Multi-Echo fMRI Atlas of Seed-Based Functional Connectivity with Power Analysis

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Background Multi-echo (ME) fMRI methodology has recently been adopted by several groups for large cohort studies on typical development and neuropsychiatric disorders (e.g. autism, addiction, chronic pain). Here we present a novel atlas of group-level seed-based functional connectivity from a large sample of normal control datasets (N=139), using the unbiased seed-connectivity estimator achieved by combining multi-echo (ME) fMRI and ICA (ME-ICA)[1]. This estimator, called multi-echo independent coefficients regression (ME-ICR), interprets ICA as a transformation of data into approximately independent/sparse coefficients, enabling: classification of components as BOLD/non-BOLD based on component-level TE-dependence (κ) in ME-fMRI data; denoising by non-BOLD component rejection; correlation between the BOLD coefficient vectors of voxels; and finally BOLD degree of freedom (DOF) regularization within the Fisher R-Z transform. As an unbiased estimator, ME-ICR produces nearly normally distributed subject-level correlation distributions for any given seed, and group-level analysis with type I error control when comparing datasets with BOLD DOF differences (due to acquisition sensitivity variation from motion). By comparison, conventional seed-based functional connectivity using correlation between "denoised" single-echo fMRI time series suffers from ineffective denoising, unaccounted DOF variability across datasets, high type I error from group analysis, and poor understanding of statistical power with increasing N. Here we demonstrate group ME-ICR seed-connectivity maps for numerous cortical and subcortical regions, alongside power analysis using subsampling at N=10,25,50,75,100 to assess N required to make specific connectivity observations. **Methods** *Subjects and Acquisition* 139 subjects were scanned for 10 min. with multi-echo EPI (TR=2.47s; flip angle=78°; 3.75x3.75x4.4mm^3; 32 oblique alternating slices, iPAT 3; 1698 Hz/pixel; TE = 12,28,44,60ms) [2], and MRPAGE (1mm^3 iso., TI=1100ms) on Siemens 3T Tim Trio. *Preprocessing* ME-ICA v2.5 implemented slice and volume realignment, nonlinear coregistration (AFNI *Qwarp*[3]), T_2* weighted combination[4], BOLD/non-BOLD ME-PCA dimensionality detection and BOLD/non-BOLD ME-ICA decomposition and component separation (97% dataset variance explained on average) [1]. *Subject-level ME-ICR* The ICA mixing matrix was fit to the T_2* weighted combination of ME data, and concatenated (unthresholded) maps of "high-κ" BOLD components produced the coefficient vector dataset. After computing Pearson correlation *(R)* between seed and target coefficient vectors, R values were converted to standard (Z_{corr}) scores using the Fisher R-Z transform, which adjusted for BOLD DOF (i.e. number of high-κ components) using the canonical standard error term. *Group ME-ICR* Subject-level ME-ICR coefficient datasets and dataset-level standard error terms were input to AFNI *3dGroupInCorr*, which produced 1-sample T-test group connectivity maps for several seeds. T-values were converted to standard scores (Z_T). **Results** Group ICR maps are shown in Figure 1a, with Z_{corr} overlay and Z_T threshold (Z_T=6[σ]). Overall: maps are sparse; conform well to anatomy; show cortical and subcortical connectivity with comparable performance (note thalamic nuclei); do not show anticorrelation (thus rendered all positive); and agree with localization seen from task activation. Maps are rendered here to convey power gains from group analysis. At subject level, Z_{corr} is both effect size and the basis of significance (p). At group level, significance is determined by Z_T, and smaller Z_{corr} effect sizes are observed with greater Z_T significance. Warm and yellow colors indicate Z_{corr}≥1 and Z_{corr}≥2 (i.e. p≤0.05), so yellow connectivity is significant at subject level, while cooler colors indicate weaker magnitude connectivity exposed by group analysis. Cooler regions may extend yellow cores, or show long-range connectivity (e.g. fusiform face area to amygdala). Small displacements in seed localization produce connectivity differences, e.g. posterior putamen seed shows connectivity to Brodmann area 4 while anterior putamen seed shows connectivity to area 6. Figure 1b demonstrates power gain with higher N for connectivity analysis of the orbitofrontal cortex (OFC), and reveals that a Z_T=3[σ] OFC-hippocampus connectivity is observable at N=25 but in a noisy map, while a 6σ observation is achievable at N~75, and higher N>75 does not proportionally add power to this 1-sample analysis. **Discussion** Group ME-ICR enables high-quality whole-brain functional connectivity analysis for hypotheses regarding individual brain regions, producing well-localized connectivity maps that have stable behavior across varying N. **Conclusion** Current and future studies on functional connectivity using ME data may benefit substantially from the sensitivity of ME-ICR to cortical and subcortical connectivity, directness of analysis, simplicity of use, and statistical stability.

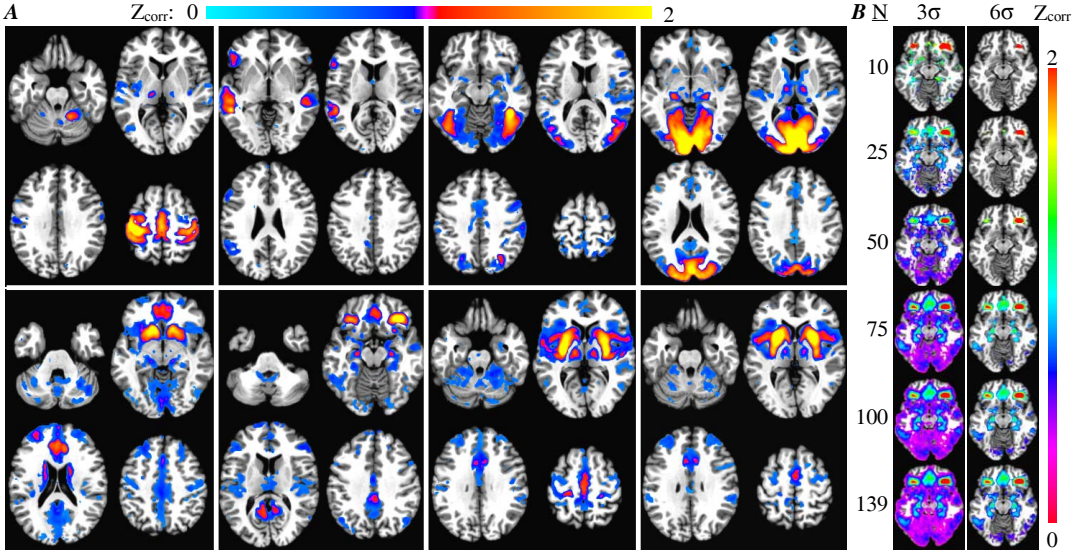

Fig. 1 Underlay is high-resolution MNI template **(a)** Group ICR maps of seeds (clockwise) in MNI coordinates. Overlay is mean Z_{corr} thresholded by Z_T≥6[σ]: right hand area (-33,-29,57), Wernicke's area (-53,-41,2), fusiform face area (43,-44,-18), primary visual (-5,-96,-4), ant. putamen (-24,10,1), pos. putamen (-29,-8,4,), orbitofrontal cortex (36,34,-16), ventral striatum (-13,20,5). **(b)** Orbitofrontal connectivity at 3σ and 6σ, for varying N. Note stable 6σ connectivity for N≥75.

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