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 mm^2 / 1.5x1.5 mm^2 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 preprocessing, including application of COMPCOR [6] to each echo to reduce physiological noise, was applied. The effective 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 over all voxels of each tissue type at each time point. For each voxel, the adjusted R_2^* was $R_2^{*shrink} = \overline{R_2^*} + (1-\lambda)\times(R_2^* - \overline{R_2^*})$. The shrinkage factor λ is given by $\lambda = (n-3)\sigma^2 / \sum_{i=1}^{n}(R_{2\,i}^* - \overline{R_2^*})^2$, where σ^2 is the temporal variance in R_2^* prior to band-pass filtering, and $\overline{R_2^*}$ denotes the spatial mean within the tissue type.
Functional connectivity analysis: Seed-based correlation was applied to R_2^* volumes using seeds for the DMN and M1N. Correlation coefficients were converted to Z scores using the Fisher transformation. One-sample T-tests on the 8 Z score maps (i.e., two runs in each of four participants) used permutation-based family-wise error correction for multiple comparisons to achieve a false positive rate of 0.05. Outcomes using least-squares ("original") R_2^* values were compared to those computed from the James-Stein ("improved") R_2^* values.

	DMN	M1N
Original	2166	2156
Shrinkage	2201	2844

Table 1. Spatial extent (number of significant voxels) in default mode network (DMN) and primary motor network (M1N).

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.

	Number of high Z score voxels concordant over both runs in all subjects.		Average Z score within each network		Average temporal variation of R_2^* within each network	
	DMN	M1N	DMN*	M1N	DMN	M1N
Original	73	30	0.410±0.074	0.386±0.028	0.67±0.16%	0.55±0.20%
Shrinkage	77	38	0.407±0.076	0.377±0.030	0.66±0.16%	0.55±0.20%

Table 2. Network measures; asterisk denotes significance by paired T test at $p<0.05$.

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.

References: 1. Posse *et al.*, Magn. Reson. Med. 42:87, 1999. **2.** Poser & Norris, NeuroImage 45:1162, 2009. **3.** Kundu *et al.*, NeuroImage 60:1759, 2012. **4.** Stein, Proc. 3rd Berkeley Symp. Math. Statist. Prob. 1:197, 1956. **5**. James & Stein, Proc. 4th Berkeley Symp. Math. Statist. Prob. 1:361, 1961. **6.** Behzadi *et al.,* NeuroImage 37:90, 2007.

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