Minimizing spurious functional connectivity findings from resting state fMRI

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Background The validity of functional brain connectivity assessments from resting state fMRI (rs-fMRI) has recently been called into question by studies showing that artifacts from small head in-scanner movements (~0.1mm) severely bias functional connectivity (FC) estimates [1]. Here we show that removing non-BOLD fluctuations from rs-fMRI data based on *a priori* knowledge of linear dependence between BOLD signal and echo time (TE) comprehensively removes motion artifact from rs-fMRI data. We present an integrated methodology that involves: multi-echo EPI acquisition to sample T2* decay of fMRI signal fluctuations, decomposition of data with multi-echo independent component analysis (ME-ICA) to separate BOLD from non-BOLD sources, and finally estimation of FC between brain regions by computing correlation of independent BOLD component coefficients, which simplifies accounting for effective degrees of freedom (DOF) for statistical inference and hypothesis testing. **Methods** Resting state fMRI data from 33 normal volunteers were used in this study, which was approved by the Local Research Ethical Committee at the University of Cambridge. Data were acquired with a Siemens Trio 3T MRI scanner and a 32-channel receive-only head coil (Siemens Medical Solutions, AG, Erlangen, Germany). Functional images were acquired with a multi-echo EPI sequence (TE = 12,28,44,60 ms, TR 2.47 s, flip angle 78, matrix size 64 × 64, resolution 3.75mm isotropic, 32 oblique alternating oblique slices with 10% gap, GRAPPA 3, 1698 Hz/pixel). Images were reconstructed online using the scanner's reconstruction engine. Anatomical images were acquired using a T1-weighted MPRAGE sequence (176 × 240 FOV, 1mm in-plane resolution). Functional data were preprocessed as follows: slice (temporal) and volume realignment, non-linear coregistration to MNI space anatomical, and 4mm FWHM smoothing. Multi-echo data were decomposed by ME-ICA as follows: principal components analysis (PCA) followed by TE-dependence analysis to compute κ and ρ metrics [2] to identify the principal space, ICA followed by TE-dependence analysis to identify the BOLD subspace. FC was estimated as correlation of BOLD spatial ICA component coefficients (*r*) followed by Fisher *(r-Z)* transformation including the standard error term, factoring DOF as the number of high κ components. **Results** ME-ICA robustly denoised linear and non-linear manifestations of in-scanner head motion and other nuisance sources, with equivalent efficacy for datasets with different levels of motion artifact without arbitrary processing such as data censoring ("scrubbing") or band pass filtering. Figure 1 shows the effect of separating BOLD and non-BOLD time series in terms of removing the effects of subject motion. Figure 1(a) shows that motion regression does not remove artifact or recover functional contrast nearly as well as isolating BOLD fluctuations in high-κ time series. Figure 1(b) shows that low-κ non-BOLD time series have a DVARS trace nearly identical to that of raw data. In comparison, high-κ BOLD time series have a nearly flat DVARS trace. Denoising and then factoring effective degrees of freedom (i.e. number of high-κ components) into subject level FC analysis equalized FC maps from datasets with categorically different levels of motion, while conditioning FC distributions to enable robust statistical inference at the subject level (Figure 2a). Subsequently, group level seed-based FC patterns based on ME-ICA were found to closely follow activation patterns associated with respective seeds (Figure 1b). Finally and critically, ME-ICA FC group contrasts produced low false positive error rates that did not increase in permuted groupings that were increasingly biased by motion. In contrast, conventional FC maps were inconsistent at subject level and highly susceptible to motion-related bias in contrasts between groups. **Conclusion** ME-ICA mitigates motion artifact for both subject and group level FC analysis, solving a critical problem in the study of functional connectivity using a physically and statistically principled approach.

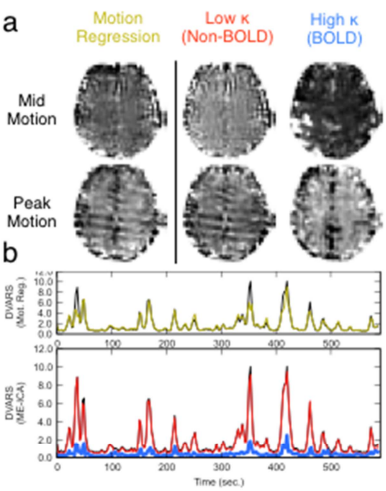

Figure 1 (a) fMRI images, from two points in time series, after motion regression, and low and high κ time series. (b, top row) DVARS traces of raw and motion regressed data. (bottom row) DVARS of raw, low κ, and high κ time series. Raw and low κ DVARS strongly overlap.

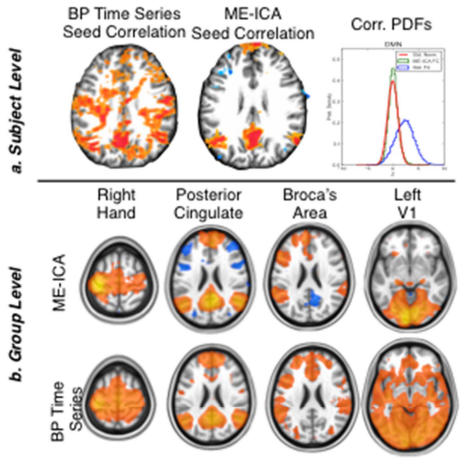

Figure 2 (a) Maps for seed-based correlation analysis of the default mode network after denoising with standard (left, R>0.5) and ME-ICA (right, p<0.05). approaches. (b) Group level random effects analysis of ME-ICA (p<0.01, FDR q<0.05) and standard FC (p<10-7, FDR q<10-6.)

References [1] Power et al, Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion, *NeuroImage,* 2011. [2] Kundu et. al, Differentiating BOLD and non-BOLD signals in fMRI time series using multi-echo EPI, *NeuroImage*, 2012.