Empirical Bayesian Estimation Improves Analysis of Resting-State Functional Connectivity from Multi-Echo BOLD Data

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Target Audience: Investigators using (or considering using) multi-echo acquisitions for functional MRI or other applications.

Purpose: Multi-echo fMRI acquisitions can improve sensitivity (by acquiring more data per unit time) and specificity (by facilitating rejection of nuisance variance) in functional MRI [1-3], compared with conventional EPI. Analysis of the multi-echo decays, yielding estimates of transverse relaxation rates in each brain voxel, is a case of parallel estimation of many parameters at once; statistical theory states that popular maximum likelihood methods (least-squares under Gaussian errors) are inferior to “shrinkage” approaches, such as the James-Stein estimator [4,5]. The purpose of this study was to assess application of the James-Stein shrinkage approach to estimation of transverse relaxation rates from multi-echo data.

Methods: Acquisition: Four healthy adults gave informed consent to participate in IRB-approved research. Resting-state data were acquired at 7 T using multi-echo BOLD: Following each RF excitation, echo-planar images were acquired at echo times of 10, 30, 50, and 70 ms, using a SENSE acceleration factor of 4.0. The TR was 2.6 s, and 140 volumes were acquired in each of two runs; acquired/reconstructed voxel size was 2.5x2.5 mm² / 1.5x1.5 mm² with a slice thickness of 3 mm plus a 0.5 mm gap. Twenty-nine slices were acquired, from the superior aspect of the cerebrum, covering the primary motor network (M1N) and most regions of the default mode network (DMN). A high resolution MP-RAGE image was acquired at isotropic 1 mm resolution. Initial analysis: Standard transverse relaxation rate, \( R_2 \), was computed for each voxel of each volume using least-squares fitting to the echo time decay. A goodness-of-fit threshold was used; only voxels within a 95% confidence interval of +/- 20 s⁻¹ were retained. The \( R_2 \) time series were temporally filtered using a band-pass filter of 0.01 – 0.1 Hz. For each subject, segmentation of the anatomical image was used to classify voxels by tissue type (grey matter, white matter, and cerebrospinal fluid). Shrinkage: The James-Stein estimator was applied to each echo planar image (EPI) to reduce physiological noise, was applied. The effective voxel size was 2.5x2.5 mm² / 1.5x1.5 mm² with a slice thickness of 3 mm plus a 0.5 mm gap. Twenty-nine slices were acquired, from the superior aspect of the cerebrum, covering the primary motor network (M1N) and most regions of the default mode network (DMN). A high resolution MP-RAGE image was acquired at isotropic 1 mm resolution. Initial analysis: Standard transverse relaxation rate, \( R_2 \), was computed for each voxel of each volume using least-squares fitting to the echo time decay. A goodness-of-fit threshold was used; only voxels within a 95% confidence interval of +/- 20 s⁻¹ were retained. The \( R_2 \) time series were temporally filtered using a band-pass filter of 0.01 – 0.1 Hz. For each subject, segmentation of the anatomical image was used to classify voxels by tissue type (grey matter, white matter, and cerebrospinal fluid). Shrinkage: The James-Stein estimator was applied to each EPI voxel to reduce physiological noise, was applied. The effective voxel size was 2.5x2.5 mm² / 1.5x1.5 mm² with a slice thickness of 3 mm plus a 0.5 mm gap. Twenty-nine slices were acquired, from the superior aspect of the cerebrum, covering the primary motor network (M1N) and most regions of the default mode network (DMN). A high resolution MP-RAGE image was acquired at isotropic 1 mm resolution. Initial analysis: Standard transverse relaxation rate, \( R_2 \), was computed for each voxel of each volume using least-squares fitting to the echo time decay. A goodness-of-fit threshold was used; only voxels within a 95% confidence interval of +/- 20 s⁻¹ were retained. The \( R_2 \) time series were temporally filtered using a band-pass filter of 0.01 – 0.1 Hz. For each subject, segmentation of the anatomical image was used to classify voxels by tissue type (grey matter, white matter, and cerebrospinal fluid). Shrinkage: The James-Stein estimator was applied to each EPI voxel to reduce physiological noise, was applied. The effective voxel size was 2.5x2.5 mm² / 1.5x1.5 mm² with a slice thickness of 3 mm plus a 0.5 mm gap. Twenty-nine slices were acquired, from the superior aspect of the cerebrum, covering the primary motor network (M1N) and most regions of the default mode network (DMN). A high resolution MP-RAGE image was acquired at isotropic 1 mm resolution. Initial

Results: The James-Stein estimator increased the spatial extent (number of significant voxels) of the DMN and M1N by about 2% and 4%, respectively. Table 1 compares the extent of seed-based functional networks derived from original vs. improved \( R_2 \) estimates. Shrinkage also improved the consistency of spatial maps across subjects; the first two columns of Table 2 summarize increased spatial concordance in high Z score voxels following application of the James-Stein estimator. The shrinkage decreased Z scores in DMN by 0.7% (p=0.01 paired T test); the corresponding decrease was not significant in M1N.

Discussion: Parallel estimation is typically accomplished using maximum-likelihood approaches, even though the empirical Bayes / shrinkage approach is theoretically superior [4,5]. In this study, application of the James-Stein estimator yielded modest improvements in the sensitivity of seed-based correlation outcome measures.

Conclusion: The James-Stein estimator improves outcome measures derived from multi-echo BOLD data acquired in the resting state.