Deriving Unbiased Seed-based Functional Connectivity Maps with An Iteration Strategy

W-J. Pan[1], and H. Lei[1]

[1]State Key Laboratory of Magnetic Resonance and Atomic & Molecular Physics, Wuhan Institute of Physics and Mathematics, Chinese Academy of Science, Wuhan, Hubei, China, People's Republic of

Introduction Seed-based cross-correlation analysis (sCCA) has been widely used in functional connectivity MRI (fcMRI) studies, such as exploring the resting-state networks in human brain [1, 2]. However, the detected network may be biased by empirical and often subjective selection of the initial seed [3]. To address this problem, here we propose a novel approach, seed-iteration cross-correlation analysis (siCCA), to examine the brain default network at rest. The method was shown to give results that are not dependent on the choice of the initial seed.

Materials and Methods Twelve healthy adults underwent a 7.6-min resting-state fMRI scan (i.e., 215 time points) in a 1.5T Eclipse scanner (GE-EPI: TR/TE 2074/50 ms, FOV 240 mm×240 mm, matrix size 64×64, slice thickness 6 mm, inter-slice interval 1 mm and 20 axial slices), during which the subjects were awake with eyes closed and ear-plugged, and instructed to keep motionless and quiet. The pre-processing steps for the time-series data were conducted in SPM2 and Matlab and included slice timing correction, head motion correction, spatial normalization, spatial smoothing with a 6-mm FWHM kernel, removing linear drift and temporal band-pass filtering (0.01-0.08 Hz). Spurious signals from different sources (i.e., head-motion, variations in global signal intensity and signals from ventricular and white matter ROIs) were removed from the data through linear regression. The data were then subjected to the sCCA and siCCA analyses.

In the traditional sCCA approach, two seeds of spherical shape (r=8 mm) were selected from the posterior cingulate cortex (PCC, MNI: [3, 48, 0]) and the ventral anterior cingulate cortex (vACC, MNI: [0, -57, 24]), respectively. Individual whole-brain connectivity maps were calculated with the seeds. In the siCCA approach, group-level connectivity maps were first derived with the initial seeds (random-effect one-sample t-test ($p < 0.005$, FDR-corrected, cluster threshold 15 voxels). The ensembles of all the significant voxels in the group-level connectivity maps were then used as a new seed, from which the averaged time courses treated as reference function to derive new connectivity maps. The procedure was iterated continued until the connectivity maps became stable. For both approaches, the connectivity maps derived from different initial seeds were compared pixel-by-pixel with a random-effect two-sample t-test ($p < 0.05$, FDR-corrected).

Results The connectivity maps derived with vACC and PCC as the seeds should involve the so-called default network [2]. However, with the sCCA approach, different seeds yielded somewhat different results (Fig. 1A-D). With the initial seed positioned in the vACC, the connectivity map obtained showed larger involvements of bilateral ACC and anterior insulae (Fig. 1C); With the initial seed positioned in the PCC, the connectivity map obtained showed larger involvements of PCC as well as lateral parietal lobe and cerebellum (Fig. 1D). However, with the siCCA approach, no significant differences were found between the maps derived from different seeds (Fig. 1E-F).
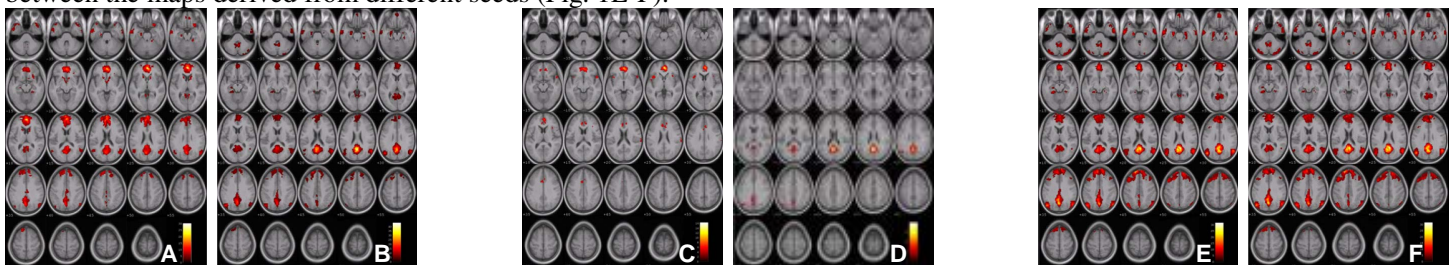

Fig. 1 Group-level connectivity maps derived with the sCCA (A and B) or siCCA (E and F) approach employing two initial seeds positioned in the vACC (A and E) and PCC (B and F), respectively. The statistically significant (two-sample t-test, $p < 0.05$, FDR-corrected) differences between (A) and (B) are shown in (C) and (D) (C: vACC>PCC, D: vACC<PCC). No statistically significant differences were found between (E) and (F).

Discussion The connectivity maps derived with the sCCA approach are known to be susceptible to bias originated from the empirical, and often subjective, selection of the position and the size of the initial seed, making the results less comparable among different fcMRI studies [3]. The seed-selection-induced bias is at least partially related to the signal-to-noise ratio and contrast-to-noise ratio of the raw data [3]. The dependence of the resultant connectivity map on seed-selection could also be due to so-called node specificity (i.e., not all nodes in a given network behaves exactly the same). In this work, we propose to derive connectivity maps using cross-correlation analysis in an iterative manner. The data showed that, with the siCCA approach, consistent connectivity maps could be obtained regardless of the selection of the initial seed. This could be due to that fact that, in the siCCA approach, the effects of random thermal noise and node specificity on the derivation of connectivity maps are greatly reduced because of signal averaging over the entire network and iteration processes.

References [1] Biswal, B., et al., Magn Reson Med, 1995. **34**(4): p. 537-41. [2] Greicius, M.D., et al., Proc Natl Acad Sci U S A, 2003. **100**(1): p. 253-8. [3] Ma, L., et al., Magn Reson Imaging, 2007. **25**(1): p. 47-56.