# A Novel Test Statistic allowing a General Linear Contrast Vector for Local Canonical Correlation Analysis in fMRI

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***Introduction*** Local canonical correlation analysis (CCA) is a multivariate method that takes into account the spatial correlation of neighboring voxels rather than treating each voxel time series individually. Mathematically, CCA is a generalization of the general linear model (GLM), and is defined by maximizing the correlation of a linear combination of voxel time series in a local region and a linear combination of set of temporal basis functions (regressors). The unknown coefficients of these linear combinations are determined by CCA. In this research, we derive a novel statistic using the vector of the temporal regressors in CCA that project the original space of basis functions onto a vector space maximizing the correlation with the observed voxel time series and allows for an arbitrary temporal contrast vector. This statistic makes CCA feasible for multiple-regressor designs. A non-parametric approach [1] is adapted to estimate the family-wise error rate of the newly developed CCA statistic.

***Theory*** Considering a group of $K$ local neighboring voxels, the multivariate multiple-regression model can be written as:

$$\mathbf{Y}=\mathbf{XB}+\mathbf{E} \qquad (1)$$

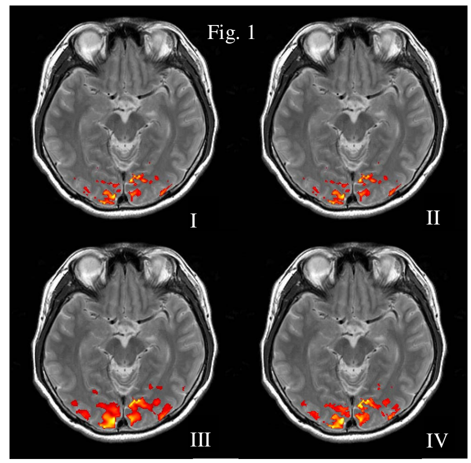
where $\mathbf{X}$ is fixed (i.e. the $n\times p$ design matrix), $\mathbf{Y}=(\mathbf{y}_1,\ldots,\mathbf{y}_K)$ is the matrix containing $K$ neighboring voxels, $\mathbf{B}=(\boldsymbol\beta_1,\ldots,\boldsymbol\beta_K)$ is the parameter matrix to be estimated, and $\mathbf{E}=(\boldsymbol\varepsilon_1,\ldots,\boldsymbol\varepsilon_K)$ is the error matrix. The least-squares solution of the model (1) is

$$\mathbf{B}^*=(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{Y} \qquad (2)$$

We can see that the estimator in Eq. (2) is just the matrix form of the GLM leading to equivalent solutions. However, the hypothesis tests in the multivariate case are different on including the interactions among voxels, such as Wilks' Λ [2]. In order to increase detection power of weak activations, local spatial smoothing is usually applied to decrease the noise variance. Let $\boldsymbol\alpha$ be the vector containing the spatial smoothing coefficients. Multiplication of both sides of Eq. (2) with $\boldsymbol\alpha$ gives

$$\mathbf{Y}\boldsymbol\alpha=\mathbf{X}\boldsymbol\beta+\boldsymbol\varepsilon \qquad (3)$$

where $\boldsymbol\beta\equiv\mathbf{B}\boldsymbol\alpha$ and $\boldsymbol\varepsilon\equiv\mathbf{E}\boldsymbol\alpha$. In conventional fixed Gaussian smoothing, both $\mathbf{Y}$ and $\boldsymbol\alpha$ are fixed and treated as known, and only $\boldsymbol\beta$ has to be estimated, i.e. $\mathbf{y}\equiv\mathbf{Y}\boldsymbol\alpha=\mathbf{X}\boldsymbol\beta+\boldsymbol\varepsilon$ (*). In the formalism of CCA, both $\boldsymbol\alpha$ and $\boldsymbol\beta$ have to be determined simultaneously to achieve maximum canonical correlation. The vector $\boldsymbol\alpha$ can be treated as a locally adaptive spatial (smoothing) kernel (with positive constraint). Based on CCA with the unit variance requirement of canonical variables, the solution of (3) can be derived as

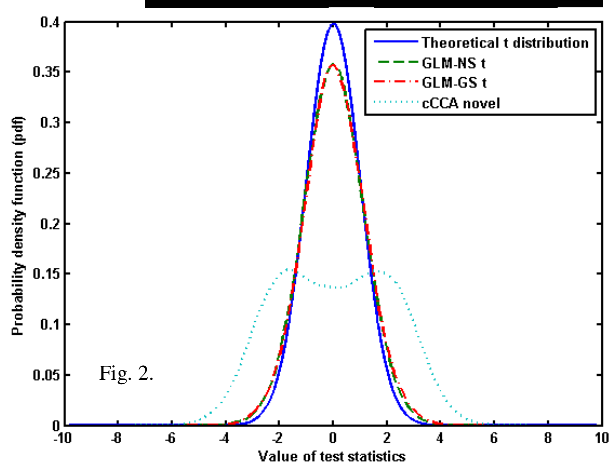



$$\tilde{\boldsymbol\beta}_C=\frac{1}{r}\mathbf{S}_{xx}^{-1}\mathbf{S}_{xy}\tilde{\boldsymbol\alpha}_C=\frac{1}{r}\tilde{\boldsymbol\beta}\tilde{\boldsymbol\alpha}_C \qquad (4)$$

where $\mathbf{S}_{xx}=\mathbf{X}'\mathbf{X}/(n\text{-}1)$, $\mathbf{S}_{yy}=\mathbf{Y}'\mathbf{Y}/(n\text{-}1)$, and $\mathbf{S}_{xy}=\mathbf{X}'\mathbf{Y}/(n\text{-}1)$ are sample variance/covariance matrices (assuming $\mathbf{X}$ and $\mathbf{Y}$ temporally centered), $r$ is the maximum canonical correlation, and $\tilde{\boldsymbol\beta}$ is the GLM solution when $\tilde{\boldsymbol\alpha}_C$ is used as a local spatial filter (see (*)). Now we can use $\tilde{\boldsymbol\beta}_C$ as the temporal vector in constructing the test statistic in a way similar to the GLM t-statistic. For a general linear contrast $\mathbf{c}$, this novel test statistic for CCA can be derived as

$$t_C=\frac{\mathbf{c}'\tilde{\boldsymbol\beta}_C\sqrt{n-p-K^*}}{\sqrt{\mathbf{c}'(\mathbf{X}'\mathbf{X})^{-1}\mathbf{c}}\sqrt{(\mathbf{Y}^*\tilde{\boldsymbol\alpha}_C/r-\mathbf{X}\tilde{\boldsymbol\beta}_C)'(\mathbf{Y}^*\tilde{\boldsymbol\alpha}_C/r-\mathbf{X}\tilde{\boldsymbol\beta}_C)}} \qquad (5)$$

where $\mathbf{Y}^*$ represents the observed time series of a group of $K^*$ neighboring voxels. Note that when $K^*=1$, Eqn. (5) is the same as the GLM t-statistic. $\mathbf{Y}^*$ can either be fixed in conventional CCA or be found by constrained CCA in a prescribed local region. Because of the adaptive smoothing scheme, the random field theory [3] is not applicable and a non-parametric method [1] by resampling of order statistics was used to determine corrected p-values.




***Methods and results*** Functional MRI (fMRI) was performed in a 3.0T GE HDx MRI scanner equipped with an 8-channel head coil and parallel imaging facility using the following options: ASSET=2, ramp sampling, TR/TE=2sec/30ms, FA= 70deg, FOV=22cmx22cm, thickness/gap=4mm/1mm, 25 axial slices, in-plane resolution 96x96 interpolated to 128x128. A visual paradigm was performed on five healthy adult subjects and fMRI data were collected according to local IRB approval. For each subject 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 looking at a flashing checkerboard (10Hz flashing frequency, duration 2 sec) which alternated with a fixation period of random duration (2 sec to 10 sec, uniformly distributed). We collected 150 volumes and the first 5 volumes were discarded to establish signal equilibrium of the imaging sequence.

Shown in Fig. 1. are typical activation maps of contrast "Visual minus Fixation" with corrected $p<0.05$: (I) is t-statistic of GLM without smoothing ("GLM-NS"); (II) is a statistic of CCA on single voxel; (III) is t-statistic of GLM with Gaussian smoothing (FWHM=2.24 pixels, "GLM-GS"); and (IV) is a statistic of CCA with a positive constraint on spatial coefficients $\boldsymbol\alpha$ ("cCCA"). (I) and (II) are exactly the same as the theory predicted. The GLM-GS yields the smoothest activation map at the expense of blurring at edges. The single voxel analysis (I and II) methods preserves fine structures of activation much better but with more unappealing broken links between activated voxels. Activation map using cCCA (representing an adaptive smoothing) provides a good compromise between a smooth appearance of activations and preservation of fine cortical structure.

Fig. 2. shows the plots of the null distribution of the proposed statistic along with t-statistics used in the GLM obtained from resampled resting-state data. Compared to a theoretical t-distribution (blue curve), GLM t-statistics are somewhat different and the difference of proposed novel CCA statistic is substantial. This is an important reason to use a non-parametric method to determine the family-wise error rate (p-values adjusted for multiple comparisons).

***References and Acknowledgement*** [1] Nandy, R., Cordes, D., 2007. NeuroImage 34, 1562-1576. [2] Rencher, A., 1998. JOHN WILEY and SONS, INC. [3] Worsley, K.J., et al., 1996. Hum. Brain Mapp. 4, 58−73. *This work is partially supported by the NIH (1R21AG026635).*