

Voxelwise Bootstrap Resampling of Time Series Blocks in the Analysis of fMRI Resting State Data

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Introduction

Functional connectivity maps acquired from resting state data are a useful way to analyze connectivity inside the brain without tasks or stimuli. They are generated by identifying low frequency fluctuations that are highly correlated between voxels in an fMRI resting state acquisition.¹ Such low frequency signals might be responsible for the non-Gaussian noise seen in fMRI data. In addition, low-pass filters are generally applied to resting state data to remove unwanted physiological fluctuations caused by respiration and cardiac motion.¹ Thus, non-parametric methods of obtaining a null distribution for a test statistic become increasingly important when analyzing resting state data. Previous non-parametric attempts to determine the null distribution have used wavelet resampling or phase shifting in the Fourier domain.² Here, a simple method, which resamples random blocks of the time series,³ was devised to account for temporal autocorrelations on a voxelwise basis. The major disadvantage with voxelwise bootstrap resampling is that normally it can be either inaccurate or prohibitively time-consuming. Our approach circumvents both of these problems.

Methods

One female subject (aged 45) was imaged in a Bruker Biospec 30/60 3 Tesla scanner using a local gradient coil and an end-capped birdcage RF coil. An EPI sequence was used. A functional experiment, consisting of a gum chewing task, was followed by a resting state acquisition (TR = 1000 ms, TE = 30.9 ms, FOV = 24 cm, matrix = 96 × 96, BW = 166 kHz, 9 6-mm-thick axial slices) with 500 repetitions.

Analysis

Data were analyzed with AFNI and MATLAB (Mathworks, Natick, MA). Cross-correlation analysis was used. Elimination of motion artifacts in the functional experiment was achieved through methods outlined by another abstract at this conference.⁴ The first five images from the resting state acquisition were discarded, leaving 495 total time points. A 2 × 2 region of highly activated voxels in the jaw and tongue area of the sensorimotor cortex was identified from the functional experiment. Time series from the resting state acquisition of these voxels were then detrended, averaged and low-pass filtered (0.08 Hz) to create the reference time series. The reference time series was reordered, low-pass filtered, and correlated with the original to obtain a null distribution. It was found that a Gaussian curve, fit by a least squares approach to a histogram generated from 1,000 iterations (taking about four minutes), produced a null distribution nearly identical to one generated from one million iterations (taking four days) (Fig. 1). Cross-correlation analysis was then performed between the reference time series and the detrended, low-pass filtered resting state voxel time courses. Using the fitted distribution, 228 voxels were identified as having a P value less than 10⁻⁴.

Next, blocks of 11 time points were randomly resampled in each of the 228 voxel time courses to create new time series with similar temporal autocorrelations. Voxelwise bootstrap resampling followed by low-pass filtering was performed only on these significant voxels. This allowed a great saving of computational time as the determination of null distributions for every voxel (82,944 total) using this method would take around 242 days, but for the 228 identified voxels, it only took about 16 hours. Gaussian curves were fit to each histogram to determine null distributions and significance for the statistic of each voxel. The non-parametrically-determined P values were then converted back to corrected correlation values for this dataset. Cluster analysis was then applied (minimum of 6 voxels with P < 10⁻⁴ yielding $\alpha = 0.05$ as revealed by Monte Carlo simulations) to account for multiple comparisons.

Results

A comparison of corrected functional connectivity maps for one slice is shown in Figure 2. A correlation (r) threshold of 0.420 was determined to correspond to a P value of 10⁻⁴ by single point resampling of the reference time series, which ignores temporal autocorrelations (Fig. 2a). After bootstrap resampling, voxelwise null distributions were found for significant voxels. The functional connectivity map with corrected correlation values was thresholded at 0.174, which corresponds to a P value of 10⁻⁴ (Fig. 2b). The results after the bootstrap resampling method revealed a smaller region of activation, but showed fewer correlated voxels in white matter, where activation is not expected.

Discussion

A simple, time effective approach has been designed to determine voxelwise null distributions for correlations of waveforms with fMRI resting state voxel time series. Bootstrap resampling of blocks of the the time series has been shown to preserve temporal autocorrelations. Fitting histograms to Gaussian curves and determining voxelwise distributions only on significant voxels are two method of maintaining accuracy and time efficiency. Initial results reveal that the bootstrap resampling method reduced the number of voxels found in white matter.

References

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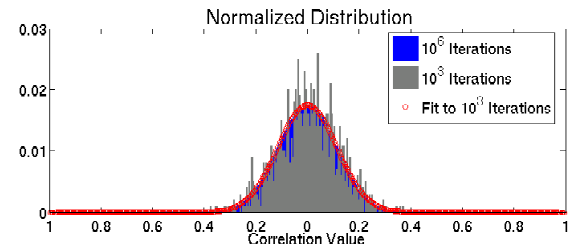


Figure 1. Distributions generated from 1,000 iterations (gray) and from 1 million iterations (blue) and the Gaussian curve fit (red) to the distribution generated from 1,000 iterations.

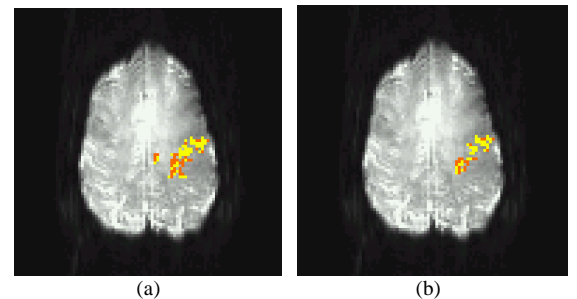


Figure 2. Functional connectivity maps for (a) single point resampling, $r > 0.420$, and (b) bootstrap resampling, $r_{cor} > 0.174$. Cluster threshold $\alpha = 0.05$. (Orange: P < 10⁻⁴, Yellow: P < 10⁻⁵)