125. ROI-based Analysis of fMRI Data Incorporating Individual Differences in Brain Anatomy

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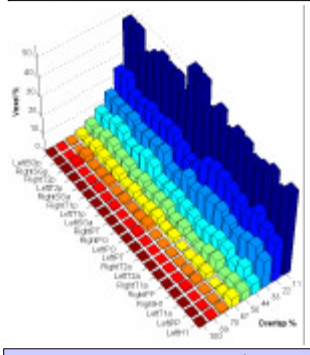
Introduction

Most current fMRI analysis techniques do not include information concerning individual brain anatomy in the statistical analysis and are thus forced to spatially smooth the functional data to accommodate intersubject anatomical variability. Here, high-resolution T1-weighted structural MRI scans for each subject are segmented and parcellated using an interactive tool that makes use of automatic methods combined with manual outlining to create region-of-interest (ROI) masks. ROI-based functional hypotheses are then tested using multivariate analysis techniques. Intersubject averaging is performed in a nonphysical space of functional eigenvariates, and the averaged results can be mapped back to each subjects' brain (structural MRI). This allows relaxation of the fundamental unit of analysis from voxels to ROI's (for which inter-subject pooling is more justifiable) while maintaining the spatial resolution of the original data. By parcellating the individual brains and performing across-subject statistical analyses within ROI boundaries, the procedure avoids the need for spatial averaging and the subsequent loss of clear ROI boundaries. Furthermore, the reduced size of the ROIs allows the application of multivariate techniques that do not assume any form of the spatial covariance of the activation profile (cf. random field theory), nor of the spatial mapping between subjects' specific ROIs (cf. between-subject coregistration). This allows for an increased sensitivity to small and medium effect sizes. The tools that perform ROI definition and statistical hypothesis testing are designed as add-ins to the SPM statistical package.

Statistical Methods for ROI analysis: The general linear modeling (GLM) framework is used to test specific hypotheses concerning all voxels within an ROI defined for multiple subjects. As opposed to tests based on pixel-level statistics (that would require inter-subject coregistration) a multivariate likelihood ratio approach (LRT) is proposed to test the significance of an effect over all ROI voxels. Temporally autocorrelated noise is explicitly modeled by a preprocessing whitening step, while spatially autocorrelated noise is implicitly accounted for by the multivariate nature of the statistical test. A data reduction step is performed to obtain a series of temporal eigenvariates describing the signal over the ROI's, and a likelihood ratio test is performed over these eigenvariates to test the desired contrasts.

Anatomic Variability



T1 weighted MRI scans and ROI definitions of 9 subjects were normalized using SPM (affine and nonlinear basis functions). The normalized structural images and ROI definitions were then manually checked for co-registration. The voxel count for each ROI was calculated as the total number of all voxels that are present in that ROI definition for at least one subject. The above plot shows the relationship between percentage of voxels in each region and the corresponding percentage of overlap. For example, in the right planum temporale (RightPT), 50% of the voxels have a 11% overlap. For the data set size of 9, this implies that each of these voxels is present in only one subject. In most fMRI analyses, normalized images of subjects are averaged on a pixel basis, without paying attention to local anatomical differences, under the assumption that pixels at the same normalized location are functionally equivalent. The above results show that there is a lot of variability at the level of co-registered pixels.

ASAP

A Segmentation and Parcellation Toolbox

Preprocessing

The T1-weighted images are preprocessed to extract a white-gray boundary and a gray-csf boundary.

Segment Edit

The preprocessed images are then manually edited for segmentation errors. For purposes of functional analysis an overestimate of the gray-csf boundary is maintained.

Sulci Drawing

Sulcal lines corresponding to major sulci and fissures are drawn on the three planes. Nodes are identified to aid in labeling.

Parcellation

The segmentation outline and the sulci provide cues for parcellating the cortical ribbon into smaller units (Rademacher et al, 1992).

Labeling

The parcellated pieces of cortex are then assigned labels based on the nearest node positions.

Processing Steps

Modeling Temporal Noise Characteristics

All pixel temporal profiles within an ROI are low-pass filtered and fitted using the General Linear Model with the given set of predictors.

Residuals are used to model noise as filtered Gaussian noise with unknown width of autocorrelation. All pixel temporal profiles are then band-pass filtered and whitened using estimated noise temporal autocorrelation.

Data Reduction

To allow a valid estimation of the noise multivariate spatial covariance, the dimensionality of the signal (number of pixels) is reduced using a singular value decomposition (SVD). This produces a set of temporal eigenvariates comprising most of the signal covariance.

This step has the added advantage of increasing the signal to noise ratio by removing part of the noise covariance while maintaining most of the signal.

General Linear Model & Hypothesis Testing (LRT)

The General Linear Model is used to estimate the matrix of regressors fitting the set of temporal eigenvariates with the given set of predictors. Residuals are used to estimate the multivariate noise spatial covariance.

Likelihood Ratio Test is used to test the pre-specified contrasts between regression parameter estimates. This provides a natural multivariate extension to the standard univariate chi-square test for pixel-wise contrasts (to which it reduces when one-pixel ROI's are considered).

The effects are characterized by projecting the eigenvariate contrasts back onto a temporal and a spatial profile (for each contrast tested) using the reverse transformation from the previously computed SVD decomposition.

Mathematical Model

Original Model

$SY = SXB + SKz$

$c^TB = 0$

Data Reduction

$Y^TS^TK^{-2}SY = VDV^T$

$Y = K^{-1}SYV$

Revised Model

$Y = K^{-1}SXBV + Sz$

Estimation

$\underline{B} = (X^TS^TK^{-2}SX)^{-1}X^TS^TK^{-1}Y$

Hypothesis Testing

$H = (c^T\underline{B})^T(c^T\underline{B})$

$E = (Y - K^{-1}SX\underline{B})^T(Y - K^{-1}SX\underline{B})$

$\lambda_1 = \mathrm{trace}(HE^{-1}) \sim n/r\, F_{n,r}$

n = number of eigenvariates

r = rank(S) – rank(X) – n + 1

Characterizing the effect

$\underline{y}_t = SYVB^Tc$

$\underline{y}_s = VB^Tc$

Y: Pixel-wise time-course matrix
X: Design matrix
B: Unknown regressors
K: Gaussian temporal filter with unknown width and energy
S: Band-pass filter
z: Gaussian white noise
c: Contrast vector
Y: Temporal eigenvariates matrix
$\underline{B}$: Estimated regressors matrix
$\underline{y}_t$: Estimated temporal profile of the effect
$\underline{y}_s$: Estimated spatial profile of the effect

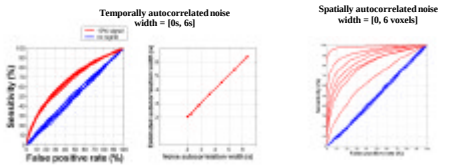
Simulations

Unless otherwise stated the simulated data consists of 4 subjects with 128 scans per subject (TR=2s) over an ROI of 16 voxels with white noise filtered temporally (FWHM = 7s) and spatially (FWHM = 2voxels). Two sinusoidal task-related predictors (T_1=16s, T_2=32s) were used. A signal was added following the first task time-course with 10% RMS signal-to-noise ratio and distributed over 12% of the extent of the ROI. In order to obtain sensitivity and false positive rate measures 1000 simulations were run for each condition tested.

Simulation 1: Correlated noise

Fixed-effect analyses with variable amount of noise temporal autocorrelation width (s = [0, 6]; FWHM = [0, 16] seconds), and noise spatial autocorrelation width (s = [0, 6]; FWHM = [0, 16] voxels) were performed to observe its effect on sensitivity and false positive rate.

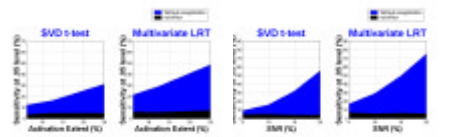
Results: Statistical analysis remains valid under all conditions of temporally and spatially autocorrelated noise tested



Simulation 2: Extent of activation, effect size, and sensitivity

Fixed-effect analysis with variable extent of activation in ROI ([5%, 25%]), and with variable signal-to-noise ratio (SNR=[5%, 20%]) were performed. Multivariate LRT was compared to SVD t-test results

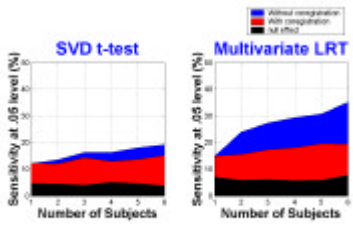
Results: Multivariate LRT shows higher sensitivity than univariate SVD t-test



Simulation 3: Multiple subjects fixed-effect analysis

Fixed-effect analysis with variable number of subjects (n=[1,6]). Inter-subject variability was introduced by randomly permuting the activation loci. Simulated coregistration results were obtained by across-subject averaging the pixel time-courses.

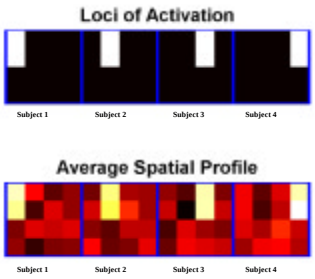
Results: Power of multivariate LRT increases with increasing number of subjects. If the data is spatially coregistered increasing the number of subjects does *not* result in an equivalent increase in power.



Simulation 4: Spatial profile of the effect

The signal is distributed differentially throughout the ROI's of 4 simulated subject datasets. Spatial profiles of positive test results (p<.05) were compared to the actual spatial signal distributions.

Results: Multivariate LRT correctly estimates the spatial loci of the activation maintaining the spatial resolution of the original data.



Results

- When no signal is present (test for second task effect) then no effects are detected (with the pre-specified false-positive rate), for all conditions tested; I.e. **valid test**
- Noise temporal autocorrelation is appropriately estimated by the whitening preprocessing step, allowing the statistical test to remain valid on a wide range of noise temporal correlation widths.
- Noise spatial autocorrelation is intrinsically accounted for by the multivariate nature of the statistical test, performing robustly on a wide range of noise spatial correlation widths.
- Sensitivity of multivariate LRT is consistently better than equivalent univariate SVD t-test for all conditions tested, with equivalent increases in power with increasing activation extent, and with increasing effect size.
- If loci of activation varies between subjects, coregistration decreases sensitivity. A multivariate test gets an increase in power with increasing number of subjects without the need to coregister the data.
- The spatial loci of the activation within an ROI are correctly estimated in the presence of inter-subject variability, thus maintaining the intra-ROI spatial resolution possible with current fMRI techniques.

Acknowledgement

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References

1. Rademacher et al. 1992, J. Cog. Neurosci., 4: 352-374
2. SPM toolbox: http://www.fil.ion.ucl.ac.uk/spm/