2. Increased resting state dorsal lateral prefrontal and medial temporal fMRI activation in early Alzheimer's disease

X. Song[1], K. Rockwood[2], R. D'Arcy[1], A. Major[3], J. Fisk[4], S. Darvesh[5], E. Asp[2], J. Rioux[1], C. Bowen[1], and S. Beyea[1]

[1]Institute for Biodiagnostics - Atlantic, National Research Council Canada, Halifax, Nova Scotia, Canada, [2]Centre for Health Care of the Elderly, QEII Health Sciences Centre, Halifax, Nova Scotia, Canada, [3]Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada, [4]Department of Medicine, Dalhousie University, [5]Medicine, Dalhousie University

Introduction

Alzheimer's disease (AD), characterized by insidious onset and gradual progressive memory loss, is the most common cause of dementia in elderly populations. Both the alterations in the complex cognitive process associated with early stages of AD, and the neural correlates underneath such changes, have elicited much research attention. Functional neuroimaging studies have yielded interesting results as to the differences in brain activation between mild AD patients and cognitively intact older adults. During the encoding and retrieval of new memory, deceased fMRI activation in the medial temporal lobe (MTL) and increased fMRI activation and metabolism in the dorsal lateral prefrontal cortex (DLPFC) have been reported, indicating that MTL is compromised early while DLPFC is damaged later in the course of the disease. However, most of these fMRI studies examine task-related changes by comparing images taken during one cognitive state with those of a reference state. It has been suggested that when the resting state serves as the reference, changes in fMRI activation that are found during the cognitive state may actually reflect changes of neural activity during resting state. We conducted this study to investigate the characteristic fMRI fluctuation that exists at rest and how this differs between early AD patients and cognitively healthy adults. Our focus is on the MTL (which is essential for declarative memory) and the DLPFC (which is responsible for the executive functions and also plays a critical role in working memory) regions.

MRI acquisition

A 4-Tesla Varian-Oxford human imaging system was used for imaging data acquisition. Functional data were acquired using two-shot spiral readout (TR/TE=1000/15ms, flip angle=60°); 22 axial slices (5.5mm thick, 0.5mm gap, 240mm FOV, 64×64 matrix). A high resolution T1-weighted whole brain anatomic image was acquired using MPFLASH (240×240×192 FOV) and was used for co-registration of the functional images.

Methods

Two female mild AD patients and six healthy older adults (two females and four males) aged 67-90 years were scanned using fMRI in a resting state. The subjects were instructed to remain relaxed and to focus their eyes on the cross presented in the middle of the screen for over 60 seconds. Each subject was scanned twice. Data were preprocessed for motion correction, co-registration, spatial normalization, and smoothing. Data were processed first using an independent component analysis (ICA) and artifacts attributed to physical and physiological sources were identified and filtered. Representative components (IC) that were common across subjects in both groups were identified and a general linear model (GLM) was generated for each of them based on the time course of the component. A canonical haemodynamic response function with time and dispersion derivations was applied to the model. Two regions of interests (ROI; i.e., MTL and DLPFC) were defined and an analysis was performed for each ROI. Signal changes measured as the percentage difference between the highest and lowest consecutive raw fMRI data points during a scan was calculated within each ROI. Brain activation maps within the ROIs were obtained for each individual. Significance of effects of interest was set at p=0.001 (uncorrected, extent=6). Data analysis was performed using FSL (including ICA) and SPM (including Marsbar).

Results

For all subjects, the fMRI signals filtered for imaging SNR and known physiological variations in both MTL and DLPFC fluctuated during the resting state, suggesting variations in brain activity in the two regions during rest. Patients with mild AD showed a relatively higher level of brain signal change in both MTL and DLPFC on average. The signal changes were more marked in the DLPFC (0.8% vs 0.5%) than in the MTL (0.5% vs 0.4%; Figure 1). Among a set of ICs detected, three were representative among the subjects of both groups. They were characterized by a low frequency of 1-3 cycles per minute (Figure 2). Brain activation maps in relevant to each IC were obtained inside both MTL and DLPFC bilaterally (Figure 3). Relative to cognitive intact older adults, the mild AD patients showed increased resting state activation in DLPFC and MTL (Figure 3).

Figure 1 Percentage fMRI signal changes in resting phase in AD patients (filled) and healthy subjects (open)

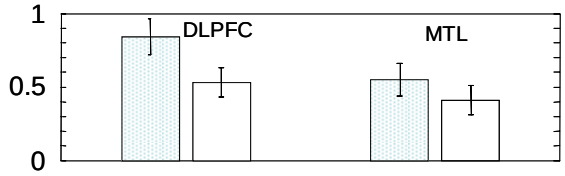


Figure 2 Common components in the subjects of both groups

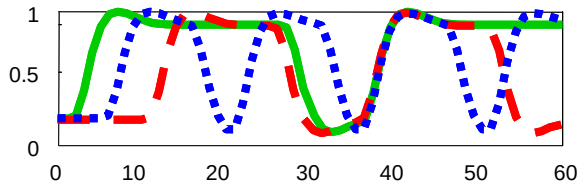
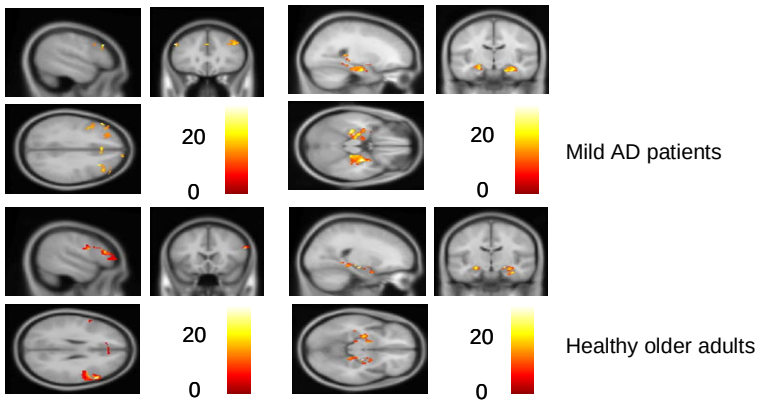


Figure 3 fMRI activation in the DLPFC and MTL during rest



Conclusion

This study suggests that there exist common patterns of neural activity fluctuation across subjects during rest. Further research is required to understand the neural processes underneath the "regular" resting state activity fluctuations. Importantly, patients with mild AD have increased resting state neural activity in both MTL and DLPFC, suggesting the neural compensation effect in the early stages of AD progression. This study suggests that careful control for resting state is critical. Care needs to be taken with inferring cognitive task fMRI results when referenced to the resting state.