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UNCOVERING ACTIVE STRUCTURAL SUBSPACES ASSOCIATED WITH CHANGES IN INDICATORS FOR ALZHEIMER'S DISEASE

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ABSTRACT

We present a framework for identifying subspaces in the brain that are associated with changes in biological and cognitive indicators for a given disorder. By employing a method called active subspace learning (ASL) on structural MRI features from an Alzheimer's disease dataset, we identify subsets of regions that form co-varying subspaces in association with biological age and mini-mental state exam (MMSE) scores. Features generated by projecting structural MRI components onto these subspaces performed equally well on regression tasks when compared to non-transformed features as well as PCA-based transformations. Thus, without compromising on predictive performance, we present a way to extract sparse subspaces in the brain which are associated with a particular disorder but inferred only from the neuroimaging data along with relevant biological and cognitive test measures.

Clinical relevance— This work provides a way to identify active structural subspaces in the brain, i.e. subsets of brain regions which collectively change the most, in association with changes in the indicators of a given disorder.

1. INTRODUCTION

Studying the risk of progression into various brain disorders has become increasingly important in the field of neuroscience. Many machine learning based methods have been developed to study neuroimaging data towards this goal. While some methods involve prediction and diagnosis [1], many studies have worked on identifying associated indicators for the disorders [2, 3]. These indicators could be based on putative biomarkers inferred from neuroimaging data, often defined by taking into account biological traits and cognitive performance scores of the subjects. Studying neuroimaging-based biomarkers not only helps diagnose a condition better, but also to understand its working in the brain in terms of involved regions and networks. Recent work has shown that rather than changes in only individual brain regions, many brain disorders involve collective co-varying changes in various subspaces of the brain defined by the structural or functional sub-networks [4]. Thus there is an increased interest in frameworks that do not account for individual brain regions separately, but synthesize patterns from all regions when studying subspace structures in the brain.

In this paper, we use a mathematical framework called active subspace learning (ASL) to identify structural subspaces in the brain that are associated with AD-related predictors including age and Mini-Mental State Examination (MMSE) scores. The active subspace analysis performs eigen-decomposition on the outer-product of the gradient of a mapping function defined from structural MRI based features to the target variables. The most prominent eigen-vectors are then used to determine the directions (subspaces) that covary the most with respect to the given mapping between structural features and the target variables. Finally, we demonstrate that the features generated by projecting structural MRI (sMRI) component features onto these active subspaces are very similar to baseline methods in terms of predictive performance for age and MMSE scores. Thus, the ASL framework helps in learning active structural subspaces in the brain that co-vary together in association with the target variables, while still maintaining a comparably good performance to baseline feature transformation methods that do not take the target variable information into account while computing subspaces.

2. METHODS

2.1. Dataset Pre-Processing and scICA Components

Structural MRI (sMRI) features from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset [5] were used with 828 subjects (M/F = 443/385) that passed the specific requirements for class selection and pre-processing quality. The dataset includes 237 cognitively normal (CN), 189 progressive mild cognitive impairment (pMCI), 245 stable mild

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cognitive impairment (sMCI) and 157 Alzheimer's Disease subjects. Target variables used for the analysis include age (range=59.7-89.6, mean=74.3, std=5.9 years) and MMSE scores (range=19-30, mean=27.1, std=2.65). Due to brevity requirements in this manuscript, details on group-wise distribution of age and MMSE can be accessed in [6].

Pre-processing of sMRI data, subject exclusion and usage of scan visits were done as in [6] using standard preprocessing pipeline with SPM12 toolbox and Matlab 2016. The pre-processed images were warped onto the standard MNI space, each resulting in a voxel-level gray matter volume (GMV) map from the MRI data.

Spatially constrained independent component analysis (scICA) [7] was done on the pre-processed data using the Neuromark framework [2], resulting in 30 covarying structural components. From each component, top 1% best scoring voxel-level GMV features were selected based on univariate statistical tests on separate training data. This finally resulted in 5373 features belonging to 30 structural scICA components.

2.2. Active Subspace Analysis

Let $\mathbf{x} \in \mathbb{R}^m$ be a point in the space of the input data with m features. Consider a function $f : \mathbb{R}^m \rightarrow \mathbb{R}$ that maps the input space to the real space. f could be the regression function for a given score in our case. The Active Subspace Analysis framework [8] is based on the eigen-decomposition of the expected covariance (outer-product) of the gradient of f given as follows:

$$\mathbf{C} = \mathbb{E}\left[(\nabla_x f)(\nabla_x f)^T\right] \tag{1}$$

The matrix $\mathbf{C}$ can be estimated as $\hat{\mathbf{C}}$ from the data. We use the fact that if f is the Gaussian Process Regression function, then $\hat{\mathbf{C}}$ can be computed as a closed-form estimation of $\mathbf{C}$ from the dataset of sample size n, $[\mathbf{X}, \mathbf{y}]$ with input features $\mathbf{X} \in \mathbb{R}^{m \times n}$, and target variable $\mathbf{y} \in \mathbb{R}^n$ [9].

The eigen-decomposition of $\mathbf{C}$ can be used to create a set of active subspaces based on the eigenvectors corresponding to significantly larger set of eigenvalues as below. These active subspaces, as subset of active eigen-vectors of $\mathbf{C}$ can also be used to recreate a set of transformed features $\hat{\mathbf{X}}$.

$$\mathbf{C} = \mathbf{W}\mathbf{\Lambda}\mathbf{W}^T \tag{2}$$

$$\mathbf{\Lambda} = \begin{bmatrix} \mathbf{\Lambda}_1 & \\ & \mathbf{\Lambda}_2 \end{bmatrix}, \ \mathbf{W} = [\mathbf{W}_1 \ \mathbf{W}_2], \tag{3}$$

$$\text{such that } \mathbf{\Lambda}_2 \approx \mathbf{0}, \text{and } \lambda_i \gg 0 \ \forall \lambda_i \in \mathbf{\Lambda}_1$$

$$\hat{\mathbf{X}} = \mathbf{W}_1^T \mathbf{X} \tag{4}$$

In the case of structural MRI data, this analysis can have two-fold usage involving subspace identification and generation of transformed features as discussed subsequently.

2.3. Identification of Structural Subspaces in the Brain

If a given active eigenvector represented by a column of $\mathbf{W}_1$ is sparse, we can identify features (components or brain-regions in case of structural data) which together form the active subspace corresponding to that eigenvector. This subspace can be said to be associated with the quantity that the target variable $\mathbf{y}$ for the regression function f in Equation 1 represents, which in this case could be a certain cognitive or clinical score. In terms of structural MRI features, this can be interpreted as identifying structural subspaces in the brain (subsets of regions) corresponding to active variables from the data. These subspaces are essentially a linear combination of structural features that co-vary the most in association with changes in a given cognitive or biological trait.

2.4. Using Transformed Features for Learning

In addition to subspace identification, the transformed feature matrix $\hat{\mathbf{X}}$ (referred to as ASL features in the paper) in Equation 4 can be used as input features to various machine learning algorithms. After an initial trial of regression methods, Support Vector Regression (SVR) with radial kernel was used to study the performance of the ASL features with age and MMSE scores as target variables. The non-transformed structural features matrix $\mathbf{X}$ (referred to as STR features hereafter) was used as a baseline for performance comparison.

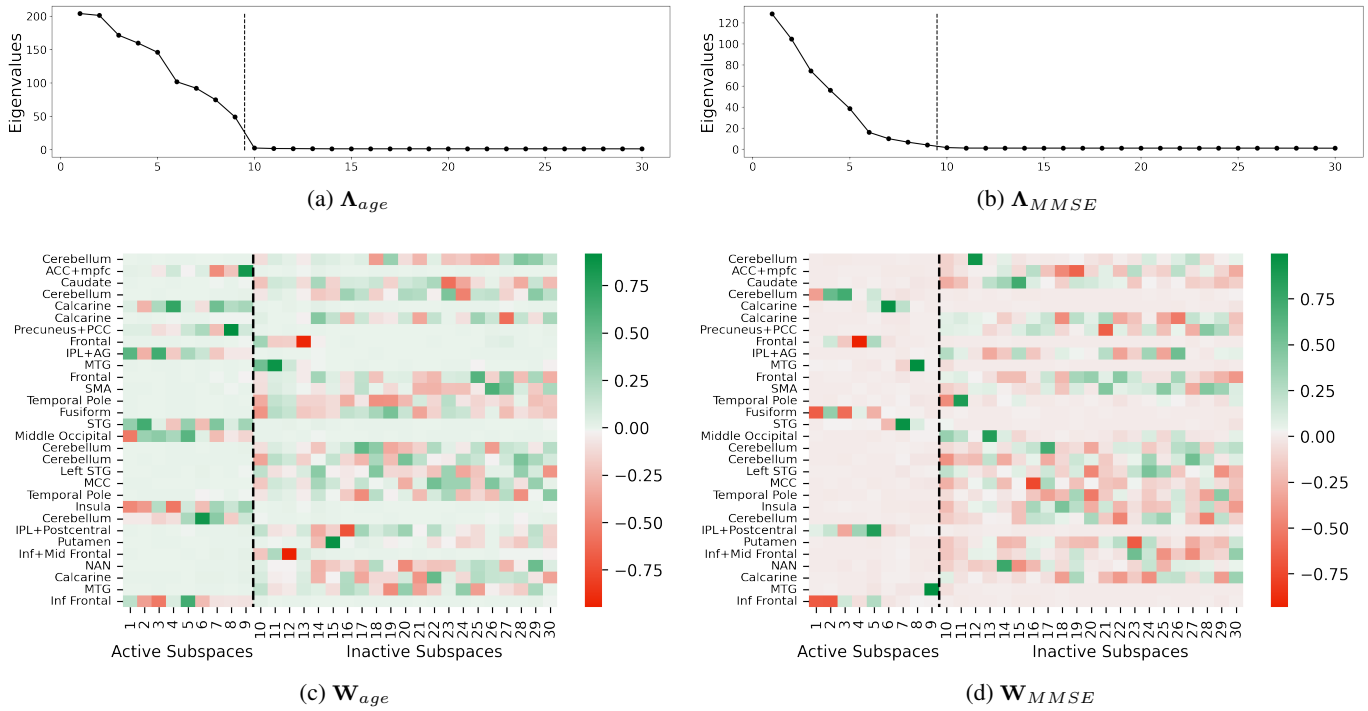
ASL features were compared with other feature transformation methods based on principle component analysis (PCA), including the standard PCA, kernel PCA with linear (kPCAl) as well as radial kernels (kPCAr), and also sparse PCA (sPCA). Principle components with significantly non-zero value of explained variance were used for reconstructing transformed features for comparison. A total of 100 repetitions of SVR analysis with age and MMSE score as target variables were done for all the aforementioned methods (STR, ASL, PCA, kPCAl, kPCAr and sPCA), with 4-fold cross validation of the training set and testing on 20% held-out data.

3. RESULTS

3.1. Active Structural Subspaces

ASL analysis was done as in 2.2 to compute the eigen-matrix $\mathbf{W} = [\mathbf{W}_1 \ \mathbf{W}_2]$, with division into $\mathbf{W}_1$ and $\mathbf{W}_2$ being done based on a threshold eigenvalue ($\lambda \geq 1$). This value was selected based on the observation of the eigenvalue spectrum shown in Figure 1a,1b. The matrix $\mathbf{W}_1$ indeed is sparse in the case of structural MRI features based on this threshold, with each of its sparse column vector representing a structural subspace associated with the target variable at hand (Figure 1).

As it can be noted, there are multiple active structural subspaces formed by the structural components in association with age (Figure 1c) as well as MMSE score (Figure 1d).

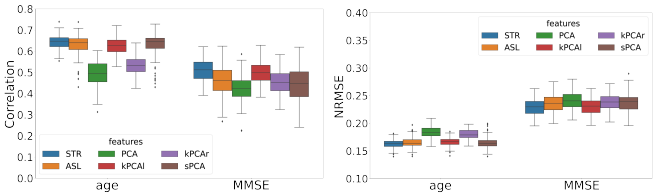


(a) $\mathbf{\Lambda}_{age}$ (b) $\mathbf{\Lambda}_{MMSE}$

(c) $\mathbf{W}_{age}$ (d) $\mathbf{W}_{MMSE}$

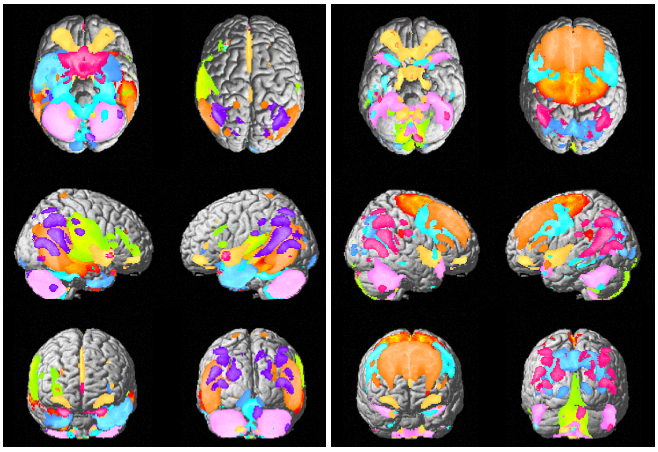
Fig. 1: Eigenvalues for subspaces associated with (a) age, and (b) MMSE score. In this context, eigenvalues represent the extent to which the subspace features co-vary together in association with the target variable. Corresponding subspace matrices are shown for (c) age, and (d) MMSE scores. Each column of the matrix represents a structural subspace of the brain, with each row element representing the weighted contribution (between -1 and 1) of the brain component in the corresponding subspace column. Active and inactive subspaces based on eigenvalue threshold (=1) are separated by the vertical dashed black line. It can be noticed that the active subspaces are indeed sparse.

The subspaces related to age include components from precuneus, posterior/anterior cingulate cortex (PCC/ACC), inferior parietal lobule (IPL), superior temporal gyrus (STG), insula, cerebellum, inferior frontal region. The regions forming subspaces associated with the MMSE scores include IPL, fusiform gyrus, and cerebellum as well as temporal regions including medial temporal gyrus (MTG) and STG. These associated components are visualized in Figure 3.



(a) Pearson's Correlation Coefficient (b) NRMSE

Fig. 2: Support Vector Regression (SVR) performance comparison on age and MMSE scores. (a) pearson correlation and (b) normalized root mean square error are shown for ASL features generated by projecting structural component features onto the active subspaces. Comparison is done with non-transformed structural features (STR) and PCA-based feature transformations: standard PCA, kernel PCA with linear (kPCAl), radial kernels (kPCAr), and sparse PCA (sPCA).



(a) Age (b) MMSE

Fig. 3: Maps for structural brain components (in different colors) that constitute active subspaces associated with (a) Age, (b) MMSE.

3.2. Performance in Comparison with Baseline methods

Results from the performance for age and MMSE regression are shown in Figure 2 for non-transformed baseline structural features (STR) as well as transformed ASL and PCA fea-

tures described in 2.4. Pearson correlation and normalized root mean squared error (NRMSE) were used for performance comparison. ASL features performed comparably well to STR and PCA based methods. Despite the significance ($p < .05$), the differences in mean performance was very small (within .02, .05 in correlation for age, MMSE respectively; within .01 for NRMSE). This indicates that the transformation from $\mathbf{X}$ to $\hat{\mathbf{X}}$ in ASL analysis (Equation 4) retains the predictive information in the structural features like other transformations. However, unlike PCA which only transforms the feature data, ASL analysis additionally utilizes information from the target variable to identify structural subspaces associated with it.

4. CONCLUSIONS

Through this work, we demonstrate an effective way to identify subspaces in the brain associated the most with changes in indicators for Alzheimer's Disease. Structural brain components forming these subspaces involve alteration patterns that co-vary together the most in coherence with age and MMSE scores as targets. Our analysis shows that the subspaces indeed are sparse, indicating the effectiveness in identifying specific brain regions associated with the condition at hand.

The structural subspaces associated with age included components from the PCC, thalamus, insula, cerebellum and temporal regions, all of which are known to be affected in AD and MCI [10–12]. Similarly, the subspaces associated with MMSE were comprised of areas with previously known associations [11, 13, 14], including IPL and temporal regions including fusiform, STG, MTG along with frontal regions. Moreover, our method performs comparably well compared to existing baseline and PCA-based feature transformation methods. While PCA is a very generic approach to compute principle components of variance inherent in the data without considering target variables, ASL analysis identifies subspaces that specifically associate with a target variable at hand.

Our work provides a general framework to identify associated structural subspaces in the brain for a given biological, cognitive or behavioral measure. Rather than analyzing individual brain components separately for associative patterns, the ASL framework computes the structural subspaces using features from all components. While this work is limited to measures related to biological age and cognitive performance (MMSE), the same model can be extended to other measures associated with various disorders or other cognitive properties in a healthy subjects. Future work could include frameworks with more measures and modalities to create subspaces from multimodal neuroimaging data, as well as usage of this framework as a semi-supervised learning method for diagnosis and characteristic differentiation of brain disorders.

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