

1 **Predicting Brain Amyloid using Multivariate Morphometry Statistics,**
2 **Sparse Coding, and Correntropy: Validation in 1,101 Individuals**
3 **from the ADNI and OASIS Databases**

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5 Jianfeng Wu BS^{1a}, Qunxi Dong, PhD^{2,1a}, Jie Gui PhD³, Jie Zhang PhD¹, Yi Su PhD⁴,
6 Kewei Chen PhD⁴, Paul M. Thompson PhD⁵, Richard J. Caselli MD⁶,
7 Eric M. Reiman MD⁴, Jieping Ye PhD³, Yalin Wang PhD¹,
8 for the Alzheimer's Disease Neuroimaging Initiative^{*}

9 **¹School of Computing, Informatics, and Decision Systems Engineering,**
10 **Arizona State University, Tempe, AZ, USA**

11 **²Institute of Engineering Medicine, Beijing Institute of Technology, Beijing, China**

12 **³Department of Computational Medicine and Bioinformatics, University of**
13 **Michigan, Ann Arbor, MI, USA**

14 **⁴Banner Alzheimer's Institute, 100 Washtenaw Avenue, Phoenix, AZ, USA**

15 **⁵Imaging Genetics Center, Stevens Neuroimaging and Informatics Institute,**
16 **University of Southern California, Marina del Rey, CA, USA**

17 **⁶Department of Neurology, Mayo Clinic Arizona, Scottsdale, AZ, USA**

18 **^aAuthors contributed equally**

19

20 Please address correspondence to:

21 Dr. Yalin Wang

22 School of Computing, Informatics, and Decision Systems Engineering

23 Arizona State University

24 P.O. Box 878809

25 Tempe, AZ 85287 USA

26 **Phone:** (480) 965-6871

27 **Fax:** (480) 965-2751

28 **E-mail:** ylwang@asu.edu

29

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35 **ABSTRACT (248 words)**

36 Biomarker-assisted preclinical/early detection and intervention in Alzheimer's disease (AD)
37 may be the key to therapeutic breakthroughs. One of the presymptomatic hallmarks of AD is
38 the accumulation of beta-amyloid (A β) plaques in the human brain. However, current methods
39 to detect A β pathology are either invasive (lumbar puncture) or quite costly and not widely
40 available (amyloid PET). Our prior studies show that MRI-based hippocampal multivariate
41 morphometry statistics (MMS) are an effective neurodegenerative biomarker for preclinical
42 AD. Here we attempt to use MRI-MMS to make inferences regarding brain A β burden at the
43 individual subject level. As MMS data has a larger dimension than the sample size, we propose
44 a sparse coding algorithm, Patch Analysis-based Surface Correntropy-induced Sparse coding
45 and max-pooling (PASCS-MP), to generate a low-dimensional representation of hippocampal
46 morphometry for each subject. Then we apply these individual representations and a binary
47 random forest classifier to predict brain A β positivity for each person. We test our method in
48 two independent cohorts, 841 subjects from the Alzheimer's Disease Neuroimaging Initiative
49 (ADNI) and 260 subjects from the Open Access Series of Imaging Studies (OASIS).
50 Experimental results suggest that our proposed PASCS-MP method and MMS can discriminate
51 A β positivity in people with mild cognitive impairment (MCI) (Accuracy (ACC)=0.89 (ADNI))
52 and in cognitively unimpaired (CU) individuals (ACC=0.79 (ADNI) and ACC=0.81 (OASIS)).
53 These results compare favorably relative to measures derived from traditional algorithms,
54 including hippocampal volume and surface area, shape measures based on spherical harmonics
55 (SPHARM), and our prior Patch Analysis-based Surface Sparse-coding and Max-Pooling
56 (PASS-MP) methods.

57

58 **Keywords:**

59 Alzheimer's disease, Hippocampal Multivariate Morphometry Statistics (MMS), Dictionary
60 and Correntropy-induced Sparse Coding, Beta-amyloid (A β) burden.

61

62 1. INTRODUCTION

63 Alzheimer's disease (AD) is a major public health concern with the number of affected
64 individuals expected to triple, reaching 13.8 million by the year 2050 in the U.S. alone
65 (Brookmeyer et al., 2007). Current therapeutic failures in patients with dementia due to AD
66 may be due to interventions that are too late, or targets that are secondary effects and less
67 relevant to disease initiation and early progression (Hyman, 2011). Preclinical AD is now
68 viewed as a gradual process that begins many years before the onset of clinical symptoms.
69 Measuring brain biomarkers and intervening at preclinical AD stages are believed to improve
70 the probability of therapeutic success (Brookmeyer et al., 2007; Jack et al., 2016; Sperling et
71 al., 2011). In the A/T/N system - a recently proposed research framework for understanding the
72 biology of AD - the presence of abnormal levels of A β in the brain or cerebrospinal fluid (CSF)
73 is used to define the presence of biological Alzheimer's disease (Jack et al., 2016). An
74 imbalance between production and clearance of A β occurs early in AD and is typically followed
75 by the accumulation of tau protein tangles (another key pathological hallmark of AD) and
76 neurodegeneration detectable on brain magnetic resonance imaging (MRI) scans (Hardy and
77 Selkoe, 2002; Jack et al., 2016; Sperling et al., 2011). Brain A β pathology can be measured
78 using positron emission tomography (PET) with A β -sensitive radiotracers, or in CSF. Even so,
79 these invasive and expensive measurements are less attractive to subjects in preclinical stage
80 and PET scanning is also not as widely available as MRI.

81 Blood-based biomarkers (BBBs) are somewhat effective for inferring A β burden in the
82 brain and CSF, and are less expensive than imaging (Bateman et al., 2019; Janelidze et al.,
83 2020; Palmqvist et al., 2020). Even so, structural MRI biomarkers are largely accessible, cost-
84 effective, and widely used in AD imaging research as well as for clinical diagnosis.
85 Consequently, there is great research interest in using MRI biomarkers to predict brain A β
86 burden (Pekkala et al., 2020; Reisa A. Sperling et al., 2011; Tosun et al., 2016, 2014). Tosun et
87 al. (2014) combine MRI-based measures of cortical shape and cerebral blood flow to predict
88 A β status for early-MCI individuals and achieve an 83% accuracy with the LASSO approach
89 (least absolute shrinkage and selection operator). Pekkala et al. (2020) use brain MRI measures

90 (volumes of the cortical gray matter, hippocampus, accumbens, thalamus and putamen) to infer
91 A β positivity in cognitively unimpaired (CU) subjects; they achieve a 0.70 area under the
92 receiver operator curve (AUC) with their Disease State Index (DSI) algorithm. Although brain
93 structural volumes are perhaps the most commonly used neuroimaging measures in AD
94 research (Cacciaglia et al., 2018; Crivello et al., 2010; Reiter et al., 2017), surface-based
95 subregional structure measures can offer advantages over volume measures as they contain
96 more detailed and patient-specific shape information (Apostolova et al., 2010; Ching et al.,
97 2020; Costafreda et al., 2011; Dong et al., 2020b, 2019; Morra et al., 2009; Qiu et al., 2009;
98 Shen et al., 2009; Styner et al., 2004; Paul M Thompson et al., 2004; Younes et al., 2014).

99 Our prior studies (Shi et al., 2014; Wang et al., 2011, 2010) propose novel multivariate
100 morphometry statistics (MMS) and apply them to analyze APOE4 dose effects on brain
101 structures of nondemented and CU groups from the ADNI cohort (Dong et al., 2019; Li et al.,
102 2016; Shi et al., 2014). Our proposed MMS approach uses multivariate tensor-based
103 morphometry (mTBM) to encode morphometry along the surface tangent direction and radial
104 distance (RD) to encode morphometry along the surface normal direction. This approach
105 performs better for detecting clinically-relevant group differences, relative to other TBM-based
106 methods including those using the Jacobian determinant, the largest and smallest eigenvalues
107 of the surface metric and the pair of eigenvalues of the Jacobian matrix (Wang et al., 2011,
108 2010). Our recent studies (Dong et al., 2020b, 2019) show that MMS outperforms volume
109 measures for detecting hippocampal and ventricular deformations in groups at high risk for AD
110 at the preclinical stage. Our other related work (Wu et al., 2018) has studied hippocampal
111 morphometry in cohorts consisting of A β positive AD patients (A β + AD) and A β negative
112 cognitively unimpaired subjects (A β - CU) using the MMS measure. We find significant A β +

113 AD vs. A β - CU group differences, using Hotelling's T^2 tests. As MMS have a high dimension,
114 it is not suitable for classification research directly. Therefore, we apply a Patch Analysis-based
115 Surface Sparse-coding and Max-Pooling (PASS-MP) system for a low-dimensional
116 representation of hippocampal MMS, and the binary group random forest classification of A β +

117 AD and A β - CU, achieving an accuracy rate of 90.48%. These studies show that MMS can

118 distinguish clinical groups with different A β status. We have also successfully applied PASS-
119 MP for MMS-based AD cognitive scores and autism spectrum disorder predictions (Dong et
120 al., 2020a; Fu et al., 2021).

121 In this work, we optimize the objective function of the PASS-MP system by introducing
122 correntropy measure (Gui et al., 2017) and propose an improved sparse coding, dubbed as the
123 Patch Analysis-based Surface Correntropy-induced Sparse-coding and max-pooling (PASCS-
124 MP) method. PASCS-MP does not only take the advantage of the computational efficiency of
125 PASS-MP in its new optimization strategy, but also effectively reduces the negative influence
126 of non-Gaussian noise in the data, which tremendously improves the prediction accuracy.
127 PASCS-MP is an unsupervised learning method to generate a low-dimensional representation
128 for each sample. We leverage the novel PASCS-MP method on MMS to further explore
129 hippocampal morphometry differences for the following contrasts at the individual subject level:
130 (1) A β positive individuals with mild cognitive impairment (A β + MCI) vs. A β negative
131 individuals with mild cognitive impairment (A β - MCI) from ADNI, and (2) A β positive
132 cognitively unimpaired subjects (A β + CU from ADNI and OASIS) versus A β negative
133 cognitively unimpaired subjects (A β - CU from ADNI and OASIS). We apply the proposed
134 PASCS-MP and a binary random forest classifier to classify individuals with different A β status.
135 We hypothesize that our MMS-based PASCS-MP may provide stronger statistical power
136 relative to traditional hippocampal volume, surface area and spherical harmonics (SPHARM)
137 based hippocampal shape measurements, in predicting subjects' A β status. We expect that the
138 knowledge gained from this type of research will enrich our understanding of the relationship
139 between hippocampal atrophy and AD pathology, and thus help in assessing disease burden,
140 progression, and treatment effects.

141 2. SUBJECTS and METHODS

142 2.1 Subjects

143 Data for testing the performance of our proposed framework and comparable methods are
144 obtained from the ADNI database (Mueller et al., 2005, adni.loni.usc.edu) and the OASIS

145 database (Marcus et al., 2010). ADNI is the result of efforts of many co-investigators from a
146 broad range of academic institutions and private corporations. Subjects are recruited from over
147 50 sites across the U.S. and Canada. The primary goal of ADNI is to test whether biological
148 markers, such as serial MRI and positron emission tomography (PET), combined with clinical
149 and neuropsychological assessments, can measure the progression of MCI and early AD.
150 Subjects originally recruited for ADNI-1 and ADNI-GO have the option to be followed in
151 ADNI-2. For up-to-date information, see www.adniinfo.org.

152 From the ADNI cohort, we analyze 841 age and sex-matched subjects with florbetapir PET
153 data and T1-weighted MR images, including 151 AD patients, 342 MCI and 348 asymptomatic
154 CU individuals. Among them, all the 151 AD patients, 171 people with MCI and 116 CU
155 individuals were A β positive. The remaining 171 MCI and 232 CU individuals were A β
156 negative. From OASIS database, we analyze age-and-sex-matched 260 subjects with florbetapir
157 PET data and T1-weighted MR images, including 52 A β positive CU and 208 A β negative CU.

158 **Table 1.** Demographic information for the subjects we study from the ADNI and OASIS cohorts.

Database	Group	Sex (M/F)	Age	MMSE	Centiloid
ADNI Cohort	A β + AD (n=151)	79/72	74.6 \pm 7.8	22.6 \pm 3.1	86.3 \pm 27.4
	A β + MCI (n=171)	92/79	74.1 \pm 7.4	27.7 \pm 1.7	76.8 \pm 26.4
	A β - MCI (n=171)	92/79	74.0 \pm 7.4	28.3 \pm 1.6	8.9 \pm 14.9
	A β + CU (n=116)	45/71	75.9 \pm 6.1	28.9 \pm 1.1	71.1 \pm 26.4
	A β - CU (n=232)	90/142	75.7 \pm 6.3	29.0 \pm 1.3	7.5 \pm 14.5
OASIS Cohort	A β + CU (n=52)	22/30	70.5 \pm 7.5	29.0 \pm 1.3	71.4 \pm 20.9
	A β - CU (n=208)	88/120	68.5 \pm 6.8	29.0 \pm 1.3	8.5 \pm 9.5

159 Values are mean \pm standard deviation where applicable.

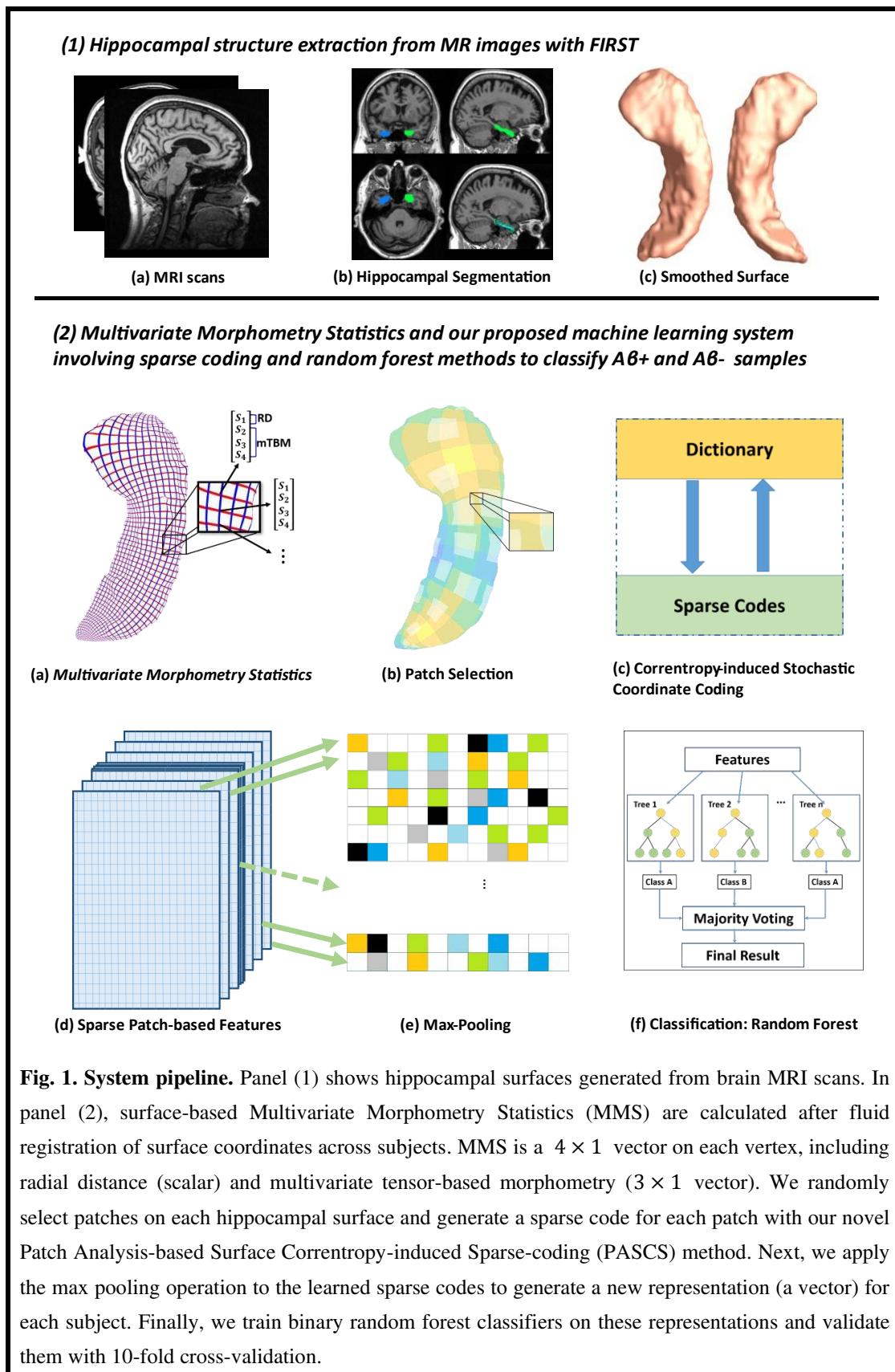
160 In addition to each MRI scan, we also analyze the corresponding Mini-Mental State Exam
161 (MMSE) scores (Folstein et al., 1975) and centiloid measures (Navitsky et al., 2018).
162 Operationally, the *positivity* of A β biomarkers is defined using standard cut-offs, with some
163 efforts to reconcile differences among different A β radiotracers using a norming approach
164 called the centiloid scale (Klunk et al., 2015; Rowe et al., 2017). ADNI florbetapir PET data
165 are processed using AVID pipeline (Navitsky et al., 2018), and OASIS florbetapir PET data are
166 processed using PUP (Lee et al., 2013; Su et al., 2015). Both are converted to the centiloid

167 scales according to their respective conversion equations (Navitsky et al., 2018; Su et al., 2019).
168 A centiloid cutoff of 37.1 is used to determine A β positivity, this threshold corresponds to
169 pathologically determined moderate to frequent plaques (Fleisher et al., 2011). **Table 1** shows
170 demographic information we analyze from the ADNI and OASIS cohorts.

171 **2.2 Proposed pipeline**

172 This work develops the PASCS-MP framework to predict individual A β burden (see **Fig. 1** for the processing pipeline). In panel (1), hippocampal structures are segmented from
173 registered brain MR images with FIRST from the FMRIB Software Library (FSL) (Paquette et
174 al., 2017; Patenaude et al., 2011). Hippocampal surface meshes are constructed with the
175 marching cubes algorithm (Lorensen and Cline, 1987). In panel (2), hippocampal surfaces are
176 parameterized with the holomorphic flow segmentation method (Wang et al., 2007). After the
177 surface fluid registration algorithm, the hippocampal MMS features are calculated at each
178 surface point. We propose a PASCS-MP and classification system to refine and classify MMS
179 patches in individuals with different A β status. We randomly select patches on each
180 hippocampal surface and generate a sparse code for each patch with our novel PASCS. Next,
181 we adopt a max-pooling operation on the learned sparse codes of these patches to generate a
182 new representation (a vector) for each subject. Finally, we train binary random forest classifiers
183 on individual sparse codes in people with different A β status; we validate them with 10-fold
184 cross-validation. The whole system is publicly available¹.
185

¹<http://gsl.lab.asu.edu/software/pass-mp/>



187 **2.2.1 Image Processing**

188 Firstly, we use FIRST (FMRIB's Integrated Registration and Segmentation Tool)
189 (Paternaude et al., 2011) to segment the original MRI data and map the hippocampus
190 substructure. After obtaining a binary segmentation of the hippocampus, we use a topology-
191 preserving level set method (Han et al., 2003) to build surface models. Based on that, the
192 marching cubes algorithm (Lorensen and Cline, 1987) is applied to construct triangular surface
193 meshes. Then, to reduce the noise from MR image scanning and to overcome partial volume
194 effects, surface smoothing is applied consistently to all surfaces. Our surface smoothing process
195 consists of mesh simplification using *progressive meshes* (Hoppe, 1996) and mesh refinement
196 by the Loop subdivision surface method (Loop, 1987). Similar procedures adopted in a number
197 of our prior studies (Colom et al., 2013; Luders et al., 2013; Monje et al., 2013; Shi et al., 2015,
198 2013b, 2013a; Wang et al., 2012, 2010) have shown that the smoothed meshes are accurate
199 approximations to the original surfaces, with a higher signal-to-noise ratio (SNR).

200 To facilitate hippocampal shape analysis, we generate a conformal grid (150×100) on
201 each surface, which is used as a canonical space for surface registration. On each hippocampal
202 surface, we compute its conformal grid with a holomorphic 1-form basis (Wang et al., 2010;
203 Wang et al., 2007). We adopt surface conformal representation (Shi et al., 2015, 2013a) to
204 obtain surface geometric features for automatic surface registration. This consists of the
205 conformal factor and mean curvature, encoding both intrinsic surface structure and information
206 on its 3D embedding. After we compute these two local features at each surface point, we
207 compute their summation and then linearly scale the dynamic range of the summation into the
208 range 0-255, to obtain a feature image for the surface. We further register each hippocampal
209 surface to a common template surface. With surface conformal parameterization and conformal
210 representation, we generalize the well-studied image fluid registration algorithm (Bro-Nielsen
211 and Gramkow, 1996; Agostino et al., 2003) to general surfaces. Furthermore, most of the image
212 registration algorithms in the literature are not symmetric, i.e., the correspondences between
213 the two images depending on which image is assigned as the deforming image and which is the
214 non-deforming target image. An asymmetric algorithm can be problematic as it tends to

215 penalize the expansion of image regions more than shrinkage (Rey et al., 2002). Thus, in our
216 system, we further extend the surface fluid registration method to an inverse-consistent
217 framework (Leow et al., 2005). The obtained surface registration is diffeomorphic. For details
218 of our inverse-consistent surface fluid registration method, we refer to (Shi et al., 2013a).

219 **2.2.2 Surface-based Morphometry Feature Extraction**

220 After parameterization and registration, we establish a one-to-one correspondence map
221 between hippocampal surfaces. This makes it effective for us to compare and analyze surface
222 data. Besides, each surface has the same number of vertices (150×100) as shown in panel 2
223 of **Fig. 1**. The intersection of the red curve and the blue curve is a surface vertex, and at each
224 vertex, we adopt two features, the radial distance (RD) and the surface metric tensor used in
225 multivariate tensor-based morphometry (mTBM). The RD (a scalar at each vertex) represents
226 the thickness of the shape at each vertex to the medical axis (Pizer et al., 1999; Thompson et
227 al., 2004), this reflects the surface differences along the surface normal directions. The medial
228 axis is determined by the geometric center of the isoparametric curve on the computed
229 conformal grid (Wang et al., 2011). The axis is perpendicular to the isoparametric curve, so the
230 thickness can be easily calculated as the Euclidean distance between the core and the vertex on
231 the curve. The mTBM statistics (a 3×1 vector at each vertex) have been frequently studied
232 in our prior work (Shi et al., 2015, 2013b; Wang et al., 2010, 2009). They measure local surface
233 deformation along the surface tangent plane and show improved signal detection sensitivity
234 relative to more standard tensor-based morphometry (TBM) measures computed as the
235 determinant of the Jacobian matrix (Wang et al., 2013). RD and mTBM jointly form a new
236 feature, known as the surface multivariate morphometry statistics (MMS). Therefore, MMS is
237 a 4×1 vector at each vertex. The surface of the hippocampus in each brain hemisphere has
238 15,000 vertices, so the feature dimensionality for each hippocampus in each subject is 60,000.

239 **2.2.3 Surface Feature Dimensionality Reduction**

240 The above mentioned vertex-wise surface morphometry feature, MMS, is a high-fidelity
241 measure to describe the local deformation of the surface and can provide detailed localization

242 and visualization of regional atrophy or expansion (Yao et al., 2018) and development
243 (Thompson et al., 2000). However, the high dimensionality of such features is likely to cause
244 problems for classification. Feature reduction methods proposed by (Davatzikos et al., 2008;
245 Sun et al., 2009) may ignore the intrinsic properties of a structure's regional morphometry.
246 Therefore, we introduce the following feature reduction method for the vertex-wise surface
247 morphometry features.

248 The surface MMS feature dimension is typically much larger than the number of subjects,
249 i.e., the so-called *high dimension-small sample problem*. To extract useful surface features and
250 reduce the dimension before making predictions, this work first randomly generates square
251 windows on each surface to obtain a collection of small image patches with different amounts
252 of overlap. In our prior AD studies (Wu et al., 2018; Zhang et al., 2016a, 2016b), we discuss
253 the most suitable patch size and number. Therefore, in this work, we adopt the same optimal
254 experimental settings, as 1,008 patches (patch size=10 × 10 vertices) for each subject (504
255 patches for each side of the hippocampal surface). As these patches are allowed to overlap, a
256 vertex may be contained in several patches. The zoomed-in window in subfigure (b) of panel
257 (2) in **Fig.1** shows overlapping areas on selected patches. After that, we use the technique of
258 sparse coding and dictionary learning (Mairal et al., 2009) to learn meaningful features.
259 Dictionary learning has been successful in many image processing tasks as it can concisely
260 model natural image patches. In this work, we propose a novel sparse coding and dictionary
261 learning method with an l_1 -regularized correntropy loss function named *Correntropy-induced*
262 *Sparse-coding (CS)*, which is expected to improve the computational efficiency compared to
263 Stochastic Coordinate Coding (SCC) (Lin et al., 2014). Formally speaking, correntropy is a
264 generalized similarity measure between two scalar random variables U and V, which is defined
265 by $\mathcal{V}_\sigma(U, V) = \mathbb{E}\mathcal{K}_\sigma(U, V)$. Here, \mathcal{K}_σ is a Gaussian kernel given by $\mathcal{K}_\sigma(U, V) =$
266 $\exp\{-(u - v)^2/\sigma^2\}$ with the scale parameter $\sigma > 0$, $(u-v)$ being a realization of (U, V)
267 (Feng et al., 2015; Gui et al., 2017). Utilizing the correntropy measure as a loss function will
268 reduce the negative influence of non-Gaussian noise in the data.

269 Classical dictionary learning techniques (Lee et al., 2007; Olshausen and Field, 1997)

270 consider a finite training set of feature maps, $X = (x_1, x_2, \dots, x_n)$ in $R^{p \times n}$. In our study, X is
 271 the set of MMS features from n surface patches of all the samples. All the MMS features on
 272 each surface patch, x_i , is reshaped to a p -dimensional vector. And we desire to generate a new
 273 set of sparse codes, $Z = (z_1, z_2, \dots, z_n)$ in $R^{m \times n}$ for these features. Therefore, we aim to
 274 optimize the empirical cost function as **Eq. (1)**.

275
$$f(D, z_i) \triangleq \sum_{i=1}^n l(x_i, D, z_i) \quad (1)$$

276 where $D \in R^{p \times m}$ is the dictionary and $z_i \in R^m$ is the sparse code of each feature vector.
 277 $l(x_i, D, z_i)$ is the loss function that measures how well the dictionary D and the sparse code
 278 z_i can represent the feature vector x_i . Then, x_i can be approximated by $x_i = Dz_i$. In this
 279 way, we convert the p -dimensional feature vector, x_i , to a m -dimensional sparse code, z_i ,
 280 where m is the dimensionality of the sparse code and the dimensionality could be arbitrary. In
 281 this work, we introduce the correntropy measure (Gui et al., 2017) to the loss function and
 282 define the l_1 -sparse coding optimization problem as **Eq. (2)**

283
$$\min_{D, z_i} \frac{1}{2} \sum_{i=1}^n \exp\left(-\frac{\|Dz_i - x_i\|_2^2}{\sigma^2}\right) + \lambda \sum_{i=1}^n \|z_i\|_1 \quad (2)$$

284 where λ is the regularization parameter, σ is the kernel size that controls all properties of
 285 correntropy. $\|\cdot\|_2$ and $\|\cdot\|_1$ are the l_2 -norm and l_1 -norm and $\exp()$ represents the exponential
 286 function. The first part of the loss function measures the degree of the image patches' goodness
 287 and the correntropy may help remove outliers. Meanwhile, the second part is well known as the
 288 l_1 penalty (Fu, 1998) that can yield a sparse solution for z_i and select robust and informative
 289 features. Specifically, there are m columns (atoms) in the dictionary D and each atom is $d_j \in$
 290 $R^p, j = 1, 2, \dots, m$. To avoid D from being arbitrarily large and leading to arbitrary scaling of
 291 the sparse codes, we constrain each l_2 -norm of each atom in the dictionary no larger than one.
 292 We will let C become the convex set of matrices verifying the constraint as **Eq. (3)**.

293
$$C \triangleq \{D \in R^{p \times m} \text{ s.t. } \forall j = 1, 2, \dots, m, d_j^T d_j \leq 1\} \quad (3)$$

294 Note that, the empirical problem cost $f(D, z_i)$ is not convex when we jointly consider the
 295 dictionary D and the coefficients Z . But the function is convex concerning each of the two

296 variables, D , and Z , when the other one is fixed. Since it takes much time to solve D and Z
 297 when dealing with large-scale data sets and a large-size dictionary, we adopt the framework in
 298 the stochastic coordinate coding (SCC) algorithm (Lin et al., 2014), which can dramatically
 299 reduce the computational cost of the sparse coding, while keeping a comparable performance.

300 To solve this optimization problem, we reformulate the first part of the equation by the
 301 half-quadratic technique (Nikolova and Ng, 2006) and then the objective can be solved as the
 302 minimization problem **Eq.(4)**:

$$303 \min_{D, z_i} \frac{1}{2} \sum_{i=1}^n h_i \|Dz_i - x_i\|_2^2 + \lambda \sum_{i=1}^n \|z_i\|_1, h_i = \exp\left(-\frac{\|Dz_i - x_i\|_2^2}{\sigma^2}\right). \quad (4)$$

304 Here the auxiliary variable, h_i , will be updated in each update iteration. At each iteration, we
 305 update D and Z alternately, which means we firstly fix D and update the sparse code Z
 306 with coordinated descent (CD) and then fix Z to update the dictionary D via stochastic
 307 gradient descent (SGD).

308 As our optimization method is stochastic, we only update the sparse code and dictionary
 309 with only one signal for each iteration. In the following paragraphs, we will discuss the
 310 optimization in one iteration with only one signal. If a signal, $x = (x_1, x_2, \dots, x_p)^T \in R^p$, is
 311 given, we first update its corresponding sparse code, $z = (z_1, z_2, \dots, z_m)$, via CD. Let z_l
 312 denote the l -th entry of z and d_{kl} represents the k -th item of d_l . d_l is the l -th
 313 atom/column of the dictionary D . Then, we can calculate the partial derivative of z_l in the
 314 first part of the function, $f(D, z_i)$, as **Eq. (5)**

$$315 \frac{\partial}{\partial z_l} c(D, z) = \frac{\partial}{\partial z_l} \frac{1}{2} h \|Dz - x\|_2^2 = -h \sum_{k=1}^p d_{kl} \left(x_k - \sum_{r=1}^m d_{kr} z_r \right) \\ 316 = -h \sum_{k=1}^p d_{kl} \left(x_k - \sum_{r \neq l}^m d_{kr} z_r - d_{kl} z_l \right) \\ 317 = -h \sum_{k=1}^p d_{kl} \left(x_k - \sum_{r \neq l}^m d_{kr} z_r \right) + h z_l \sum_{k=1}^p (d_{kl})^2 \\ 318 = -\rho_l + h z_l v_l \quad (5)$$

319 where $\rho_l = h \sum_{k=1}^p d_{kl} (x_k - \sum_{r \neq l}^m d_{kr} z_r)$, $v_l = \sum_{k=1}^p (d_{kl})^2$ and h is the auxiliary variable
 320 for the signal. Since we normalize the atom, d_l , in each iteration, v_l can be ignored. Then, we

321 compute the subdifferential of the lasso loss function and equate it to zero to find the optimal
 322 solution as follows:

323
$$\frac{\partial}{\partial z_l} f(D, z) = \frac{\partial}{\partial z_l} c(D, z) + \frac{\partial}{\partial z_l} \lambda \|z\|_1 = -\rho_l + hz_l v_l + \frac{\partial}{\partial z_l} \lambda \|z\|_1 = 0 \quad (6)$$

324 Then, according to the derivative of the l_1 -norm, we can have the following equations.

325
$$\begin{cases} -\rho_l + hz_l v_l - \lambda = 0 & \text{if } z_l < 0 \\ -\rho_l - \lambda \leq 0 \leq -\rho_l + \lambda & \text{if } z_l = 0 \\ -\rho_l + hz_l v_l + \lambda = 0 & \text{if } z_l > 0 \end{cases} \quad (7)$$

326 Finally, we can get the soft thresholding function as:

327
$$z_l = \begin{cases} \frac{\rho_l + \lambda}{hv_l} & \text{for } \rho_l < -\lambda \\ 0 & \text{for } -\lambda \leq \rho_l \leq \lambda \\ \frac{\rho_l - \lambda}{hv_l} & \text{for } \rho_l > \lambda \end{cases} \quad (8)$$

328 After we update the sparse code, we propose the following strategy to accelerate the
 329 convergence for updating the dictionary D . The atom, d_l will stay unchanged if z_l is zero
 330 since $\nabla_{d_l} = h(Dz - x)z_l = 0$. Otherwise, as shown in **Fig. 2**, we can update the l -th atom of
 331 the dictionary D as $d_l \leftarrow d_l - \gamma_l h(Dz - x)z_l$. γ_l is the learning rate provided by an
 332 approximation of the Hessian: $R \leftarrow R + zz^T$ and γ_l is given by $1/r_{ll}$, where r_{ll} is the item
 333 at the l -th row and l -th column of the Hessian matrix R . The pseudo-code of the model was
 334 shown in **Alg. 1**, dubbed as PASCS.

Alg. 1 Patch Analysis-based Surface Correntropy-induced Sparse-coding

Require: Data set $\mathbf{X} = (\mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_n)$ in $\mathbb{R}^{p \times n}$
 Ensure: Dictionary $\mathbf{D} \in \mathbb{R}^{p \times m}$ and sparse codes $\mathbf{Z} = (\mathbf{z}_1, \mathbf{z}_2, \dots, \mathbf{z}_n) \in \mathbb{R}^{m \times n}$
 Initialize: $\mathbf{D}^{1,1}, \mathbf{R} = \mathbf{0}, \mathbf{z}_i^0 = \mathbf{0}, \mathbf{h}_i^0 = \mathbf{1}, i = 1, \dots, n$
 1: for $t = 1$ to τ do
 2: for $i = 1$ to n do
 3: Get an image patch \mathbf{x}_i from \mathbf{X} .
 4: Update \mathbf{z}_i^t via coordinate descent:

$$\mathbf{z}_i^t \leftarrow \mathbf{CD}(\mathbf{x}_i, \mathbf{D}^{i,t}, \mathbf{z}_i^{t-1}).$$

 5: Update Hessian matrix and the learning rate:

$$\mathbf{R} \leftarrow \mathbf{R} + \mathbf{z}_i^t (\mathbf{z}_i^t)^T, \gamma_{i,l} = 1/r_{ll}.$$

 6: Update the support of the dictionary via SGD for non-zero entry $\mathbf{z}_{i,l}^t$ (and
 normalize it):

$$\mathbf{d}_l^{i+1,t} \leftarrow \mathbf{d}_l^{i,t} - \gamma_{i,l} \mathbf{h}_i (\mathbf{D}^{i,t} \mathbf{z}_i^t - \mathbf{x}_i) \mathbf{z}_{i,l}^t.$$

 7: Update auxiliary variable \mathbf{h}_i :

$$\mathbf{h}_i = \exp(-\|\mathbf{D}^{i,t} \mathbf{z}_i^t - \mathbf{x}_i\|_2^2 / \sigma^2).$$

 8: If $i = n$, Then $\mathbf{D}^{1,t+1} = \mathbf{D}^{n,t}$.
 9: end for
 10: end for
 Output: $\mathbf{D} = \mathbf{D}^{n,\tau}$ and $\mathbf{z}_i = \mathbf{z}_i^\tau$ for $i = 1, \dots, n$

335

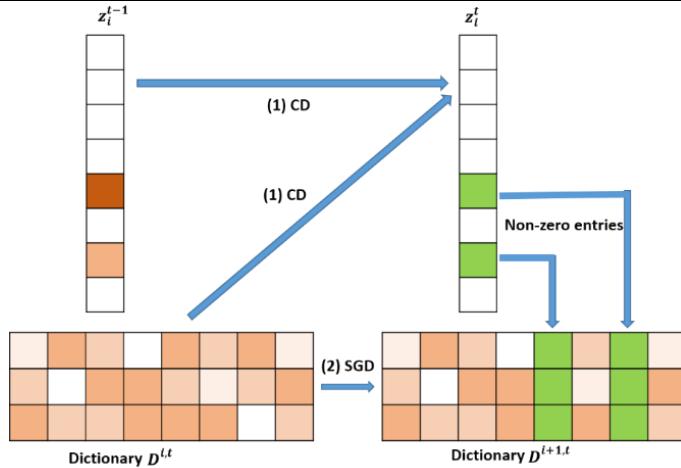


Fig. 2. Illustration of one iteration of the proposed Patch Analysis-based Surface Correntropy-induced Sparse-coding (PASCS) algorithm. The input is many 10×10 patches on each surface based on our multivariate morphometry statistics (MMS). With an image patch \mathbf{x}_i , PASCS performs one step of coordinate descent (CD) to find the support and the sparse code. Meanwhile, PASCS performs a few steps of CD on supports (non-zero entries) to obtain a new sparse code \mathbf{z}_i^k . Then, PASCS updates the supports (green boxes in the figure) of the dictionary by stochastic gradient descent (SGD) to obtain a new dictionary $\mathbf{D}^{i+1,t}$. Here, t represents the t -th epoch; i represents the i -th patch.

336 **2.2.4 Pooling and Classification**

337 After we get the sparse code (the dimension is m) for each patch, the dimensionality of
338 sparse codes for each subject is still too large for classification, which is $m \times 1008$. Therefore,
339 we apply Max-pooling to reduce the feature dimensionality for each subject. Max-pooling
340 (Boureau et al., 2010) is a way of taking the most responsive node of a given region of interest
341 and serves as an important layer in the convolutional neural network architecture. In this work,
342 we compute the maximum value of a particular feature over all sparse codes of a subject and
343 generate a new representation for each subject, which is an m -dimensional vector. These
344 summary representations are much lower in dimension, compared to using all the extracted
345 surface patch features; this can improve results generalizability via less over-fitting.

346 With these dimension-reduced features, we choose the random forest algorithm (Liaw and
347 Wiener, 2002) for the binary classification. Random forests are a combination of tree predictors
348 such that each tree depends on the values of a random vector sampled independently and with
349 the same distribution for all trees in the forest. This algorithm adopts a learning process called
350 *feature bagging*. In this process, we select a random subset of the features several times and
351 then train a decision tree for each subset. If some features are strong predictors of the response,
352 they will be selected in many decision trees and this makes them correlated. In comparison with
353 decision trees, random forests have the same bias but lower variance, which means they can
354 overcome the drawback of overfitting caused by a small data set. For our sparse surface
355 features, when the size of the training set becomes small, diversification becomes more subtle,
356 and the method can better detect these subtle differences. In this project, we use the random
357 forest classifier in the *scikit-learn* package (<https://scikit-learn.org/>) with the default settings.
358 Besides, under the imbalanced-data condition (such as 116 A β + CU and 232 A β - CU in the
359 ADNI data set), the classifier tends to classify all the training data into the major class, as it
360 aims to maximize training accuracy. Therefore, we adopt *random undersampling* (Dubey et al.,
361 2014) to balance the numbers of training subjects in the two classes. All the experiments in this
362 work use the same setups for the random forest classifier and random undersampling.

363 **2.3 Performance Evaluation Protocol**

364 Before using hippocampal MMS features for A β status classification, we need to apply
365 PASCS-MP to extract sparse codes from these high dimensional MMS features. The
366 performance of PASCS-MP has a close relationship to four key parameters: the patch size, the
367 dimensionality of the learned sparse coding, the regularization parameter for the l_1 -norm (λ),
368 and the kernel size (σ) in the exponential function (see Eq.(2)). Patch-based analysis has been
369 widely used for image segmentation and classification (Kao et al., 2020). Leveraging patches
370 in our MMS can preserve well the properties of the regional morphometry of the hippocampal
371 surface since the vertices that carry strong classification power are always clustered on the
372 surface and a set of such vertices typically has a stronger classification ability compared to
373 using just a single vertex. However, the size of the set of such vertices is unknown. Therefore,
374 we select the vertices by randomly selecting the same number of square patches with different
375 sizes and compared the performance of the final classification accuracy for the different patch
376 sizes. The dimensionality of the learned sparse coding (m) is also the dimensionality of the
377 representation for each subject. The model might miss some significant information if the
378 dimensionality is too low. Also, the representations will contain too much redundant
379 information when the dimensionality is too large. The regularization parameter for the l_1 -norm
380 (λ) will control the sparsity of the learned sparse codes. A suitable regularization parameter will
381 select significant features meanwhile reducing noise. The kernel size in the exponential
382 function controls all properties of correntropy. Correntropy is directly related to the probability
383 of how similar two random variables are in a neighborhood of the joint space controlled by the
384 kernel bandwidth, i.e., the kernel bandwidth acts as a zoom lens, controlling the *observation*
385 *window* over which similarity is assessed. This adjustable window provides an effective
386 mechanism to eliminate the detrimental effect of outliers (Liu et al., 2007).

387 Thus, we adopt 10-fold cross-validation to evaluate the classification accuracy on another
388 dataset from ADNI 2 with a series of key parameter candidates and select the optimal parameter
389 setups. The detailed information about the dataset and the key parameter candidates will be
390 introduced in next section. For the 10-fold cross-validation, we randomly shuffle and split the

391 dataset into ten groups. We take one group as the test data set and use the remaining groups to
392 train a model. Then, the candidate model is evaluated using the test data. In this way, we can
393 get a predicted class label for all the samples. Then, the output of each classification experiment
394 is compared to the ground truth, and the accuracy is computed to indicate how many class labels
395 are correctly identified. The key parameters with the highest classification accuracies are
396 selected.

397 Once we get an optimized PASCS-MP model, we can compare the performances of MMS,
398 volume, and surface area measurements for classifying individuals of different A β status. We
399 use the volume from the left and right hippocampi (i.e., hippocampi in each brain hemisphere)
400 as two features to train the classifier instead of adding them together. The same classification
401 strategy is applied to surface areas from both sides. Moreover, we will compare the
402 classification performances based on PASCS-MP, PASS-MP (Zhang et al., 2017b, 2016b) and
403 SPHARM (Chung et al., 2008, 2007; Shi et al., 2013a). We evaluate these classification
404 performances with the same 10-fold cross-validation method. Four performance measures: the
405 Accuracy (ACC), Balanced Accuracy (B-ACC), Specificity (SPE) and Sensitivity (SEN) are
406 computed (Bhagwat et al., 2018; Hinrichs et al., 2011; Ritter et al., 2015; Salvatore et al., 2018;
407 Zhang et al., 2017b). We also compute the area-under-the-curve (AUC) of the receiver
408 operating characteristic (ROC) (Bhagwat et al., 2018; Fan et al., 2008; La Joie et al., 2013;
409 Nakamura et al., 2018). By considering these performance measures, we expect the proposed
410 system integrating MMS, PASCS-MP and the binary random forest classifier to perform better
411 than similar classification strategies for identifying individuals with different A β status.

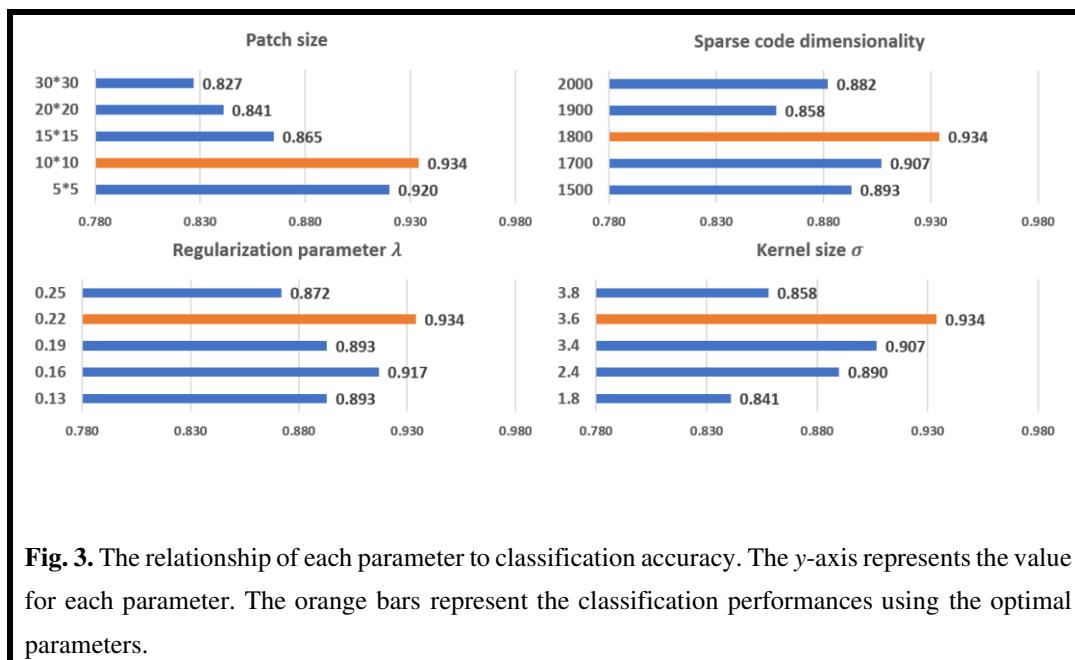
412 3. RESULTS

413 3.1 Key Parameter Estimations for the PASCS-MP Method

414 To apply PASCS-MP method on hippocampal MMS, four parameters need to be
415 empirically assigned, namely: the patch size, the dimensionality of the learned sparse coding,
416 the regularization parameter for the l_1 -norm (λ) and the kernel size (σ) in the exponential
417 function. Selecting suitable parameters will lead to superior performance in refining lower

418 dimensional MMS representations related to AD pathology. With 10-fold cross-validation,
419 these key parameters are evaluated from PASCS-MP based classification performance on 109
420 AD patients and 180 CU subjects of ADNI-2 cohort. To avoid data leakage, these subjects are
421 not used in the following study of A β burden classification.

422 In **Fig. 3**, we illustrate the classification accuracy for different values of each parameter.
423 When we evaluate one parameter, we fix the rest parameters. For example, in the first bar chart
424 in **Fig. 3**, we try different patch sizes including 5 \times 5, 10 \times 10, 15 \times 15, 20 \times 20 and 30 \times 30 while we
425 fix the sparse code dimensionality as to 1800, and set λ to 0.22, and σ to 3.6. By testing varied
426 sets of parameters, we find that the optimal patch size is 10 \times 10, the optimal sparse code
427 dimensionality is 1800, the optimal λ is 0.22 and the optimal σ is 3.6 and these optimal
428 parameters will be adopted in the study of A β burden classification.



429 **3.2 Classification of A β Burden**

430 To explore whether there is a significant gain in classification power with our new system,
431 based on our surface MMS, we generate two different kinds of sparse codes with our previous
432 framework (PASS-MP) (Fu et al., 2021; Zhang et al., 2017; Zhang et al., 2016b) and the new
433 framework (PASCS-MP). The parameter settings for the two sparse coding methods are the
434 same. Additionally, we apply the popular SPHARM method (Chung et al., 2008; Shi et al.,

435 2013a) to calculate hippocampal shape features. Based on these three kinds of feature sets, we
 436 apply the random forest classifier to detect individuals with different A β status. Moreover, we
 437 also examine the classification performances using hippocampal MMS, surface area and
 438 volume measures. These classification performances are evaluated using ACC, B-ACC, SPE,

439 **Table 2.** Classification Results for four contrasts.

Area	A β + AD vs. A β - CU	A β + MCI vs. A β - MCI	A β + CU vs. A β - CU (ADNI)	A β + CU vs. A β - CU (OASIS)
ACC	0.68 \pm 0.01	0.55 \pm 0.02	0.54 \pm 0.01	0.47
B-ACC	0.69 \pm 0.02	0.55 \pm 0.02	0.54 \pm 0.02	0.43
SPE	0.66 \pm 0.02	0.54 \pm 0.02	0.55 \pm 0.02	0.49
SEN	0.71 \pm 0.03	0.56 \pm 0.03	0.53 \pm 0.04	0.37
Volume	A β + AD vs. A β - CU	A β + MCI vs. A β - MCI	A β + CU vs. A β - CU (ADNI)	A β + CU vs. A β - CU (OASIS)
ACC	0.71 \pm 0.01	0.53 \pm 0.02	0.50 \pm 0.03	0.51
B-ACC	0.72 \pm 0.01	0.53 \pm 0.01	0.50 \pm 0.03	0.52
SPE	0.68 \pm 0.01	0.52 \pm 0.01	0.51 \pm 0.02	0.54
SEN	0.75 \pm 0.01	0.54 \pm 0.02	0.49 \pm 0.04	0.50
SPHARM	A β + AD vs. A β - CU	A β + MCI vs. A β - MCI	A β + CU vs. A β - CU (ADNI)	A β + CU vs. A β - CU (OASIS)
ACC	0.71 \pm 0.02	0.56 \pm 0.02	0.52 \pm 0.02	0.60
B-ACC	0.71 \pm 0.02	0.56 \pm 0.03	0.51 \pm 0.04	0.60
SPE	0.74 \pm 0.02	0.61 \pm 0.03	0.56 \pm 0.03	0.61
SEN	0.68 \pm 0.04	0.51 \pm 0.03	0.46 \pm 0.05	0.60
PASS-MP	A β + AD vs. A β - CU	A β + MCI vs. A β - MCI	A β + CU vs. A β - CU (ADNI)	A β + CU vs. A β - CU (OASIS)
ACC	0.79 \pm 0.01	0.73 \pm 0.02	0.71 \pm 0.02	0.74
B-ACC	0.79 \pm 0.01	0.73 \pm 0.02	0.70 \pm 0.03	0.73
SPE	0.78 \pm 0.02	0.75 \pm 0.02	0.73 \pm 0.03	0.74
SEN	0.79 \pm 0.01	0.72 \pm 0.03	0.67 \pm 0.03	0.73
PASCS-MP	A β + AD vs. A β - CU	A β + MCI vs. A β - MCI	A β + CU vs. A β - CU (ADNI)	A β + CU vs. A β - CU (OASIS)
ACC	0.91\pm0.01	0.89\pm0.01	0.79\pm0.02	0.81
B-ACC	0.91\pm0.01	0.89\pm0.01	0.79\pm0.03	0.80
SPE	0.91\pm0.01	0.91\pm0.01	0.80\pm0.02	0.82
SEN	0.90\pm0.01	0.88\pm0.01	0.79\pm0.05	0.79

440 Values are mean \pm 95% confident interval where applicable.

441 SEN. For each binary classification of ADNI cohort, we repeat the 10-fold cross-validation 5
442 times; the mean and 95% confident interval of the evaluation measures are calculated as
443 (Vanwinckelen and Blockeel, 2012) and shown in the middle three columns of **Table 2**. To
444 further evaluate the performance of our new framework, we firstly generate new representations
445 with our proposed PASCS-MP for all the CU subjects from ADNI and OASIS cohorts. Then,
446 we train a binary random forest model on the ADNI dataset and test it with the OASIS dataset.
447 Since there is no cross-validation here, there is no confident interval in the last column of **Table**
448 **2**. We also compute the area-under-the-curve (AUC) of the receiver operating characteristic
449 (ROC). The ROC curve and AUC for these classification tasks are illustrated in **Fig. 4**. This
450 comparison analysis classification performance shows that the combination of PASCS-MP and
451 hippocampal MMS measures have superior performance when detecting individuals with
452 different A β status, compared to other similar methods.

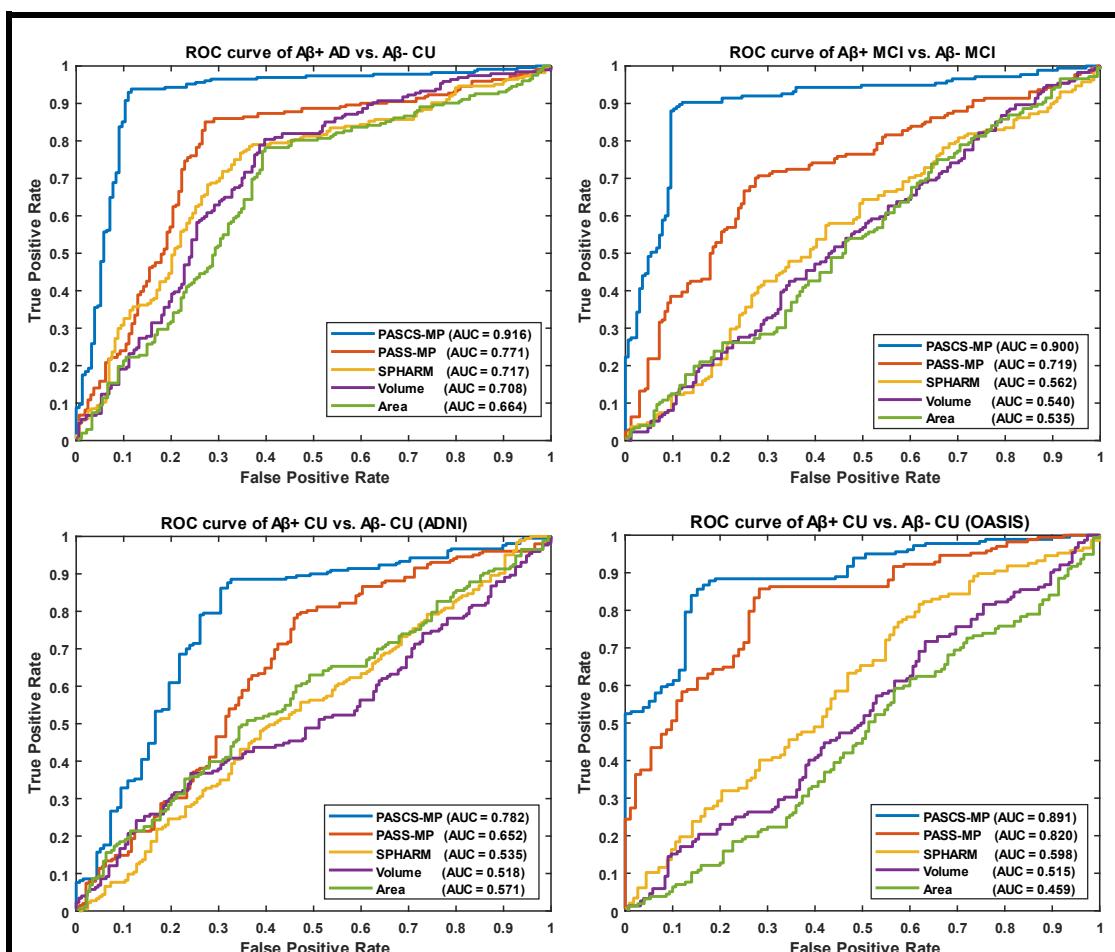


Fig. 4. ROC curves for the classification tasks, A β + AD vs. A β - CU, A β + MCI vs. A β - MCI, A β + CU vs. A β - CU (ADNI), and A β + CU vs. A β - CU (OASIS).

453 **4. DISCUSSION**

454 In this paper, we propose a novel surface feature dimension reduction scheme, PASCS-MP,
455 to correlate the hippocampus MMS with different levels of A β burden in individual subjects.
456 We develop a hippocampal structure-based A β burden prediction system that involves
457 hippocampal MMS computing, sparse coding and classification modules. We apply the
458 proposed system on two independent datasets, ADNI and OASIS. We have two main findings.
459 Firstly, the hippocampal surface-based MMS measure practically encodes a great deal of
460 neighboring intrinsic geometry information that would otherwise be inaccessible or overlooked
461 in classical hippocampal volume and surface area measures. Experimental results show that the
462 MMS measure provides better classification accuracy than hippocampal volume, surface area
463 measures and SPHARM for detecting the relationships between hippocampal deformations and
464 A β positivity. Secondly, we propose a novel sparse coding method, PASCS-MP. It has all the
465 advantages of our previous proposed PASS-MP (Zhang et al., 2016b, 2016a) and improves the
466 follow-up classification performance compared to PASS-MP.

467 **4.1 Comparison Analysis of Hippocampal MMS, Volume and Surface Area**

468 The hippocampus is a primary target region for studying early AD progression. Its structure
469 can be measured using the widely used overall hippocampal volume, surface area and our
470 proposed hippocampal MMS. Our prior studies (Dong et al., 2019; Li et al., 2016; Shi et al.,
471 2011; Wang et al., 2011) show that hippocampal MMS performs robustly in distinguishing
472 clinical groups at different AD risk levels. In particular, we previously found that hippocampal
473 MMS can detect *APOE4* gene dose effects on the hippocampus during the preclinical stage,
474 while the hippocampal volume measure cannot (Dong et al., 2019). A study by Wu et al. (2018)
475 demonstrates that hippocampal MMS performs better than traditional hippocampal volume
476 measures in classifying 151 A β + AD and 271 A β - CU subjects.

477 This work evaluates the performance of the above three hippocampal measurements for
478 predicting A β status at the individual subject level. Classification results (see **Table 2** and **Fig.**
479 **4**) show that hippocampal MMS has better performance as measured by ACC, SPE, SEN and

480 AUC. These results validate our hypothesis that hippocampal MMS-based analysis methods
481 provide improved statistical accuracy than hippocampal volume and surface area measures in
482 predicting the subjects with different A β status in the AD continuum. Our prior work (Wang et
483 al., 2011) shows that MMS may offer a surrogate biomarker for PET/CSF A β biomarkers. This
484 work further shows it can be used to classify brain A β burden on an individual basis.

485 **4.2 Comparative Analysis of PASCS-MP, PASS-MP and SPHARM**

486 The MMS measure for brain structures performs well in clinical group comparisons (Dong
487 et al., 2020b, 2019; Li et al., 2016; Shi et al., 2015, 2014b; Wang et al., 2013; Yao et al., 2018),
488 and as we have shown, it has the potential to further be applied for individual A β classification.
489 To achieve this goal, we need to solve the challenge that the MMS dimension is usually much
490 larger than the number of subjects, i.e., the so-called *high dimension, small sample size problem*.
491 A reasonable solution is to reduce the feature dimension. Existing feature dimension reduction
492 approaches include feature selection (Fan et al., 2005; Jain and Zongker, 1997), feature
493 extraction (Guyon et al., 2008; Jolliffe, 2002; Mika et al., 1999) and sparse learning methods
494 (Donoho, 2006; Vounou et al., 2010; Wang et al., 2013). In most cases, information is lost when
495 mapping data into a lower-dimensional space. By defining a better lower-dimensional subspace,
496 this information loss can be limited. Sparse coding (Lee et al., 2007; Mairal et al., 2009) has
497 been previously proposed to learn an over-complete set of basis vectors (also called a *dictionary*)
498 to represent input vectors efficiently and concisely (Donoho and Elad, 2003). Sparse coding
499 has been shown to be effective for many tasks such as image imprinting (Moody et al., 2012),
500 image deblurring (Yin et al., 2008), super-resolution (Yang et al., 2008), classification (Mairal
501 et al., 2009), functional brain connectivity (Lv et al., 2017, 2015), and structural morphometry
502 analysis (Zhang et al., 2017).

503 Our previous studies (Zhang et al., 2017; Zhang et al., 2016b, 2016a) propose a patch
504 analysis-based surface sparse-coding and max-pooling (PASS-MP) method, consisting of
505 sparse coding (Lee et al., 2006; Mairal et al., 2009) and max-pooling (LeCun et al., 2015), for
506 surface feature dimension reduction. PASS-MP has excellent impressive performance for the

507 sparse coding of our MMS features. Our prior studies successfully apply these sparse codes in
508 detecting individual brain structure abnormalities and obtain state-of-art performance (Dong et
509 al., 2020a; Fu et al., 2021; Wu et al., 2018).

510 Even so, there typically exists non-Gaussian and localized sources of noise in surface-based
511 morphometry features, this can dramatically influence the learned dictionary and further lead
512 to poor sparse coding based on the loss function of PASS-MP. The correntropy measure is a
513 very robust method for correcting such sources of noise (He et al., 2012; Liu et al., 2007;
514 Nikolova and Ng, 2006). In this paper, we improve upon the PASS-MP method by introducing
515 correntropy measures into the loss function (Gui et al., 2017). Therefore, our proposed sparse
516 coding method, PASCS-MP, incorporates all the advantages of PASS-MP and meanwhile
517 improves the classification performance. We also test SPHARM-based hippocampal shape
518 features as they have frequently been studied in prior AD research (e.g., (Cuingnet et al., 2011;
519 Gerardin et al., 2009; Gutman et al., 2013)). In such an approach, we use a series of spherical
520 harmonics to model the shapes of the hippocampus segmented by FSL. The SPHARM
521 coefficients are computed using SPHARM-PDM (Spherical Harmonics-Point Distribution
522 Model) software developed by the University of North Carolina and the National Alliance for
523 Medical Imaging Computing (Styner et al., 2006). The classification features are based on
524 these SPHARM coefficients, which are represented by two sets of three-dimensional SPHARM
525 coefficients for each subject (in fact, one set for the hippocampus in each brain hemisphere). In
526 Gerardin et al. (2009), they use a feature selection step because the subject groups are much
527 smaller (fewer than 30 subjects in each group). When the number of subjects is small, the
528 classifier can be more sensitive to uninformative features. In the current study, the number of
529 subjects is relatively large, so a feature selection step is less necessary and may increase the
530 risk of overfitting. We adopt the same approach in Cuingnet et al. (2011), who chose to avoid
531 this selection step. The classification results (see **Table 2** and **Fig. 4**) based on PASCS-MP,
532 PASS-MP and SPHARM meet our expectation that the classification performances based on
533 PASCS-MP have an apparent improvement measured by ACC, B-ACC, SPE, SEN and AUC.
534

535 **4.3 A β Burden Prediction using MRI Biomarkers**

536 A β accumulation is a major feature of AD neuropathology (Brier et al., 2016; Cummings,
537 2019). Detecting it early and accurately provides a potential opportunity for effective
538 therapeutic interventions before the advanced stages of AD (Tosun et al., 2014). Compared to
539 PET and CSF A β measurement techniques, MRI is less expensive (than PET) and less invasive
540 (than both PET and lumbar puncture). AD-related biomarker studies (Jack et al., 2018; Jack
541 and Holtzman, 2013; Sperling et al., 2011b) have shown that abnormal brain A β accumulation
542 typically precedes detectable structural brain abnormalities. There is emerging literature using
543 MRI biomarkers to predict brain A β burden, and hippocampal structural measurement is one
544 of the major predictors (Ansart et al., 2020; Pekkala et al., 2020; Tosun et al., 2016, 2014).
545 Tosun et al. (2014) applied LASSO penalized logistic regression classifier to MRI-based voxel-
546 wise anatomical shape variation measures and cerebral blood flow measures to predict A β
547 positivity in 67 people with early MCI (34 A β +); the classification accuracy was 83%. Ansart
548 et al. (2020) applied LASSO feature selection and a random forest classifier to MRI- based
549 cortical thickness and hippocampal volume measures to classify 596 people with MCI scanned
550 as part of ADNI MCI (375 A β +); the AUC was 0.80. Our proposed classification framework
551 has a higher ACC=89% or AUC=0.90 than each of these two studies (Ansart et al., 2020; Tosun
552 et al., 2014) for predicting A β status in people with MCI. Of the studies predicting A β positivity
553 in CUs, Ansart et al. (2020) applied LASSO feature selection and random forest classifier to
554 MRI-derived cortical thickness and hippocampal volume measures to classify 431 ADNI CUs
555 (162 A β +) and 318 INSIGHT CUs (88 A β +); the AUCs were 0.59 and 0.62, respectively.
556 Pekkala et al. (2020) used the Disease State Index machine learning algorithm and MRI-based
557 biomarkers (total cortical and gray matter volumes, hippocampus, accumbens, thalamus and
558 putamen volumes) to predict A β burden in 48 CUs (20 A β +); the AUC was 0.78. Our proposed
559 classification framework has AUC=0.78 on 348 ADNI CUs (116 A β +) and AUC=0.89 on 260
560 OASIS CUs (52 A β +) **Table 3** and **Fig. 4** present the AUC or ACC values from this work and
561 from similar studies predicting A β positivity using brain MRI biomarkers. Compared to these
562 similar studies, our proposed classification system only uses hippocampal structural features

563 but still consistently outperforms other recently published methods for predicting A β positivity
564 in people with MCI and CUs.

565 **Table 3.** Studies to impute A β status from MRI biomarkers in key clinical groups in AD research.

Method	Subjects (A β +/-)	MRI Biomarkers	ACC	AUC
PASCS-MP-Random forest classifier (This work)	342 ADNI MCI (171/171) 348 ADNI CU (116/232) 260 OASIS CU (52/208)	Hippocampal multivariate morphometry statistics (MMS)	0.89 \pm 0.01 0.79 \pm 0.02 0.81	0.90 0.78 0.89
LASSO penalized logistic regression classifier (Tosun et al., 2014)	67 Early MCI (34/33)	Voxel-wise anatomical shape variation measures and cerebral blood flow (including frontoparietal cortical, hippocampal regions, among others)	0.83 \pm 0.03	
LASSO feature selection and Random Forest classifier (Ansart et al., 2020)	596 ADNI MCI (375/221) 431 ADNI CU (162/269) 318 INSIGHT CU (88/230)	Cortical thickness and hippocampal volume	0.80	0.59
Disease State Index machine learning algorithm (Pekkala et al., 2020)	48 CU (20/28)	Total cortical and gray matter volumes, hippocampus, accumbens, thalamus and putamen volumes	0.78	

566 **4.4 Limitations and Future Work**

567 Despite the promising results are obtained by applying our proposed A β positivity
568 classification framework, there are two important caveats. First, when applying the PASCS-
569 MP method to refine MMS, we generally cannot visualize the selected features. To some extent,
570 this decreases the interpretability of the effects, although it is still possible to visualize
571 statistically significant regions as in our prior group difference studies (Shi et al., 2013b; Wang
572 et al., 2013). However, in our recent work (Zhang et al., 2018), instead of randomly selecting

573 patches to build the initial dictionary, we use group lasso screening to select the most significant
574 features first. Therefore, the features used in sparse coding may be visualized on the surface
575 map. In the future, we will incorporate this idea into the PASCS-MP framework to make it
576 more interpretable. Second, this work only applies hippocampal MMS to predict A β positivity.
577 In future work, we plan to introduce more AD risk factors (such as demographic information,
578 genetic information and clinical assessments) (Ansart et al., 2020; Pekkala et al., 2020; Tosun
579 et al., 2014), and more AD regions of interest (ROIs, e.g., ventricles, entorhinal cortex, temporal
580 lobes) (Brier et al., 2016; Dong et al., 2020b; Foley et al., 2017) into our proposed framework;
581 these additional features are expected to improve the A β positivity prediction.

582 **5. CONCLUSION**

583 In this paper, we explore the association between hippocampal structures and A β positivity
584 on two independent databases using our hippocampal MMS, PASCS-MP method and a random
585 forest classifier. Compared to traditional hippocampal shape measures, MMS have superior
586 performance for predicting A β positivity in the AD continuum. Besides, the proposed PASCS-
587 MP outperforms our previous sparse coding method (PASS-MP) on refining MMS features.
588 Compared to similar studies, this work achieves state-of-the-art performance when predicting
589 A β positivity based on MRI biomarkers. In future, we plan to apply this proposed framework
590 to other AD ROIs and further improve the comprehensibility of the framework by visualizing
591 morphometry features selected in the classification.

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