Two Local Constrained Canonical Correlation Analysis Methods for fMRI

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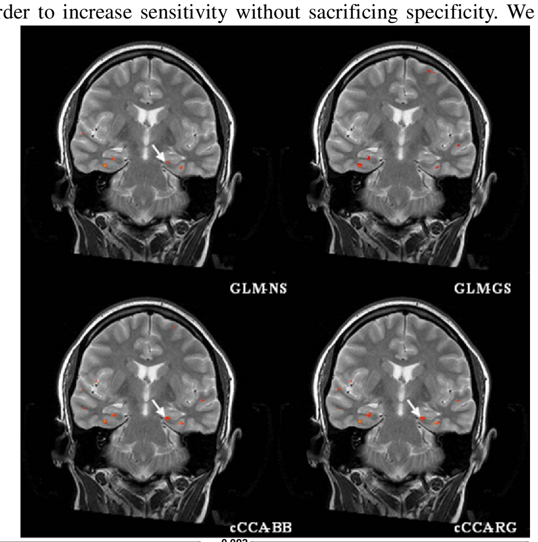
Introduction While univariate (single voxel) analysis, such as the general linear model (GLM) [1], is extensively applied to fMRI data, only a few applications investigate the spatial dependence of fMRI data. Univariate analysis uses fixed isotropic spatial Gaussian smoothing routinely to achieve more homogeneous regions of activation at the expense of blurring of the edges of activation. More severely, if the fixed isotropic filter kernel is larger than the activated area, it could potentially eliminate the detection of activated regions. Small focal regions of low CNRs are rather common in episodic memory paradigms where the task is to detect activation in the medial temporal lobes (hippocampus and parahippocampus). Therefore, fixed Gaussian spatial smoothing can potentially result in missing important (but subtle) focal activations. Local multivariate methods such as CCA [2] and its variants [3,4] have been demonstrated to be able to significantly increase the detection power of fMRI activations and improve their spatial localization. Following these developments, we propose a novel local constrained CCA (cCCA) method by requiring spatial coefficients to be positive and requiring the center voxel to have a minimum weight contribution in order to increase sensitivity without sacrificing specificity. We introduce two different search strategies to find such cCCA solutions.

Methods In proposed cCCA, the basic requirement of the spatial coefficients $\boldsymbol{\alpha}_c$ is that all its components are positive to meet the requirements of being a lowpass (smoothing) filter. The local adaptiveness of the cCCA method allows versatile filtering kernels with flexible shape and size within a pre-specified region. We also propose an additional constraint for the spatial weight α_1 of the center voxel using an empirically-determined parameter δ in [0,1] according to: $\alpha_1 \geq \delta \max(\boldsymbol{\alpha}_c)$. This additional constraint can decrease the false positives, especially at boundary regions of activations. Here we use two searching strategies to pick those CCA solutions satisfying both constraints. We denote the time courses of a local neighborhood of K voxels as $\mathbf{Y}$, the center voxel as $\mathbf{y}_1$, and the design matrix as $\mathbf{X}$.

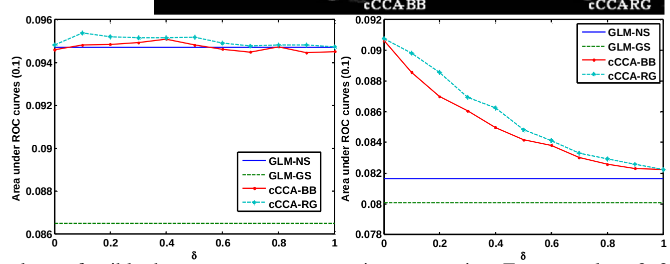


1. Branch-and-bound method (cCCA-BB)

The branch-and-bound method [5] uses the monotonicity of the canonical correlation as a function of the degrees of freedom of the spatial functions, i.e. number of components in $\mathbf{Y}$. An implementation of this method to find $\mathbf{Y}$ is as follows: (1) Try CCA using $\mathbf{Y^*}$ containing all K column vectors of $\mathbf{Y}$ and $\mathbf{X}$; (2) Try CCA using all possible $\mathbf{Y^*}$ containing K-1 column vectors of $\mathbf{Y}$ (including component $\mathbf{y}_1$) and $\mathbf{X}$; (3) Try CCA using all possible $\mathbf{Y^*}$ containing K-2 column vectors of $\mathbf{Y}$ (including component $\mathbf{y}_1$) and $\mathbf{X}$; etc. If at any step the vector $\boldsymbol{\alpha}_c$ satisfies the constraints, then the search is stopped and the optimal submatrix $\mathbf{Y^*}$ is obtained. If there are several $\mathbf{Y^*}$ found satisfying the constraints, then the one $\mathbf{Y^*}$ corresponding to the largest canonical correlation provides the optimal solution.

2. Novel local region-growing method (cCCA-RG)

To search much faster, we propose a novel local region-growing method starting from the center voxel $\mathbf{y}_1$ to find the optimal neighborhood $\mathbf{Y^*}$. This method is defined by the following three steps applied to each local neighborhood: (1) Let the growing set be $\mathbf{Y^*}=\{\mathbf{y}_1\}$ and the candidate set be $\overline{\mathbf{Y}}=\mathbf{Y}\backslash\mathbf{Y^*}$; (2) Find $\mathbf{y}_i \in \overline{\mathbf{Y}}$ so that the matrix $\tilde{\mathbf{Y}} = \mathbf{Y^*} \bigcup \{\mathbf{y}_i\}$ and $\mathbf{X}$ have maximum canonical correlation satisfying the constraints; (3) If such $\mathbf{y}_i$ can be found, let $\mathbf{Y^*} = \tilde{\mathbf{Y}}$, $\overline{\mathbf{Y}}=\mathbf{Y}\backslash\mathbf{Y^*}$ and go to step (2); else stop at current $\mathbf{Y^*}$.



The branch-and-bound method prunes the voxel space from the largest set of voxels, while the proposed region-growing method grows it from the smallest set, i.e. the center voxel. Although to do an exhaustive search should provide the optimal solution, this is not always feasible due to an enormous cost in computation. For example, a 3x3 region (as done in this research) requires an exhaustive search of 256 different configurations, and a 3x3x3 region requires a search over 2^{26} different configurations.

Results Functional MRI (fMRI) was performed in a 3.0T GE HDx MRI scanner equipped with an 8-channel head coil using the following parameters: ASSET=2, ramp sampling, TR/TE=2sec/30ms, FA= 70deg, FOV=22cmx22cm, thickness/gap=4mm/1mm, 25 oblique-coronal slices perpendicular to the long axis of the hippocampus, in-plane resolution 96x96 interpolated to 128x128. For each subject of five we acquired two fMRI data sets. The first data set was collected during resting-state where the subject tried to relax and refrain from executing any overt task with eyes closed. The second data set was collected while the subject was performing a memory paradigm. Briefly, this paradigm consisted of memorization of novel outdoor scenes containing 6 periods of encoding, distraction, and recall tasks. We tested four methods: (1) GLM without smoothing ("GLM-NS"); (2) GLM with Gaussian smoothing (FWHM=2.24 pixels, "GLM-GS"); (3) cCCA-BB; and (4) cCCA-RG.

Shown in the first figure are typical activation maps of the contrast "Encoding minus Distraction" with non-parametrically corrected $p<0.05$ [6]: Note that GLM-GS, cCCA-BB and cCCA-RG lead to symmetric (left and right) activation patterns in the hippocampus and parahippocampal gyrus. It appears that GLM-GS is not able to detect activation at the left hippocampus (white arrows). Compared to GLM-NS, both cCCA methods detect more active voxels.

We constructed pseudo-real data as in [4] by combining active data from memory paradigm with very high significant values and resting-state data, and used receiver operating characteristic (ROC) technique [7] to quantitatively evaluate different methods. The area under ROC curves (AUR), integrated over FPF∈[0,0.1], as a function of the parameter δ in cCCA-BB and cCCA-RG are shown in the plot (left: low noise case peak SNR 67%; right: high noise case peak SNR 29%). Because memory activations are more subtle and spatially localized, GLM-GS performs worse than GLM-NS whereas both cCCA-BB and cCCA-RG perform similarly and are the best. Both cCCA methods gain more detection power in the high noise case. Please also note that smaller values of δ results in more local smoothing and thus leads to a better performance of the cCCA methods in the high noise case.

For the estimation of a 2D slice with 6317 in-brain pixels, using MATLAB on a computer equipped with Intel Core 2 2.4GHz CPU and 4GB memory, it takes 2.0s for GLM-NS, 2.2s for GLM-GS, 24s for cCCA-RG, and 308s for cCCA-BB, both with $\delta=0$. Although the proposed cCCA methods take much longer time than the conventional GLM methods, they finish in a reasonable amount of time and are thus feasible for real applications in order to get greater detection power.

References and Acknowledgment [1] Worsley, K., et al., 1995. NeuroImage, 173-181. [2] Friman, O., et al., 2003. NeuroImage, 837-845. [3] Friman, O., et al., 2001. Magn. Reson. Med., 323-330. [4] Nandy, R., et al., 2004. Magn. Reson. Med. , 947-952. [5] Das, S., et al., 1994. Lin. Algebra Appl, 29-47. [6] Nandy, R., et al., 2007. NeuroImage 34, 1562-1576. [7] Metz, C. 1978. Semin. Nucl. Med. 8, 283-98. *This work is partially supported by the NIH (1R21AG026635).*