



A clustering-based method to detect functional connectivity differences

Gang Chen^a, B. Douglas Ward^a, Chunming Xie^a, Wenjun Li^a, Guangyu Chen^a, Joseph S. Goveas^b, Piero G. Antuono^c, Shi-Jiang Li^{a,b,*}

^a Department of Biophysics, Medical College of Wisconsin, Milwaukee, WI, USA

^b Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

^c Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA

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ABSTRACT

Recently, resting-state functional magnetic resonance imaging (R-fMRI) has emerged as a powerful tool for investigating functional brain organization changes in a variety of neurological and psychiatric disorders. However, the current techniques may need further development to better define the reference brain networks for quantifying the functional connectivity differences between normal and diseased subject groups. In this study, we introduced a new clustering-based method that can clearly define the reference clusters. By employing group difference information to guide the clustering, the voxels within the reference clusters will have homogeneous functional connectivity changes above predefined levels. This method identified functional clusters that were significantly different between the amnesic mild cognitively impaired (aMCI) and age-matched cognitively normal (CN) subjects. The results indicated that the distribution of the clusters and their functionally disconnected regions resembled the altered memory network regions previously identified in task fMRI studies. In conclusion, the new clustering method provides an advanced approach for studying functional brain organization changes associated with brain diseases.

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Introduction

Recently, resting-state functional magnetic resonance imaging (R-fMRI) has emerged as a powerful tool for investigating normal human brain functional organization (Biswal et al., 2010; Buckner and Vincent, 2007) and its changes in a variety of neurological and psychiatric disorders (Chen et al., 2011; Fox and Greicius, 2010; Fox and Raichle, 2007; Li et al., 2012; Rosen and Napadow, 2011; Xie et al., 2011a,b). Despite these advances, extracting valuable information hidden in the gigabytes of four dimensional images of hundreds to thousands of subjects remains a challenge (Biswal et al., 2010; The ADHD-200 Global Competition, 2011).

R-fMRI data analyses are commonly categorized into preprocessing and postprocessing steps. While numerous studies have been conducted to optimize R-fMRI preprocessing steps (Chang and Glover, 2009; Chen et al., 2012; Fox et al., 2009; Weissenbacher et al., 2009), developing the optimum techniques for R-fMRI postprocessing data analysis remains a challenge (for a recent review of the procedure and limitations of the current techniques see: Margulies et al., 2010). For example, in independent component analysis (ICA) or conventional clustering approaches in R-fMRI studies, independent components (ICs) or clusters identified using subject groups with

different brain statuses, are not identical (Helekar et al., 2010; Schrouff et al., 2011; Tyska et al., 2011). The spatial distribution and even the total numbers of ICs or clusters are usually not exactly matched. As a result, it is not clear how the unmatched ICs or clusters should be chosen as reference ICs or clusters to quantify the functional connectivity differences. There is a way to define a single set of reference ICs or clusters, using data that combine normal and diseased subjects. However, if a normal IC or cluster has disappeared in the diseased group because of the effect of the disease, it is possible that this IC or cluster will not be identified using the combined data. As a result, this approach may not be sensitive in detecting functional connectivity differences. There is a need to develop the current techniques to better detect functional connectivity differences between groups.

In this study, we introduced a new clustering-based method that clearly defines the clusters to quantify the functional connectivity differences. The new method first produces group difference information, and then, uses the information to guide the clustering. As a result, there only will be one set of clearly defined reference clusters for the entire cohort. In addition, using the group difference information to guide the clustering ensures that the voxels within the reference clusters will have homogeneous functional connectivity changes above predefined levels.

In practice, this new method can be applied to various research interests. The clustering can be guided by the functional connectivity differences between healthy and diseased states, as demonstrated

* Corresponding author at: Department of Biophysics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA. Fax: +1 414 456 6512.

E-mail address: sjli@mcw.edu (S.-J. Li).

below. It also can be guided by the correlation between functional connectivity and behavior assessments or functional connectivity improvement and an outcome measure responding to a treatment, etc.

Materials and methods

Subjects

Seventeen amnesic mild cognitively impaired (aMCI) and 22 cognitively normal (CN) subjects were recruited through the Memory Disorders Clinic at the Medical College of Wisconsin (MCW). The study was conducted with MCW Institutional Review Board (IRB) approval and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations. Written informed consent was obtained from each participant or his or her caregiver. The detailed inclusion and exclusion criteria for the two subject groups (aMCI and CN) have been described previously (Goveas et al., 2011; Xie et al., 2011a). Detailed demographic information related to these subjects is listed in Table 1.

Image acquisition

Imaging was performed using a whole-body 3 T Signa GE scanner with a standard transmit-receive head coil. During the resting-state acquisitions, no specific cognitive tasks were performed, and the study participants were instructed to close their eyes and relax inside the scanner. Sagittal resting-state functional MRI (fMRI) datasets of the whole brain were obtained in 8 min with a single-shot gradient echo-planar imaging (EPI) pulse sequence. The fMRI imaging parameters were: TE of 25 ms, TR of 2 s, flip angle of 90°; 36 slices were obtained without gap; slice thickness was 4 mm with a matrix size of 64×64 and field of view of 24×24 cm. High-resolution SPGR 3D axial images were acquired for anatomical reference. The parameters were: TE/TR/TI of 4/10/450 ms, flip angle of 12°, number of slices of 144, slice thickness of 1 mm, matrix size of 256×192. A pulse oxymeter and a respiratory belt measured physiological noise sources to minimize the potential artifacts in the low-frequency spectrum (Birn et al., 2006; Glover et al., 2000).

Data preprocessing

A series of preprocessing steps common to most fMRI analysis was conducted, using Analysis of Functional NeuroImages (AFNI) software (<http://afni.nimh.nih.gov/afni/>), SPM8 (Wellcome Trust, London, UK) and Matlab (Mathworks, Natick, MA). The preprocessing allows for T1-equilibration (removal of the first five volumes of fMRI data). It also involves cardiac and respiratory artifacts removal (3dretroicor, Birn et al., 2006; Glover et al., 2000); slice-acquisition-dependent time shift correction (3dTshift); motion correction (3dvolreg); detrending (3dDetrend); despiking (3dDespike); segmentation

(SPM8) of white matter and CSF components from each subject's SPGR image; white matter and CSF mask creation (3dcalc and 3dfrac-tionize); averaged white matter and CSF signal retrieval (3dROIstats); white matter, CSF signal and motion effect removal (3dDeconvolve); low-frequency band-pass filtering (3dFourier); and spatial normalization (original space to Talairach space, adwarp; the anat parent dataset in Talairach space used in adwarp was obtained using @auto_tsrc and the SPGR image in original space). The result was the preprocessed R-fMRI time courses.

Group difference information guided clustering method

Functional connectivity difference information between the aMCI and CN groups was used to produce voxelwise clusters. The analysis excluded motor regions and occipital cortex regions, and was applied to the remaining 10,988 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 a $10,988 \times 10,988$ r -matrix for each subject (Fig. 1A, left). The Fisher transformation ($m = 0.5 \ln[(1+r)/(1-r)]$, Zar, 1996), 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 one-tailed two-sample t -test. Specifically, let $m_{ij}(aMCI_1, \dots, aMCI_n)$ and $m_{ij}(CN_1, \dots, CN_n)$ be the (ij) -th element of the m -matrices for aMCI and CN subjects. A one-tailed two-sample t -test was conducted to examine whether m_{ij} of the aMCI group was significantly less than that of the CN group. Such a test is repeated for all elements of the m -matrix, yielding $10,988 \times 10,988$ p -values. The one-tailed test was employed because we only considered the reduced connectivity in this study to demonstrate the method. The p -values were transformed to Z -values, using the inverse of the normal cumulative distribution function. The result was a $10,988 \times 10,988$ Z -matrix. The Z -value was then thresholded at $Z < -1.96$ ($p < 0.025$, uncorrected for multiple comparisons) to keep the pairs that showed reduced connectivity when the aMCI group is compared to the CN group. Because of the problems of executing multiple comparisons, each voxel is expected to have a reduced connectivity to 2.5% ($10,988 \times 2.5\% \approx 275$) of voxels by chance. To reduce computation cost and the chance of false discovery, voxels with reduced connectivity to less than 275 voxels were removed from further analysis. As a result, 4442 voxels were retained. The retained thresholded Z -matrix is shown in Fig. 1A (right). Note that each voxel has 4442 thresholded Z -values, corresponding to a particular row in the Z -matrix. We call each row of 4442 thresholded Z -values the “ Z -vector.”

The hierarchical relationship of the 4442 voxels (Fig. 1B) was obtained based on the similarity of their Z -vectors. The clustering analysis was implemented, using the functions “linkage” and “dendrogram” in the MATLAB Statistics Toolbox. The 4442 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,

$$d_{ij} = 1 - r_{ij} \quad (1)$$

where, r_{ij} is the correlation coefficient between the Z -vectors belonging to voxel i and voxel j . Obviously, the more similar the Z -vectors are, the less distance voxels i and j will have. A detailed description of the hierarchical clustering method can be found in the reference (Friedman et al., 2009).

Each level of the hierarchy represents a particular grouping of the voxels into a unique cluster (Fig. 1C). To determine the functional homogeneity of a cluster, a homogeneity index was defined:

$$\text{homogeneity index} = \min (r_i, i \in \text{voxels in the cluster}) \quad (2)$$

Table 1
Demographics information.

Characteristic	aMCI (n = 17)		CN (n = 22)		p Value
	M	SD	M	SD	
Gender (female/male)	11/6		11/11		NS [†]
Age, years	75.1	6.6	75.3	7.7	NS
MMSE	27.3	1.8	29.0	1.2	<0.002
Delayed Recall	2.5	3.3	13.4	3.5	<0.0001

Note: significant differences were found in MMSE, Delayed Recall between the aMCI and CN groups. Abbreviation: aMCI, amnesic mild cognitive impairment; CN, cognitively normal; M, mean; SD, standard deviation; MMSE, Mini-Mental State Examination; Delayed Recall, Paragraph delayed recall of the Wechsler Memory Scale; NS, no significance. Unless otherwise indicated, data are presented as mean ± SD; p values were obtained by a two-sample two-tailed t test.

[†] p Value was obtained by χ^2 test.

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