Identification of Functional Changes in Early Alzheimer Disease using Resting-state fMRI

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Introduction

Functional deterioration in Alzheimer's disease (AD) typically starts with short-term memory loss, while varied degrees of impairment may also present in other cognitive and behavioral domains. The complexity of symptom expression has made a precise AD diagnosis difficult and suggested elaborate pathologic processes underlying the disease. BOLD fMRI has been used to examine AD-associated brain functional alterations, in particular the change in the default network connectivity as revealed by spontaneous low-frequency fMRI signal oscillations [1, 2]. Despite its clear practical advantages (*e.g.,* a resting "task" is relatively easy to perform by AD patients), the resting-state fMRI data inevitably bear a low signal-to-noise ratio and also challenge the conventional stimuli-based analysis methods that require pre-defined models. Studies of AD based on resting-state fMRI data have often employed a user-biased reference function and/or region of interest [3]. Recently, emerging data-driven methods, such as the self-organizing map (SOM) algorithm, have shown promise for automatically mapping synchronous brain activations with superior performance [4, 5]. However, such methods are yet to be applied to resting-state fMRI studies on AD. In this study, we investigated the low-frequency fMRI signal fluctuations during a resting phase to identify changes in the brain associated with AD, using an efficient un-supervised SOM-clustering method. For this study, we scanned patients with early AD and cognitively healthy controls using fMRI at high-field. We hypothesized that early AD involves altered brain regional activation and global functional connectivity.

Methods

Subjects: Patients with mild AD (n=6, age=84+/-5 years, 50% women, education=16+/-4 years, total 3MS score=74+/-7) and healthy older adults (n=14, age=74+/-6, 50% women, education=16+/-2 years, 3MS total score=97+/-5) participated in the study. Subjects were scanned on two occasions under an identical "resting" condition that involved no explicit cognitive input and/or output. During each scan, subjects were instructed to remain relaxed while looking, via a mirror, at a fixation-sign displayed in the centre of a screen. After the initial stabilization, lasting for about 30 seconds, resting-state fMRI data were acquired for 60 seconds consecutively during each scan.

MRI Acquisition: MRI experiments used a 4-Tesla Varian-Oxford human imaging system. Functional data were acquired using a two-shot spiral readout sequence (TR/TE=1000/15ms, flip angle=60°; 240x240x121mm FOV; 64×64 matrix; 22 axial slices, 5.0mm thickness plus 0.5mm gap). A high resolution T1-weighted whole brain anatomic image was acquired using MPFLASH (307.2×192×192 FOV; 256x160 matrix, 1.2mm thickness), which was used for co-registration of the functional images.

Data processing and Analysis: Data underwent a standard preprocessing scheme (motion correction, co-registration, spatial normalization, and 6-mm smoothing) using SPM and was filtered for noise attributed to known physical and physiological sources using FSL. A low-pass filter ($t > 0.1$ Hz) and a high-pass filter ($t<0.01$) were applied to remove voxels with dominate high-frequency and oscillating trends, respectively. A masking image was created to cover the brain space within the field of view. The mask had the same dimensions as that of a volume in the original fMRI data. Voxels were included for further analyses only if they passed the filters and were within the mask. A self-organizing map (SOM) algorithm was employed to the whole brain to first identify characteristic temporal patterns in the data [6]. In an iterative correlation process, voxels were arranged in a two-dimensional lattice so that neighbors are mutually similar while more distant voxels are increasingly dissimilar, according to temporal pattern of fMRI signal fluctuations. The k-means clustering algorithm is used to partition the trained map (SOM nodes) into hard clusters. Candidate voxels for each type of the temporal fMRI signal fluctuations were established using the nearest neighbor allocation [6]. Data from each scan was examined independently three times applying the same procedure and the individual mean results were generated. Comparisons were made among individuals and between groups. The maximum initial number of clusters was 10. Significant threshold for cluster assignment was set at $p=0.001$ uncorrected, extent = 2 adjacent voxels. In addition, region of interest (ROI) analysis was conducted to evaluate the intensity of the signal change within localized regions, including the medial temporal lobe and the prefrontal cortices.

Results

The total cluster numbers (i.e., characterized temporal patterns of the fMRI fluctuations) identified for the patient and control groups were not statistically different (7.5+/-1.5 vs. 6.5+/-1.4, $p>0.05$). Within a cluster (i.e., a temporal pattern identified), few members (e.g., 18+/-2% vs 28+/-3% for the biggest cluster, $p<0.05$) with greater time course variations (covariance) were found for AD patients (Figure 1), suggesting a relatively weaker signal synchronization in AD compared to healthy subjects. In both patients and controls, the cluster members included voxels located closely and those located remotely, representing various brain networks including the somato-motor, visio-spatial, and memory systems (Figure 2). However, the spatial representation of temporal patterns appeared comparatively sparse and a network often involved multiple clusters in AD (Figure 2), suggesting impaired connectivity. In contrast, the intensity of the fMRI signal fluctuations as measured by percentage signal change was greater in AD patients than in healthy controls in several cortical regions including the prefrontal lobes (0.7+/-0.1% vs 0.5+/-0.1%, $p<0.05$).

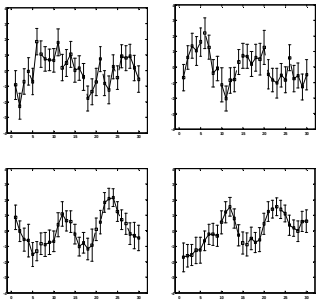

Figure 1 Example of two resting-state low-frequency fMRI signal fluctuation patterns (BOLD signal vs. Time), presented as the mean and standard deviation of the cluster member time courses in patients with mild Alzheimer's disease (top panels) and in matched healthy controls (bottom panels).

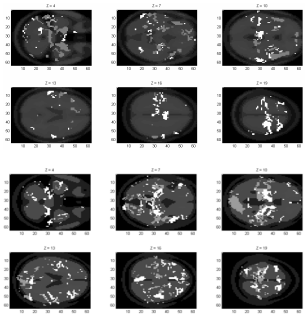

Figure 2 Example of the spatial distribution of two clusters (i.e., voxels in white and those in light gray) superimposed on the anatomical brain in patients with mild AD (top panels) and in matched healthy controls (bottom panels).

Conclusion

An efficient data-driven approach was applied to the resting-state fMRI data to investigate functional brain changes in early AD. The altered spontaneous fMRI fluctuations suggest increased functional activation in certain cortical regions and decreased global functional synchronization connecting many such regions. Nevertheless, heterogeneity exists in spontaneous neural activity in both AD patients and controls. Further research will verify the findings.

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