	80.00	87.46	75.93	75.01	85.26	80.13
20*20	**85.50**	**88.13**	**81.73**	**85.77**	**85.51**	**85.64**