A Randomization Test for Non-Parametric Inference of Filtered FMRI Time-Series Data

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Introduction

The constraints of unpredictable task performance among some patient populations often produce paradigms with sparse distribution of desired cognition events in task-locked event-related FMRI of patients [1]. This situation could arise, both from having to design stimulus paradigms with long inter-stimulus intervals (ISIs) and from incorrect or no task performance by the patients. Since the detection/estimation power of FMRI paradigms depend on the density of brain activation events in FMRI time-series [2], paradigms with sparsely distributed activation events can suffer from low FMRI SNR. Filtering methods have been demonstrated to increase FMRI SNR [3]. However filtering alters the underlying FMRI noise structure and inferences made using white-noise assumptions are rendered invalid. In this study, a randomization test (RT) designed to make non-parametric inferences on filtered FMRI time-series is presented.

Methods

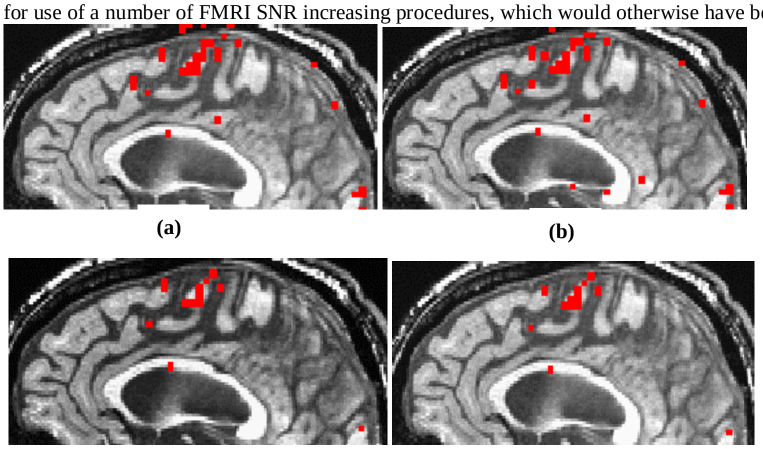
One non-fluent male aphasia patient, with left hemisphere stroke was scanned on a 3T GE LX scanner. Scanning parameters: 1-shot spiral gradient echo sequence [4]; 32 4-4.5 mm sagittal slices covering the whole brain, TR/TE/FA= 1660ms/18ms/70°, 3mm x 3mm in-plane resolution, two 161-image runs (session had to be aborted after two runs). Written informed consent was obtained. The patient was asked to generate single word responses to a series of semantic category cues. The inter-stimulus interval was varied pseudo-randomly between 24.9, 26.6, 28.2 or 29.8 sec. There were a total of 18 semantic category cues presented auditorily. The subject responses were monitored and coded with Cool Edit™ software into two categories, "correct" and "other" responses. There were a total of 7 "correct" and 11 "other" responses. Analysis was done with *AFNI* and *Matlab™*.

Data Analysis

The two functional runs were registered, detrended of low-frequency drifts and concatenated to give voxel time-series comprised of 322 images. To improve FMRI SNR, the 322-image time-series underwent two levels of wavelet decomposition and the "detail" coefficients were "soft"-thresholded. For each voxel, the wavelet-filtered observed voxel FMRI intensity time-series was modeled as the sum of convolutions of the "correct: and "other" response-locked stimulus vectors and their corresponding best-fit fifteen-lag impulse response functions (IRFs). The signal due to the "other" responses was regressed out of the FMRI time-series leaving only the "correct" response related signal plus additive noise. The resultant time-series underwent deconvolution analysis and the activation statistic, the co-efficient of determination of the General Linear Model (GLM), R^2 was calculated. The 8 ISIs, obtained from the 7 "correct" responses (and the initial and final rest periods) were randomly permuted to give 1000 different stimulus vectors which when input to the deconvolution analysis resulted in a 1000-valued randomization distribution of R^2. Voxelwise non-parametric RT inferences were made based on the position of voxel experimental R^2-statistic, R^2_{exp}, in the randomization distribution of R^2 for the voxel. Because the probability maps based on the 1000-valued distribution has a lower limit of $p = 0.001$, each voxel's randomization R^2-distribution was also fitted to a separate gamma-distribution, to permit extrapolation to lower p-values. Because a different distribution is fit to every voxel the distribution-independent multiple comparison properties [5] of the raw RT still hold. Probability maps were converted to equivalent z-score (normal distribution) maps for convenience.

Results and Discussion

R^2-map (thresholded at $R^2 > 0.2$) generated from deconvolution analysis of wavelet-filtered time-series, of a right sagittal slice containing the medial frontal cortex is shown in Fig 1 (a). Fig 1(b) shows the corresponding randomization test raw z-score map (thresholded *at* $z \geq 3.1$). The areas of activation in the 2 maps exhibit substantial correspondence. Fig 1 (c) shows wavelet filtered R^2-map (thresholded at a more stringent $R^2 > 0.25$), exhibiting more localized activation than Fig 1 (a). The raw z-score maps obtained from the 1000-valued RT distribution cannot achieve greater localization than Fig 1 (b). Fig. 1 (d) illustrates the results of fitting a gamma-like distribution to the RT distribution. The z-score map from the gamma-fit to the RT distribution (thresholded at $z >= 3.6$) is shown in Fig. 1 (d), and is visibly similar to Fig 1 (c). The robustness of inference estimates obtained by fitting gamma-like density functions to the RT distributions was confirmed by computing exact 40320-valued (all 8! realizations) RT distribution for a set of "high" threshold ($R^2 > 0.35$) voxels as well as "low" threshold ($R^2 < 0.02$) voxels. The difference between the raw RT distributions and the gamma-fit distributions were not significant (Kolomogrov-Smirnov difference test $p > 0.9999$). The results indicate that the RT method introduced is capable of making non-parametric inferences on filtered FMRI time-series data and the signal detection properties of the associated statistic, z-score are similar to those of the biased R^2-statistic obtained from deconvolution analysis of filtered (and hence non-gaussian noise) time-series. The method is extendable to any filtering scheme and thus opens the opportunity for use of a number of FMRI SNR increasing procedures, which would otherwise have been unemployable.



(a) **(b)** **(c)** **(d)**

Fig 1. R^2-maps of wavelet-filtered datasets, thresholded at $R2 > 0.2$ (a). Raw equivalent z-score map thresholded at $z \geq 3.1$ obtained from the 1000-valued RT distribution for each voxel (b). R^2-maps of wavelet-filtered datasets, thresholded at $R2 > 0.25$ (c). Equivalent z-score maps obtained from fitting gamma-like distributions to each voxel's RT distribution, thresholded at $z \geq 3.6$ (d).

References 1) Gaiefsky M., et al., *Soc Neurosci*,**32**:873, 2003. 2) Birn R., et al., *Neuroimage*, **15**:252, 2002. 3) Krueggel F., et al., *Neuroimage*, **10**:530, 1999. 4) Noll D., et al., *JMRI* **5**:49, 1995. 5) Nicholls T., et al., *Hum Brain Map*, 15:1, 2001.