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Pairing-based Ensemble Classifier Learning using Convolutional Brain Multiplexes & Multi-view Brain Networks for Early Dementia Diagnosis

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Abstract. The majority of works using brain connectomics for dementia diagnosis heavily relied on using structural (diffusion MRI) and functional brain connectivity (functional MRI). However, how early dementia affects the morphology of the cortical surface remains poorly understood. In this paper, we first introduce *multi-view morphological brain network* architecture which stacks multiple networks, each quantifying a cortical attribute (e.g., thickness). Second, to model the relationship between brain views, we propose a subject-specific *convolutional brain multiplex* composed of intra-layers (brain views) and inter-layers between them by convolving two consecutive views. By reordering the intra-layers, we generate different multiplexes for each subject. Third, to distinguish demented brains from healthy ones, we propose a *pairing-based ensemble classifier learning strategy*, which projects each pair of brain multiplex sets onto a low-dimensional space where they are fused, then classified. Our framework achieved the best classification results for the right hemisphere 90.8% and the left hemisphere 89.5%.

1 Introduction

Early diagnosis of brain dementia, specifically mild cognitive impairment (MCI) which may convert to Alzheimer's disease (AD), is critical for the early intervention, to prevent the onset of AD. Machine learning approaches have been successfully employed in diagnosing AD based on images obtained from MRI [1], which provide an efficient and non-invasive way for investigating neurological disorders at a whole-brain level. On a brain *connectional* level, network analysis of functional and structural brain connectivity (obtained from functional MRI (fMRI) and diffusion-weighted MRI (dMRI)) helped identify dementia biomarkers and brain connections affected by this neurodegenerative disorder [2]. Recently, more research has focused on accurate detection of early mild cognitive impairment (eMCI), which is essential for slowing down potential conversion to AD. For instance, [3] investigated the predictive power of various combinations

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of connectomic features, such as pairwise connectivity and maximum flow between two brain regions, extracted from dMRI images for eMCI and normal control (NC) classification problem. On the other hand, [4] computed sparse temporal networks using sliding-window approach over a time series of resting-state functional MRI. [5] extended this work by additionally considering the high-order correlation between different pairs of brain regions. By combining low-order with high-order correlations, they further improved the classification accuracy of eMCI/NC.

Although dementia has been shown to affect neuronal connections in the brain as well as the cortical surface causing cortical thinning [6], research exploring *morphological connectivity* of the cortex is almost absent [1]. More specifically, how the shape of a cortical brain region gets affected *in relation* to the shape of another cortical brain region using various shape measurements (e.g., curvature, sulcal depth) remains somewhat unexplored. To address these limitations, we propose to use morphological cortical networks for dementia onset identification. Additionally to using one-layer network (considering only one morphological view, such as cortical thickness), we construct a multi-layer network (multiplex), consisting of multiple morphological views. Previous research showed that using multi-layer networks (i.e., stacking different networks) improved the prediction accuracy for disease identification when compared to using single view networks. Some of these works included classification of NC/MCI/AD using combination of features from MRI, PET, and CSF [7], structural inter- and intra-subject brain similarities in MRI [8], both confirming that multiplex network features yield better classification results in comparison to using low-level features. Other works, not concerned with MCI/AD, used multiplexes for simultaneous analysis of anatomical and functional brain networks [9] and varied frequency in fMRI to find important functional brain regions affected by schizophrenia [10].

However, none of these multiplex-based methods explored the *relationship* between two consecutive layers in the multiplex or *cortical morphology*. Specifically, to the best of our knowledge, no previous methods explored the similarity between layers in a typical multi-layer network for modeling brain connectivity [1]. We note that simple concatenation of multiple networks hinders the investigation of potentially *complex* changes in cortical regions, which might vary jointly or independently across different brain views as they become affected by dementia onset. Hence, we introduce *inter-layers* into a multiplex structure to capture the relationship between different brain views. Basically, each brain multiplex consists of different morphological views (intra-layers) and inter-layers splipped between two consecutive intra-layers, thereby quantifying the relationship between two consecutive brain views.

Since each multiplex is not invariant to the ordering of the intra-layers, we generate multiple multiplexes for each subject while considering all possible combinations of intra-layers, thereby capturing all relationship between different brain views in a more holistic manner. Fusing information from different brain multiplexes is crucial for more accurate identification of the demented brain state since each brain multiplex captures a unique relationship between brain views,

Table 1: *Major mathematical notations used in this paper.*

Mathematical notation	Definition
$\mathbf{V}$	brain network (single view) in $\mathbb{R}^{n \times n}$
$\mathcal{M}$	brain multiplex composed of intra-layers and convolutional inter-layers
$\mathbf{C}_{i,j}$	convolutional intra-layer between consecutive brain network views $\mathbf{V}_i$ and $\mathbf{V}_j$ in $\mathcal{M}$
$\mathbb{M} = \{\mathcal{M}_1, \ldots, \mathcal{M}_N\}$	subject-specific brain multiplexes with different orderings of intra-layers
$\mathbf{M}_k$	matrix in $\mathbb{R}^{d \times N_s}$ containing the d multiplex features for all N_s training samples from multiplex $\mathcal{M}_k \in \mathbb{M}$
$\mathbf{M}_{k,l} = [\mathbf{M}_k, \mathbf{M}_l]$	paired multiplex feature matrices derived from two training multiplexes in $\mathbb{M}$
$[\mathbf{B}_k, \mathbf{B}_l]$	CCA basis matrices spanning the canonical space where $\mathbf{M}_k$ and $\mathbf{M}_l$ are projected
$\mathbf{\Sigma_{k,l}}$	covariance matrix of paired training multiplex matrices $\mathbf{M}_k$ and $\mathbf{M}_l$
$\mathbf{W}_k$	transformation matrix from the original multiplex space to the low-dimensional canonical multiplex space
$\mathbf{\Lambda}^2$	diagonal matrix of eigenvalues (i.e., canonical correlations squared)
$\tilde{\mathbf{M}}_k$	canonical representation of multiplex $\mathcal{M}_k$ projected onto CCA space
$\hat{\mathbf{M}}_{k,l}$	fused CCA-mapped multiplex feature matrices of original multiplexes $\mathcal{M}_k$ and $\mathcal{M}_l$
$\mathbf{I}$	identity matrix in $\mathbb{R}^{d \times d}$

which can help unravel the complex nature of brain disorders for more accurate diagnosis. However, most existing network fusion methods often extract features independently from each network, and then simply concatenate them into a long feature vector for classification [1], while overlooking the correlation between them. To address this issue, we propose to use canonical correlation analysis (CCA) to map two sets of features into a shared space where they become more comparable [12,11]. CCA was shown to yield more discriminative features than any of the input feature vectors alone or their simple concatenation [11]. Since we are not restricted to only two sets of features as in [11], we propose a novel pairing-based CCA mapping of multiple sets of brain multiplexes, where each pair of multiplex sets is mapped onto a CCA space then fused. Ultimately, in the spirit of ensemble classifier learning, we input the fused multiplex features to train a linear classifier in each spanned CCA space.

Overall, we propose three fundamental contributions to the state-of-the-art of brain network analysis in order to identify dementia in its early stage: (1) brain multiplex structure based on cortical morphology, (2) pairing-based ensemble classifier learning strategy using CCA-mapped sets of brain connectomic features, and (3) giving new insights into how the early stage of MCI affects *morphological* brain connectivity in left and right cortical hemispheres.

2 Ensemble Classifier using Paired CCA-mapped Convolutional Brain Mutliplexes for eMCI/NC Classification

In this section, we introduce the concept of a convolutional brain multiplex and present our novel canonical ensemble classifier learning technique using paired sets of brain multiplexes. Matrices are denoted by boldface capital letters, e.g., $\mathbf{X}$, and scalars are denoted by lowercase letters, e.g., x. We denote the transpose operator and the trace operator as $\mathbf{X}^T$ and $tr(\mathbf{X})$, respectively. For easy reference and enhancing the readability, we have summarized the major mathematical notations in **Table**

• ***Step 1: Convolutional brain multiplex construction and feature extraction.*** In a generic way, we define a brain multiplex $\mathcal{M}$ using a set of M

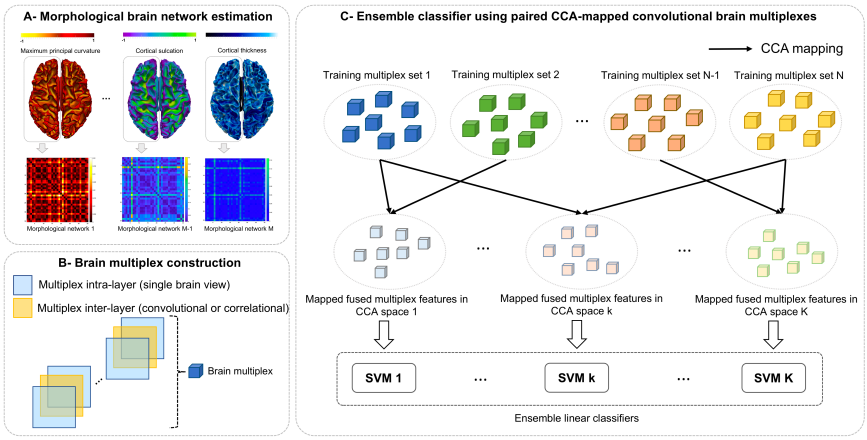

Fig. 1: *Pipeline of the proposed pairing-based ensemble classifier learning using fused convolutional brain multiplexes.* (A) Morphological brain network construction using different cortical attributes. (B) Brain multiplex construction. (C) We use canonical correlation analysis (CCA) to first project a pair of multiplex sets onto a common space where they become more comparable, then fuse them together to train a linear SVM classifier.

intra-layers $\{\mathbf{V}_1, \ldots, \mathbf{V}_M\}$, each representing a single view of the brain morphology, (i.e., cortical attribute), where between two consecutive intra-layers $\mathbf{V}_i$ and $\mathbf{V}_j$ we slide an inter-layer $\mathbf{C}_{i,j}$. This yields to the following multiplex architecture: $\mathcal{M} = \{\mathbf{V}_1, C_{1,2}, \mathbf{V}_2, \ldots, \mathbf{V}_j, \mathbf{C}_{i,j}, \mathbf{V}_j, \ldots, \mathbf{V}_M\}$. Each inter-layer is defined by convolving two consecutive intra-layers. Each element in row a and column b within the convolutional inter-layer matrix $\mathbf{C}_{i,j}$ between views $\mathbf{V}_i$ and $\mathbf{V}_j$ is defined as: $\mathbf{C}_{i,j}(a,b) = \sum_p \sum_q \mathbf{V}_i(p,q)\mathbf{V}_j(a-p+1, b-q+1)$. We note that for a specific multiplex, we are only allowed to explore similarities between consecutive layers. Hence, to explore the inter-relationship between all possible combinations of intra-layers, we generate for each subject N multiplexes through simply reordering the intra-layer networks, thereby generating an *ensemble multiplexes* $\mathbb{M} = \{\mathcal{M}_1, \ldots, \mathcal{M}_N\}$ (**Fig.**

Since the morphological brain connectivity matrices are symmetric (**Fig.**

• ***Step 2: Pairing-based ensemble classifier learning using canonical mapping of brain multiplex sets.*** Since each multiplex $\mathcal{M}_k \in \mathbb{M}$ captures a unique and complex relationship between different brain network views, one needs to examine all morphological brain multiplexes in the ensemble $\mathbb{M}$. This will provide us with a more holistic understanding of how explicit morphological brain connections can be altered by dementia onset as well as how their implicit high-order (a connection of connections) relationship can be affected. However, due to complex nature of the multiplex structure, feature reduction method is required to reduce the redundancy of the data by extracting the most representative features. Instead of extracting features from different multiplexes independently, and motivated by the fact that canonical correlation analysis is efficient in analyzing and fusing associations between two sets of variables [11,12],

we propose a pairing-based CCA mapping strategy of sets of multiplexes of our training samples for brain multiplex feature fusion.

Suppose that $\mathbf{M}_k \in \mathbb{R}^{d \times N_s}$ and $\mathbf{M}_l \in \mathbb{R}^{d \times N_s}$ are two training multiplex feature matrices derived from two different multiplexes in $\mathbb{M}$, where N_s denotes the number of training samples. For each pair of multiplexes $\mathbf{M}_{k,l} = [\mathbf{M}_k, \mathbf{M}_l]$, we define their covariance matrix $\mathbf{\Sigma}_{k,l} = \begin{pmatrix} cov(\mathbf{M}_k) & cov(\mathbf{M}_k, \mathbf{M}_l) \\ cov(\mathbf{M}_l, \mathbf{M}_k) & cov(\mathbf{M}_l) \end{pmatrix}$, where $cov(\mathbf{M}_k) = \mathbf{M}_k\mathbf{M}_k^T$ denotes the within-set covariance matrix of $\mathbf{M}_k$, and $cov(\mathbf{M}_k, \mathbf{M}_l) = \mathbf{M}_k\mathbf{M}_l^T$ denotes the between-set covariance matrix of $\mathbf{M}_k$ and $\mathbf{M}_l$. To map both training multiplex matrices onto a space where the respective distributions of their features are more 'aligned' and easily comparable, we aim to maximize the pair-wise correlation across the two matrices $\mathbf{M}_k$ and $\mathbf{M}_l$: $corr(\hat{\mathbf{M}}_k, \hat{\mathbf{M}}_l) = \frac{cov(\hat{\mathbf{M}}_k, \hat{\mathbf{M}}_l)}{var(\hat{\mathbf{M}}_k) \cdot var(\hat{\mathbf{M}}_l)}$, where $\hat{\mathbf{M}}_k$ denotes the linear CCA mapping of the multiplex feature matrix $\mathbf{M}_k$ to the canonical shared space using the estimated transformation matrix $\mathbf{W}_k^T$ such that $\hat{\mathbf{M}}_k = \mathbf{W}_k^T\mathbf{M}_k$. Similarly, the second set of training multiplex features $\mathbf{M}_l$ is mapped using the estimated transformation matrix $\mathbf{W}_l^T$. More precisely, $cov(\hat{\mathbf{M}}_k, \hat{\mathbf{M}}_l)$ is defined as $\mathbf{W}_k^T cov(\mathbf{M}_k, \mathbf{M}_l)\mathbf{W}_l$, $var(\hat{\mathbf{M}}_k)$ as $\mathbf{W}_k^T cov(\mathbf{M}_k)\mathbf{W}_k$, and $var(\hat{\mathbf{M}}_l)$ as $\mathbf{W}_l^T cov(\mathbf{M}_l)\mathbf{W}_l$.

Both canonical transformation matrices are estimated through maximizing the covariance between the mapped multiplex feature matrices $\hat{\mathbf{M}}_k$ and $\hat{\mathbf{M}}_l$, constrained to $var(\hat{\mathbf{M}}_l) = var(\hat{\mathbf{M}}_k) = I$, using Lagrange multipliers. This is achieved through solving the following eigenvector equations:

$$\begin{cases} cov(\mathbf{M}_k)^{-1} cov(\mathbf{M}_k, \mathbf{M}_l) cov(\mathbf{M}_l)^{-1} cov(\mathbf{M}_l, \mathbf{M}_k)\hat{\mathbf{W}}_k = \mathbf{\Lambda}^2\hat{\mathbf{W}}_k \\ cov(\mathbf{M}_l)^{-1} cov(\mathbf{M}_l, \mathbf{M}_k) cov(\mathbf{M}_k)^{-1} cov(\mathbf{M}_k, \mathbf{M}_l)\hat{\mathbf{W}}_l = \mathbf{\Lambda}^2\hat{\mathbf{W}}_l \end{cases},$$

where $\hat{\mathbf{W}}_k$ and $\hat{\mathbf{W}}_l$ denote the eigenvectors and $\mathbf{\Lambda}^2$ represent the diagonal matrix of eigenvalues (i.e., canonical correlations squared). The dimension of the canonical shared space is defined as the rank of covariance matrix between both multiplex feature matrices. Ultimately, each transformation matrix $\mathbf{W}_k$ is generated through sorting the eigenvectors in $\hat{\mathbf{W}}_k$ with non-zero eigenvalues. To perform paired multiplex feature fusion in the canonical space, we simply concatenate the transformed multiplex features as follows:

$$\hat{\mathbf{M}}_{k,l} = \begin{pmatrix} \hat{\mathbf{M}}_k \\ \hat{\mathbf{M}}_l \end{pmatrix} = \begin{pmatrix} \mathbf{W}_k^T\mathbf{M}_k \\ \mathbf{W}_l^T\mathbf{M}_l \end{pmatrix} = \begin{pmatrix} \mathbf{W}_k & 0 \\ 0 & \mathbf{W}_l \end{pmatrix}^T \begin{pmatrix} \mathbf{M}_k \\ \mathbf{M}_l \end{pmatrix}$$

Next, we use each fused pair of training multiplex feature matrices $\hat{\mathbf{M}}_{k,l}$ to train a linear support vector machine (SVM) classifier (**Fig.**

3 Results and Discussion

Evaluation dataset. We used leave-one-out cross validation to evaluate the proposed classification framework on 76 subjects (35 eMCI and 41 NC) from ADNI GO public dataset[1], each with structural T1-w MR image [13]. We note that the 35 eMCI samples comprise the first and last acquisition timepoints for 18 different eMCI subjects, which are largely spaced out in time. Hence,

[1] http://adni.loni.usc.edu

we assume that these two distant timepoints can simulate two different eMCI subjects. We used FREESURFER to reconstruct both right and left cortical hemispheres for each subject from T1-w MRI [**?**]. Then we parcellated each cortical hemisphere into 35 cortical regions using Desikan-Killiany Atlas. We defined $N = 6$ multiplexes, each using $M = 4$ cortical network views. For each cortical attribute (signal on the cortical surface), we compute the strength of the morphological network connection linking i^{th} ROI to the j^{th} ROI as the absolute difference between the averaged attribute values in both ROIs. Multiplex $\mathcal{M}_1$ includes cortical attribute views $\{\mathbf{V}_1, \mathbf{V}_2, \mathbf{V}_3, \mathbf{V}_4\}$, $\mathcal{M}_2$ includes $\{\mathbf{V}_1, \mathbf{V}_2, \mathbf{V}_4, \mathbf{V}_3\}$, $\mathcal{M}_3$ includes $\{\mathbf{V}_1, \mathbf{V}_3, \mathbf{V}_4, \mathbf{V}_2\}$, $\mathcal{M}_4$ includes $\{\mathbf{V}_1, \mathbf{V}_3, \mathbf{V}_2, \mathbf{V}_4\}$, $\mathcal{M}_5$ includes $\{\mathbf{V}_1, \mathbf{V}_4, \mathbf{V}_2, \mathbf{V}_3\}$, and $\mathcal{M}_6$ includes $\{\mathbf{V}_1, \mathbf{V}_4, \mathbf{V}_3, \mathbf{V}_2\}$. For each cortical region, $\mathbf{V}_1$ denotes the maximum principal curvature brain view, $\mathbf{V}_2$ denotes the mean cortical thickness brain view, $\mathbf{V}_3$ denotes the mean sulcal depth brain view, and $\mathbf{V}_4$ denotes the mean of average curvature.

Table 2. *eMCI/NC classification accuracy using our method and different comparison methods.*

		Left Hemisphere				Right Hemisphere			
Classifier	Method	Accuracy (%)	AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC	Sensitivity (%)	Specificity (%)
Single SVM	View 1	68.4	75.9	65.7	70.7	75.0	85.1	82.9	68.3
	View 2	77.6	83.9	82.9	73.2	81.6	85.3	85.7	78.0
	View 3	77.6	83.5	77.1	78.0	71.1	87.2	74.3	68.3
	View 4	53.9	53.5	0.0	100.0	53.9	46.3	0.0	100.0
	All Views Concatenated	81.6	88.3	85.7	78.0	86.8	89.1	88.6	85.4
Ensemble classifiers	Views	81.6	90.5	65.7	**95.1**	82.9	94.1	74.3	**90.2**
	Correlation	81.6	88.1	80.0	82.9	85.5	**96.7**	**91.4**	80.5
	Convolution	85.5	91.1	82.9	87.8	76.3	86.4	77.1	75.6
Ensemble paired classifiers	Views	86.8	90.7	88.6	85.4	85.5	93.2	85.7	85.4
	Correlation	78.9	87.0	80.0	78.0	84.2	96.3	88.6	80.5
	Convolution	80.3	88.6	80.0	80.5	72.4	82.0	74.3	70.7
Ensemble CCA paired classifiers	Views	80.3	86.9	77.1	82.9	**90.8**	95.7	**91.4**	**90.2**
	Correlation	85.5	89.7	88.6	82.9	84.2	94.8	88.6	80.5
	Convolution	**89.5**	**92.2**	**91.4**	87.8	84.2	90.0	85.7	82.9

Comparison methods and evaluation. For our eMCI/NC classification task, we benchmarked our pairing-based ensemble classifier strategy against: (1) using single SVM trained on each brain view, and on the concatenated views, (2) ensemble SVM classifiers (without the pairing or CCA mapping strategies), and (3) ensemble paired SVM classifiers (without CCA mapping). For each of these methods, we generate three classification results using: (1) features from brain views, (2) features from correlational multiplexes (inter-layer computed using Pearson correlation), and (3) features from convolutional multiplexes (inter-layer computed using 2D convolution). For evaluation, we report in **Table** 2 the prediction accuracy, the area under the receiver operating characteristic (ROC) curve, the sensitivity and specificity of the eMCI/NC classification task. In **Fig.**

4 Conclusion

We propose a novel pairing-based ensemble classifier strategy that fuses morphological multi-view brain networks as well as convolutional brain multiplexes for distinguishing between eMCI patients and healthy controls. The performance of our method gave us insights into how dementia might affect the right and the left

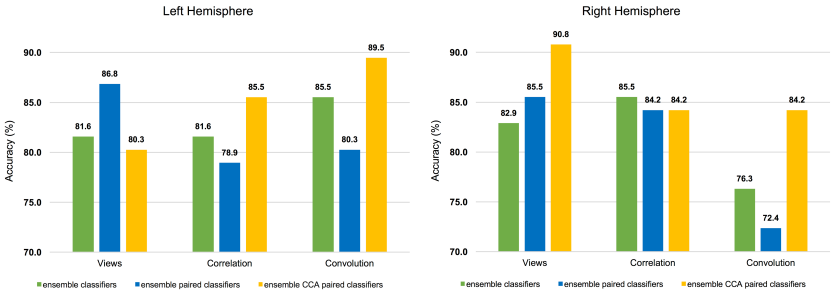

Fig. 2: *Classification accuracies for our proposed pairing-based ensemble classifier learning of CCA-mapped brain features and comparison ensemble classifier methods.* Views: concatenated brain views. Correlation: correlational brain multiplexes. Convolution: Convolutional brain multiplexes. Ensemble classifiers: one SVM trained for each view (or multiplex) without any pairing strategy or CCA mapping. Ensemble paired classifiers: pairing different views (or multiplexes) without CCA mapping. Ensemble CCA paired classifiers: pairing different views (or multiplexes) with CCA mapping.

hemispheres in its early stage: complex connectional alterations in cortical morphology spanning multiple cortical attributes of the left hemisphere (captured by the multiplex), and simple alterations across different brain views in the right hemisphere (captured by the morphological multi-view network). In our future work, we will integrate functional and diffusion networks in our multiplex structure to explore how the relationship between *multimodal* connectomic views is altered with dementia onset.

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