A Correlation-Matrix-Based Clustering Method for Extracting Correlation Patterns of Spontaneous BOLD Fluctuations

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Introduction Spontaneous blood-oxygen-level-dependent (BOLD) signals acquired in the resting state have recently been found to imply many correlation structures that are consistent with the patterns of well-known brain networks [1–2]. It was therefore hypothesized that the spontaneous BOLD signals reflect the fluctuation of ongoing brain activity and imply many resting-state networks. The hypothesis-driven seed-based correlation mapping [1] and the data-driven independent component analysis (ICA) [3] are currently two most popular methods for extracting the spatial correlation patterns (resting-state networks) hidden in spontaneous BOLD fluctuations. However, the former method needs priori defined seed regions and can only identify one pattern of interest by each mapping step, while the results of the latter one are not easy to interpret and are susceptible to noise level. In this study, we proposed a novel correlation-matrix-based clustering method for extracting the correlation structures (patterns) hidden in spontaneous BOLD fluctuations. This method has several advantages: no priori information required, easy interpretation of outcomes, easy for group level analysis (combining data from multiple runs of multiple subjects), and effective in identifying multiple resting networks with more robust patterns.

Methods **B*asic Theory***: The temporal correlation matrix for a single spontaneous BOLD signal dataset contains correlation coefficients between any pairs of image voxels. Each row (or column) of the correlation matrix includes the correlations of a specific voxel to all the voxels; therefore it is actually a seed-based correlation map (compressed to 1D) with respect to this specific voxel. For the brain voxels belonging to the same resting-state network, their corresponding correlation maps (and thus rows/columns of the correlation matrix) should be very similar. If we can find a method that can group the rows/columns of the correlation matrix according to their similarity, the patterns of multiple resting-state networks could be identified. Clustering analysis is a good solution to accomplish this task.

Data Processing: The above idea was tested on datasets acquired from rats anesthetized with 1.0% isoflurane. For detail information about the datasets, please refer to our previous study [4]. After the same pre-processing steps for resting-state data analysis, the data were further analyzed with three methods: two correlation maps were calculated with respect to two seed regions located in the right S1FL and S1BF regions, independent components (ICs) were extracted with the MELODIC tool of the FSL (FMRIB Software Library) [5], and cluster maps were obtained by averaging the correlation matrix rows belonging to the same cluster, which was determined by a K-Means clustering analysis.

Fig. 1 Two seed-based correlation maps (left) and corresponding ICs (middle) and cluster maps (right) indicating two resting-state networks.

Fig. 2 The patterns of two clusters related to resting-state motor–caudate putamen and sensory–thalamic nuclei networks, respectively.

Results Twenty-six ICs were identified by the MELODIC, and the same cluster number was applied for the K-Means clustering analysis. Generally speaking, the clusters obtained by the new method have a much clearer and well-defined pattern than ICs. Due to the space limitation, it is not practical to display and compare all ICs and clusters herein, but we show two ICs (Fig. 1, the middle panel) and two cluster maps (Fig. 1, the right panel) similar to the two seed-based correlation maps (Fig. 1, the left panel), which reflect two resting-state networks covering the bilateral S1FL and S1BF regions, respectively. Both the correlation maps and cluster maps show much clearer patterns than the ICs. Furthermore, the correlation-matrix-based clustering can identify much more interesting patterns than ICA. Through visualization, the majority of identified 26 clusters show "meaningful" patterns while only about a half of 26 ICs do so. For example, the motor–Caudate Putamen (CPu) and sensory–Thalamic Nuclei (TN) networks can be consistently (across different runs) identified with the new method (Fig. 2) but did not show up in the results of ICA.
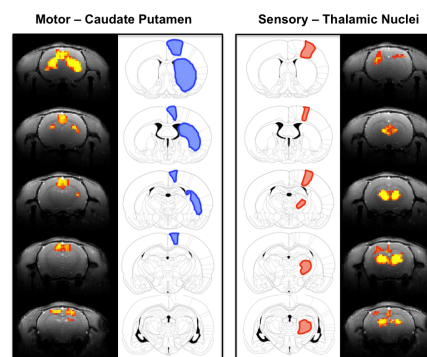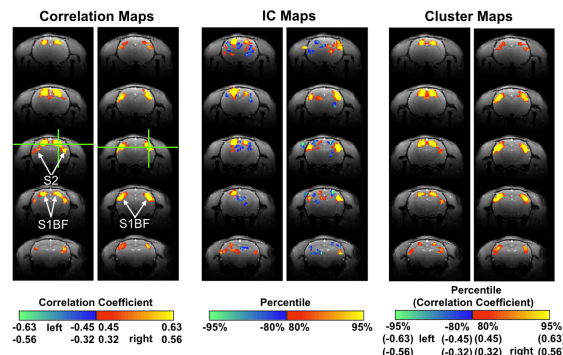
To examine the performance of correlation-matrix-based clustering method in grouping the rows of the correlation matrix according to their similarity, we reordered the rows/columns based on the clustering results: the rows/columns belonging to the same cluster were rearranged together. The original and reordered correlation matrices are plotted in Fig. 3, and one can see that the similar rows (correlation maps) were successfully grouped into the same cluster.

Discussion Similar to the seed-based correlation mapping, the novel correlation-matrix-based clustering method introduced in this study can identify robust and clear patterns hidden in spontaneous BOLD fluctuations, and the correlation strength could be easily interpreted as the functional connectivity strength between brain regions. Furthermore, it requires no priori defined seed regions and can identify multiple patterns at one time, like other data-driven strategy, e.g., ICA. Compared to the previous hierarchical clustering method based on spontaneous BOLD signal time courses [6], this spatial-domain method is more directly linked to the spatial pattern of resting-state networks, the K-Mean clustering algorithm is much computation-efficient than the agglomerative hierarchical clustering especially for datasets with a large number of voxels, and the group-level analysis can be easily achieved by concatenating correlation matrices from multiple runs (or subjects) and then performing the clustering analysis.
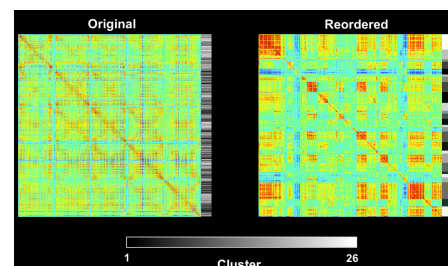

Fig. 3 The original correlation matrix and the reordered correlation with rearranged rows/columns according to the clustering results .

In summary, the correlation-matrix-based clustering method should provide a powerful analysis tool for investigating spontaneous BOLD fluctuations and associated resting-state networks, and for providing new insights into this interesting phenomenon. In addition, this method is ready to be extended to conventional fMRI applications for identifying activated brain regions in response to external stimulation or during task performance.

References   [1] *Biswal B. et al. MRM 1995* [2] *Fox MD. et al. Nat Rev Nerosci 2007* [3] *van de Ven VG. et al. HBM 2004* [4] *Liu X. et al. ISMRM 2010 p357* [5] *Smith SM. et al. NeuroImage 2004* [6] *Cordes D. et al. MRI 2002.*