The x-Guided Clustering Method and its Application to Unbiased Detection of Differences in Functional Connectivity Networks

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Introduction: In resting-state functional MRI cross-group studies, the available techniques may bias the results in choosing the specified reference. In this study, we introduced an x-guided clustering method to identify the functional clusters for unbiased detection of differences in cross-group studies.

Methods: Seventeen amnestic mild cognitive impaired (aMCI) and 22 cognitively normal (CN) subjects were included in the study. The study was conducted with Medical College of Wisconsin Institutional Review Board approval. Written informed consent was obtained from each participant. The resting-state functional connectivity fMRI datasets were obtained at a 3T Signa GE scanner.

Functional connectivity difference information between the aMCI and CN groups was employed to produce voxelwise clusters. The analysis was applied to n voxels of the cortical and subcortical brain regions. The functional connectivity of each voxel pair was calculated from the corresponding preprocessed R-fMRI time courses, using Pearson product-moment correlation coefficient (r). The result was an n-by-n r-matrix for each subject. The Fisher transformation, m=0.5ln[(1+r)/(1-r)], which yielded variants of approximately normal distribution, was applied to the individual r-matrix to generate the m-matrix. The functional connectivity difference was calculated using the m-matrices and two-sample *t*-test. The result was an n-by-n Z-matrix. Each voxel has n Z-values corresponding to a particular row in the Z-matrix. We call each row of n Z-values the Z-vector. The Z-values were thresholded at Z<-1.96 to keep the pairs that showed reduced connectivity in the aMCI group. The hierarchical relationship of the n voxels was obtained based on the similarity of their Z-vectors. The clustering analysis was implemented using the MatLab built-in function, "linkage" and "dendrogram." The n voxels' Z-vectors were sent to the "linkage" function as input. The "correlation" method was used in the "linkage" function to calculate the distance (d) between voxels. Specifically, $d_{ij} = 1 - r_{ij}$, where, r_{ij} is the correlation coefficient between the *Z*-vectors belonging to voxel *i* and voxel *j*. A detailed description of the hierarchical clustering method can be found in the references (1). To account for random false-positive findings, a correction technique that is similar to AFNI function AlphaSim was employed. Specifically, a cluster size threshold and a homogeneity threshold were employed to define the cluster of interest.

Results:

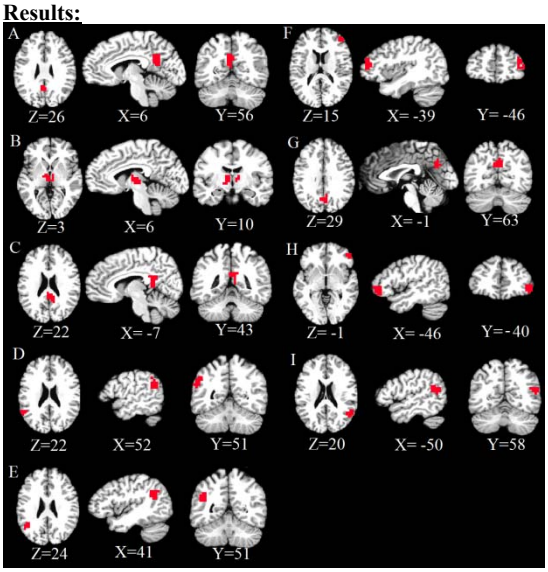

Fig1. The x-guided clustering method identified nine clusters using group difference information. (**A**) The bilateral posterior cingulate cluster. (**B**) The bilateral thalamus cluster. (**C**) The retrosplenial cingulate cluster. (**D**) The left supramarginal cluster. (**E**) The left superior temporal cluster. (**F**) The right middle frontal cluster. (**G**) The bilateral precuneus cluster. (**H**) The right inferior frontal cluster. (**I**) The right superior temporal cluster.

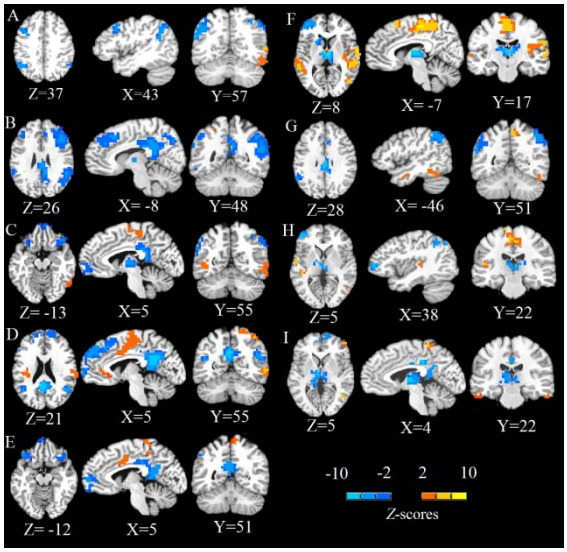

Fig2. Altered connectivity to the nine clusters shown in Fig1. The subfigures are arranged so they correspond to the same subfigures in Fig1 that show the cluster masks. The regions that showed lower connectivity to the nine clusters were selected as nine masks (i.e. regions that were highlighted by blue color) to generate the composite connectivity index (Fig3) for each subject. Color bar indicates Z scores.

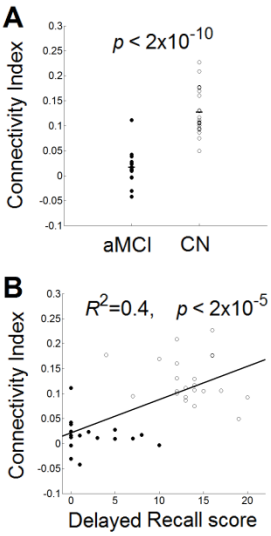

Fig3. Connectivity index and neuropsychological test score. (**A**) Connectivity index of aMCI and CN subjects. (**B**) Relationship between the connectivity index and paragraph delayed recall scores of the Wechsler Memory Scale.

Discussion:

We introduced an x-guided clustering method to define functional clusters that are not biased by subject group selection in R-fMRI-based group studies. Using the x-guided clustering method, clusters with homogeneous functional connectivity changes between the aMCI and CN groups were identified. The distribution of these clusters, as well as their disconnected regions (the areas that had decreased connectivity to these clusters), resembled the altered memory network regions identified in task fMRI studies (2). The connectivity indices were significantly different between aMCI and CN subjects and significantly correlated with memory test scores. The method has the potential to identify brain connectivity biomarkers for disease status classification, prediction of individual behavioral performance, and monitoring the efficacy of disease-modifying therapies. The application of the method may significantly advance the research field of R-fMRI.

References: 1. Friedman J, et al. 2009. Springer-Verlag New York, NY. 2. Machulda MM, et al., 2009. J Int Neuropsychol Soc 15, 372-382.

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