Identifying fMRI Dynamic Connectivity States Using An Affinity Propagation Clustering Method: Application to Schizophrenia

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Introduction

Dynamic functional network connectivity (dFNC) analysis can capture time-varying functional connectivity (FC) among brain networks over tens of seconds (Calhoun et al., 2014). The inherent connectivity states in the dynamic connectivity patterns can provide informative biomarkers for distinguishing mental disorders.

K-means clustering has been widely used to extract connectivity states from time-varying FC. However its *limitations* include susceptibility to local minima caused by poor initialization and slowness in convergence due to extensive noise in high-dimensional dynamic FC.

We propose to utilize an *affinity propagation (AP)* clustering based method to estimate the connectivity states. This method performs clustering by using similarity measures between pairs of samples and propagating information until a high-quality set of exemplars and corresponding clusters gradually emerge (Frey and Dueck, 2007). It simultaneously considers information of all samples and avoids the problem caused by poor initialization.

By applying k-means and the new method separately, we analyzed dynamic FC of 82 healthy controls (HCs) and 82 schizophrenia patients (SZs), and explored group differences in the identified connectivity states.

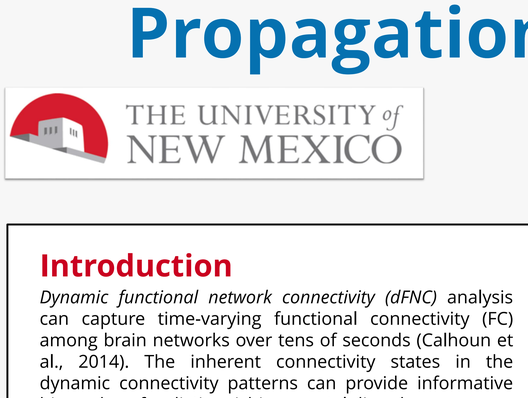


Fig. 1: Overview of Methods

Methods

Data: Resting-state fMRI data was collected from 82 healthy controls (HCs; age: 37.7 ± 10.8, 19 females) and 82 schizophrenia patients (SZs; age: 38.0±14.0, 17 females).

Scanning parameters: Subjects were scanned on a 3-Tesla Siemens Trio scanner with a 12-channel RF coil at the Mind Research Network (MRN). Subjects were asked to remain alert with eyes open and keep their head still. Scans were acquired using gradient echo planar imaging (EPI) with parameters: echo time (TE) = 29ms, repeat time (TR) = 2s, flip angle = 75◦, slice thickness = 3.5mm, slice gap = 1.05mm, field of view = 240mm, matrix size = 64 × 64, voxel size = 3.75mm × 3.75mm × 4.55mm. Scans consisted of 150 whole brain images.

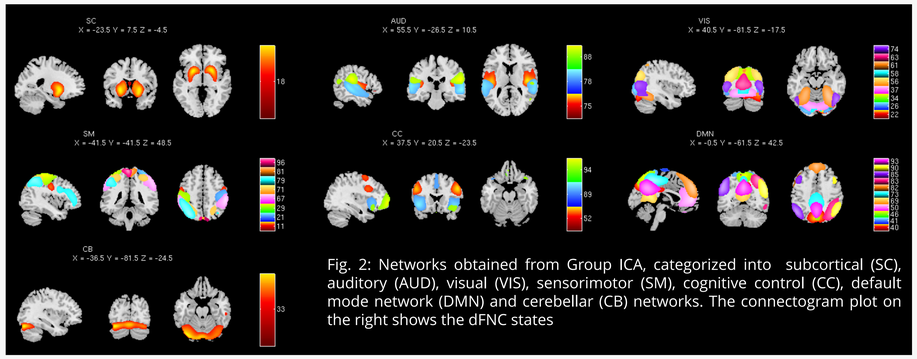
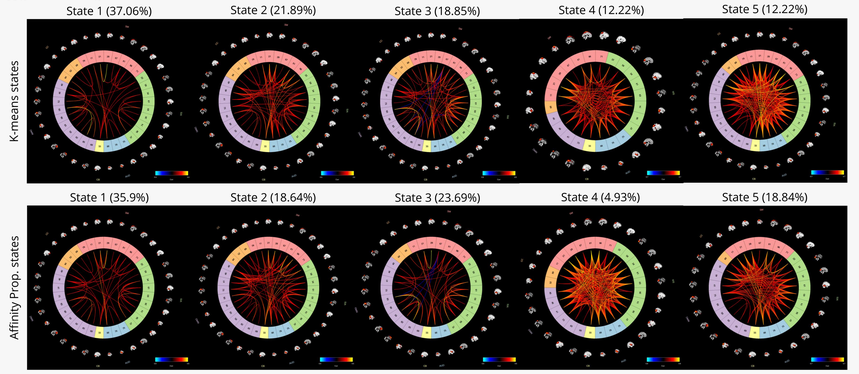


Fig. 2: Networks obtained from Group ICA, categorized into subcortical (SC), auditory (AUD), visual (VIS), sensorimotor (SM), cognitive control (CC), default mode network (DMN) and cerebellar (CB) networks. The connectogram plot on the right shows the dFNC states



Methods (contd.)

Preprocessing: The first 6 volumes from each scan were discarded to allow T1 equilibration. INRIAlign was used to realign the images. Then the data was spatially normalized to the standard Montreal Neurological Institute (MNI) space, resampled to 3mm × 3mm × 3mm voxels using the nonlinear (affine + low frequency direct cosine transform basis functions) registration implemented in the SPM12 toolbox and smoothed using a Gaussian kernel of FWHM of 8mm.

Group ICA & postprocessing: Fig. 1 shows the flowchart of processing. A group-level spatial ICA was performed on the preprocessed fMRI data using Infomax algorithm to obtain group-level independent components (ICs). Then subject-specific components and corresponding time courses (TCs) were calculated using GICA1 back-reconstruction. After discarding artifact-related ICs, the remaining 36 ICs of each subject were characterized as functional networks. The TCs of the 36 networks were postprocessed by detrending, regressing out head motion, despiking and performing low-pass filtering (< 0.15Hz).

Dynamic FNC analysis: For analyzing dynamics, a sliding window method with size of 26 TR (52s) and step of 1 TR was used to separate each TC into 118 short TCs. Each window was convolved with a Gaussian of σ = 3 TR to obtain tapering along the edges. FCs among networks were estimated based on 36 networks' short TCs in each window from a regularized inverse covariance matrix using graphical LASSO framework. The connectivity values were then Fisher-Z transformed.

Clustering: The window direction-concatenated dFNC vectors of all subjects were clustered separately using k-means and AP method to produce five clusters. The subject-specific connectivity states for each subject were estimated by averaging the associated FCs which are in windows with the same label.

Statistical comparison: Regarding each method, the difference in each connectivity strength between HCs and SZs was investigated using a two-sample T-test based on the corresponding subject-specific states.

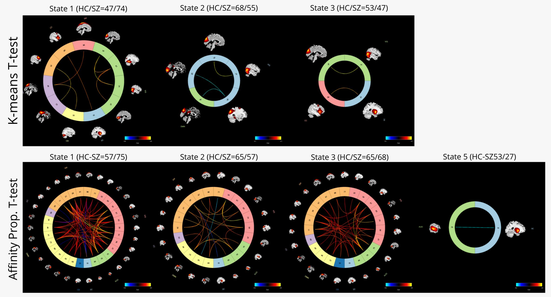


Fig. 3: HC vs SZ group difference in connectivity states estimated by two methods (k-means and AP approach). Two-sample t-tests were performed on each connectivity of HC and SZ subjects to investigate group differences. T-values are shown for connectivity where p<0.05 (FDR corrected)

Results

The 36 functional networks obtained from Group ICA are presented in Fig. 2(left). The networks are grouped by their functional domains. In Fig. 2(right), two groups of five dFNC states each obtained from k-means and AP clustering methods respectively are displayed using a connectogram plot. Compared to the other states, state 1 estimated by both approach has the highest occupancy (and lower connectivity strengths) and therefore may be the most crucial area when comparing the two approaches.

Fig. 3 shows the t-values obtained from the two-sample t-tests on the connectivity passing a significance level of $p < 0.05$ with false discovery rate (FDR) correction for multiple comparisons. Greater group differences were found using the AP clustering. In AP states 1 and 2, SZ group had significant increased FCs than HC group in subcortical and sensorimotor networks connectivity. The finding is supported by previous studies (Damaraju et al., 2014) but was absent using the k-means analysis here. Also, for states 1-3, decreased FCs in SZ group between auditory, visual and sensorimotor networks was highly conspicuous in AP results, consistent with previous studies. Furthermore, Only the AP method was able to identify the SZ group's dysconnectivity in default mode network regions in state 1.

Conclusions

Compared to k-means, the AP approach appears to estimate more meaningful connectivity states and provide more informative measures for differentiating SZ and HC by overcoming some shortcomings of k-means. The results may be further improved by taking advantage of the semi-supervised features of AP algorithm.

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