Fusing functional signals by sparse canonical correlation analysis improves network reproducibility

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Abstract. We contribute a novel multivariate strategy for computing brain network structure from arterial spin labeling (ASL) MRI. Our method, X, fuses and correlates multiple functional signals by employing an interpretable dimensionality reduction method, sparse canonical correlation analysis (SCCA). There are two key aspects of this contribution. First, we show how SCCA may be used to compute a multivariate correlation between different regions of interest (ROI). In contrast to averaging signal over the ROI, this approach exploits the full information within the ROIs. Second, we show how SCCA may simultaneoulsy exploit both the BOLD and ASL-based cerebral blood flow (CBF) time series to produce network measurements. Our approach to fusing multiple time signals in network studies improves reproducibility over standard approaches while retaining the interpretability afforded by the classic ROI seed-based methods. We show experimentally in test-retest data that our sparse CCA method extracts biologically plausible and stable network structures from ASL. We compare the ROI approach to the CCA approach while using CBF measurements alone. We then compare these results to the joint BOLD-CBF networks in a reproducibility study and in studying network structure in traumatic brain injury (TBI) patients. In TBI, standard seed-based approaches may fail due to local injury which makes averaging over a full ROI less meaningful. We detail the algorithm and show experimental evidence of its efficacy in a clinically relevant TBI population. Our results show that X ....

Introduction

Functional MRI (fMRI) is capable of measuring subject-specific and long-range correlations in brain activity (i.e. networks) as measured by changes in a direct or indirect time-series measurement of cerebral blood flow (CBF). BOLD fMRI is the standard protocol for studying network structure []. A second approach, arterial spin labeling (ASL) MRI, more directly measures CBF by tagging arterial blood and tracking changes in magnetization over time frames (FIXME). ASL-based CBF time series are are less frequently studied in network analysis in part due to the relatively recent availability of the CASL, pCASL or PASL MR sequences. One advantage of ASL is greater signal stability and reproducibility when compared to BOLD especially over the range of resting state frquencies

[**?**]. Although the temporal resolution of ASL is lower than BOLD, resting state fluctuations are thought to reside well within the range of frequencies that may be captured by ASL (x Hz to y Hz). Thus, ASL may prove to be a valuable quantitative technique for measuring human brain networks. [**?**]

To our knowledge, there is no existing work that studies seed-based connectivity based on ASL. This may be due, in part, to the fact that most ASL sequences collect relatively fewer time frames (impacting the stability of correlations) in a given amount of scan time as well as the lack of off-the-shelf methodology for computing ASL networks. A second reason may be that ASL is used primarily for computing CBF measurements in a manner similar to PET []. There is also little to no work employing ASL in traumatic brain injury. This population is difficult due to the heterogeneity of injury and the likely presence of cortical injury which may make standard analysis approaches difficult to justify.

In this work, we contribute a new multivariate method for ASL-based network analysis. We improve upon existing approaches in two ways. First, we extend standard seed-based methods with a sparse dimensionality reduction method that optimally correlates two ROIs. This is achieved by formulating the correlation between ROIs as a sparse selection optimization algorithm that finds non-uniformly weighted sub-ROIs that are most related. Second, we show how this method may jointly find these sub-ROIs by using both BOLD and CBF time series signal. Both of these advances relax some of the assumptions of standard seed-based approaches while retaining the interpretability afforded by these classic approaches.

In short, our contributions are:

1. We detail a new multivariate network analysis method.
2. We show how it may be used to fuse simultaneous time series measurements from multiple signal sources to estimate correlation matrices.
3. We evaluate these approaches in terms of reproducibility and applicability to studying TBI.

The method is freely available in a public open source toolkit [].

Methods

The class of methods encompassing non-negative matrix factorization (NMF) [**?**,**?**,**?**,**?**], sparse principal components analysis (SPCA) [**?**,**?**,**?**,**?**,**?**,**?**] and singular value decomposition [**?**,**?**,**?**] form the basis for the approach proposed here. More formally, define a $n \times p$ (rows by columns) matrix $\mathbf{X}$ where each row derives from an observed subject image such that the collection of images is given as vectors $\{x_1, ..., x_n\}$ with each vector x_i containing p entries. First, we denote each eigenanatomy component (a pseudo-eigenvector) as $\mathbf{v}_i$ where i is ordered such that each eigenanatomy from $\mathbf{v}_1$ to $\mathbf{v}_m$ provides a decreasing contribution to the variance of matrix $\mathbf{X}$. We define eigenanatomy pseudo-eigenvectors as *sparse*. Sparseness means that some entries in $\mathbf{v}_j$ will be zero.

The classic singular value decomposition (SVD) may be used to reduce the dimensionality of this data by decomposing the dataset into the eigenvectors of $C_p = \mathbf{X}^T\mathbf{X}$ and $C_n = \mathbf{X}\mathbf{X}^T$ (the right and left singular vectors, respectively). The relationship between a C_p and a C_n eigenvector is given by $\mathbf{X}\mathbf{v}^p = \mathbf{v}^n$ and $\mathbf{X}^T\mathbf{v}^n = \mathbf{v}^p$. The n eigenvectors from C_p and C_n may be used to reconstruct the matrix $\mathbf{X}$ by $\sum_i \mathbf{v}_i^n \otimes \mathbf{v}_i^p \lambda_i$ where the λ_i denotes the ith eigenvalue and $\otimes$ the outer product.

Our goal is to approximate the matrix $\mathbf{X}$ with its right and left singular vectors but where the right singular vector is *sparse*. We might, then, minimize:

$$\|\mathbf{X} - \sum_i \mathbf{v}_i^n \otimes \mathbf{v}_i^{sp}\lambda_i\|^2 \tag{1}$$

where the $\mathbf{v}_i^{sp}$ denotes the ith *sparse* right singular vector. However, it is known that the minimizer, here, is exactly $\mathbf{X}^T\mathbf{v}^n$ (if we relax sparseness constraints). Using the fact that $\mathbf{X}\mathbf{v}^p = \mathbf{v}^n$ and $\mathbf{X}^T\mathbf{v}^n = \mathbf{v}^p$, we therefore reformulate the objective in a slightly simpler form and seek:

$$\arg\min_{\mathbf{v}_i^{sp}} \quad \|\mathbf{X}\mathbf{v}_i^{sp} - \mathbf{v}_i^n\|^2. \tag{2}$$

This optimization problem is quadratic without sparseness constraints and easily solved by conjugate gradient through the normal equations $\|\mathbf{X}^T\mathbf{X}\mathbf{v}_i^{sp} - \mathbf{X}^T\mathbf{v}_i^n\|^2$.

Now, note that the vector $\mathbf{X}^T\mathbf{v}_i^n = \mathbf{v}_i^p$ might have both positive and negative values. As with non-negative matrix factorization, we seek a decomposition that is unsigned. However, an optimal solution that minimizes $\|\mathbf{X}\mathbf{v}_i^{sp} - \mathbf{v}_i^n\|^2$ will need to model both signs. We therefore make a second adjustment to our objective by modeling the positive and negative components of $\mathbf{v}_i^p$ separately.

Each eigenvector may be written in an expanded form via the use of indicator functions which are diagonal matrices with binary entries. For instance, if $\mathbf{v}$ contains entries $[\ -2,\ -1,\ 0,\ 1,\ 2\ ]$, then the positive indicator function is $I^+ = [\ 0,\ 0,\ 0,\ 1,\ 1\ ]$ and the negative indicator function is $I^- = [\ 1,\ 1,\ 0,\ 0,\ 0\ ]$. $\mathbf{v}$ may then be expressed as $\mathbf{v} = I^+\mathbf{v} + I^-\mathbf{v} = \mathbf{v}^+ + \mathbf{v}^-$. We use these indicator functions to separate the positive and negative components of our objective such that the optimization in equation 2 becomes,

$$\arg\min_{\mathbf{v}_i^{sp+},\ \mathbf{v}_i^{sp-}} \quad \|\mathbf{X}^T\mathbf{X}\mathbf{v}_i^{sp+} - \mathbf{v}_i^{p+}\|^2 + \|\mathbf{X}^T\mathbf{X}\mathbf{v}_i^{sp-} - \mathbf{v}_i^{p-}\|^2 \tag{3}$$

This minimization problem forms the basis for our novel approach to computing eigenanatomy, i.e. anatomically localized approximations to the eigenvectors of an anatomical imaging dataset. Derivation of sparse eigenanatomy is shown in Figure **??**. As noted above, we seek sparse and interpretable solutions. We define a sparse vector as one which minimizes a l_0 or l_1 penalty term i.e. has either a user-specified number of non-zero entries (l_0) or absolute sum (l_1). Although the l_1 penalty has advantages [**?**], we use the l_0 penalty because it specifies the fraction of the vector that is allowed to be non-zero. The sparseness restriction

Algorithm 1 SNLCG optimization for eigenanatomy.

Input $\mathbf{X}$, the eigenvectors of $\mathbf{X}\mathbf{X}^T$ and γ, the sparseness parameter.
for all $\mathbf{v}_i \in \{\mathbf{v}_1, \ldots, \mathbf{v}_{n-1}\}$ **do**
     $\mathbf{v}_i \leftarrow \mathbf{X}^T \mathbf{v}_i^n$ ▷ Get the p-space eigenvector from the $\mathbf{v}_i^n$.
     Compute $\mathbf{v}_i^+$ and $\mathbf{v}_i^-$.   ▷ Find the $+$ and $-$ representation of $\mathbf{v}_i$.
     $\mathbf{v}_i^{s+} \leftarrow \mathbf{v}_i^{s-} \leftarrow \frac{1}{p}$ ▷ Initialize the sparse $+$ and $-$ vectors.
     $\mathbf{v}_i^{s+} \leftarrow \text{SNLCG}(\mathbf{X}, \mathbf{v}_i^{s+}, \mathbf{v}_i^+, \gamma)$ ▷ SNLCG $+$ minimization.
     $\mathbf{v}_i^{s-} \leftarrow \text{SNLCG}(\mathbf{X}, \mathbf{v}_i^{s-}, \mathbf{v}_i^-, \gamma)$ ▷ SNLCG $-$ minimization.
     $\mathbf{v}_i^{s-} \leftarrow \mathbf{v}_i^{s-} * (-1)$ ▷ Reset $\mathbf{v}_i^{s-}$ to be positive.
end for

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is therefore easily interpreted by users of the eigenanatomy method. The eigenanatomy objective seeks to identify sparse functions $\mathbf{v}_i^{sp+}$ and $\mathbf{v}_i^{sp-}$ that closely approximate the eigenvectors in n-space, i.e. $\mathbf{v}_n^i = \mathbf{X}\mathbf{v}_i^p$. The objective function is then:

$$\arg\min_{\mathbf{v}_i} \quad \sum_{i=1}^{n} \parallel C_p \mathbf{v}_i^{sp+} - \mathbf{v}_i^{p+} \parallel^2 + \parallel C_p \mathbf{v}_i^{sp-} - \mathbf{v}_i^{p-} \parallel^2 \qquad (4)$$

$$\text{subject to:} \quad \|\mathbf{v}_i^{sp+}\|_0 = \|\mathbf{v}_i^{sp-}\|_0 = \gamma,$$

where γ defines the desired level of sparseness for each eigenanatomy vector. Eigenanatomy therefore produces $2*n$ sparse pseudo-eigenvectors whose product with $\mathbf{X}$ may be used a predictors in standard linear regression. Importantly, because these vectors are unsigned, they may be interpreted as *weighted averages of the input data.*

Sparseness can be enforced by a soft-thresholding algorithm as in [**?**,**?**]. We denote this function as $S(\mathbf{v}, \gamma)$ and (in an *adhoc* manner) allow it to also reject isolated voxels of the eigenanatomy vector that are non-contiguous (i.e. we provide a cluster threshold as in VBM). Minimization problems involving the l_0 penalty are np-hard. However, the relaxed form of this objective function (i.e. without the sparseness constraint) is purely quadratic and can easily be solved by a conjugate gradient method. Thus, we propose a new sparse, nonlinear conjugate gradient (SNLCG) method as a minimization procedure for the eigenanatomy objective function to deal with the nonlinearities induced by the S function and l_0 constraint. Such methods are efficient and reliable for sparse estimation methods [**?**]. The additional advantage of SNLCG is that its solutions approach the quadratic minimum as sparseness constraints are relaxed. We detail the minimization algorithms for the eigenanatomy objective function (equation 4) in algorithms 1 and 2. The algorithms are also available in an open-source $\mathbf{R}$ package for free use.

Results

For all uses of eigenanatomy below, we set the sparseness parameter, γ, to select 5% of the voxels in the cortex. We choose 5% because this provides interpretable

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Algorithm 2 SNLCG sub-algorithm for eigenanatomy.

Input $\mathbf{X}, \mathbf{v}_i^-, \mathbf{v}_i^{s-}, \gamma$.
$\mathbf{b} \leftarrow \mathbf{v}_i^-$
$\mathbf{x}_k \leftarrow \mathbf{v}_i^{s-}$
$\mathbf{r}_k \leftarrow (\mathbf{b} - \mathbf{X}^T (\mathbf{X} \mathbf{x}_k))$ ▷ Use the gradient of the quadratic term.
$\mathbf{p}_k \leftarrow \mathbf{r}_k$
$\Delta E \leftarrow \infty$
while $\Delta E > 0$ **do**
     $\alpha_k \leftarrow \langle \mathbf{p}_k, \mathbf{X}^T \mathbf{X} \mathbf{x}_k \rangle$ ▷ $\langle \cdot, \cdot \rangle$ denotes inner product.
     $\mathbf{x}_{k+1} \leftarrow \mathbf{x}_k + \alpha_k \mathbf{p}_k$
     $\mathbf{x}_{k+1} \leftarrow S(\mathbf{x}_{k+1}, \gamma)$
         ▷ Project $\mathbf{x}_{k+1}$ to the sparse solution space given by the objective function.
     $\mathbf{r}_{k+1} \leftarrow S(\mathbf{b} - \mathbf{X}^T (\mathbf{X} \mathbf{x}_{k+1}), \gamma)$ ▷ Use the gradient of the quadratic term.
         ▷ Project $\mathbf{r}_{k+1}$ to the sparse solution space given by the objective function.
     $\beta_k \leftarrow \|\mathbf{r}_{k+1}\|^2 / \|\mathbf{r}_k\|^2$ ▷ Standard conjugate gradient definitions below.
     $p_{k+1} = r_{k+1} + \beta_k * p_k$
     $\Delta E \leftarrow \|\mathbf{r}_k\| - \|\mathbf{r}_{k+1}\|$
     $\mathbf{r}_k \leftarrow \mathbf{r}_{k+1}; \mathbf{x}_k \leftarrow \mathbf{x}_{k+1}; \mathbf{p}_k \leftarrow \mathbf{p}_{k+1}.$
end while

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clusters of regions in the cortex and yet still allows a reasonable reconstruction of the original data matrix, as shown in Figure **??**.

Reconstruction error: We quantify the ability of the eigenanatomy algorithm to reconstruct the original dataset from sparse eigenvectors using equation 1. As a baseline, we compare the full eigenanatomy solution to the reconstruction given by applying the soft-threshold function S directly to the SVD-derived vectors $\mathbf{v}_i^p$ without further optimization. We call this "soft-SVD". We also compare reconstruction error to the eigenanatomy algorithm run with a restriction on the number of iterations in the SNLCG sub-algorithm. These experiments show that the full eigenanatomy algorithm run until convergence (error = 1.251) improves upon both the soft-SVD solution (error = 1.292) and the limited iteration eigenanatomy solution (error = 1.279). Error is measured by the frobenius norm taken between the original matrix and the reconstructed matrix.

Neuroimaging data: Our cohort consists of 61 participants, including 15 patients with AD (7 females), 23 patients with FTLD (14 females), and 23 controls (13 females). All patients were clinically diagnosed by a board-certified neurologist and cerebrospinal fluid confirmation of the underlying pathology was obtained [**?**]. No significant difference exist between disease duration, age or education in the patient or control groups. Two 3.0T MPRAGE T1-weighted magnetic resonance images were obtained for each subject. The FTLD group (time interval 1.12 years +/- 0.28) trended (p<0.081) towards having a reduced interval when compared to elderly controls (time interval 1.29+/-0.36 years), as did the AD group (time interval 1.13+/-0.25 years, p<0.12). The interval between scans was therefore factored out as a nuisance variable.

Detection power in comparison to VBM, SVD and PMD: In this section, we employ eigenanatomy to compare the ability to detect group differences in cortical atrophy rate between FTLD subjects and controls as well as AD subjects and controls. This analysis shows specificity of the approach and biological plausibility in two different neurodegenerative disorders.

We passed the same input dataset to all methods. The data consisted of unbiased voxel-wise measures of annualized atrophy rate in the cortex of all patients normalized to a group template, as described elsewhere [**?**]. The regression model employed for all methods is summarized (in **R** syntax) as: *atrophy-rate* $\approx 1+$ diagnosis + education + interval-between-images + disease-duration + gender. "Diagnosis" is the predictor of interest i.e. we test whether the presence of disease predicts atrophy rate given the presence of the covariates. The *atrophy-rate* is either a vector of voxel-wise measures or a basis function projection against the original atrophy rate image matrix $\mathbf{X}$ i.e. $\mathbf{X}\mathbf{v}_i^p$. The latter case is used for classic SVD, PMD, soft-SVD in addition to eigenanatomy. We define significance as a q-value < 0.05 where a q-value is a false discovery rate corrected p-value. For PMD and SVD, we tested n different atrophy rates (one for each eigenvector) where n is number of subjects. For eigenanatomy and soft-SVD, we used $2n$ predictors as suggested by design in the algorithm. For VBM, we tested all 50,194 voxels (the number of columns in $\mathbf{X}$).

For the FTLD subjects and the AD subjects, when classic SVD projections were used as measures of atrophy rate, *no* significant predictors emerged. The same is true for the PMD method—although we note the caveat that, potentially, a more exhaustive parameter search may have resulted in better PMD results. Both univariate VBM and soft-SVD identify significant effects although the minimum q-value and extensiveness of both soft-SVD and VBM are far less than eigenanatomy. This is particularly true for the FTLD subjects for which VBM only produces a small 20 voxel cluster that survives correction. The results are summarized further in Figure **??**. Detailed clinical interpretation is beyond the scope of the paper but the results, overall, are coincident with what is known about these disorders. In particular, the largest atrophy rate in FTLD was in right orbitofrontal cortex. For AD, this region was in the precuneus.

Conclusion

We detailed the eigenanatomy theory and algorithm and showed that eigenanatomy improves image reconstruction from a sparse set of anatomical basis functions. We showed that eigenanatomy also improves detection power for detecting group differences in longitudinal cortical change relative to SVD, PMD and univariate VBM. However, this approach is not limited to longitudinal analysis and may be applied in a variety of morphometry contexts. Future work will involve exploration of alternatives to the SNLCG algorithm, alternative penalty terms and an automation of parameter selection.