Functional MRI study of mild Alzheimer’s disease using amplitude of low frequency fluctuation analysis

XI Qian, ZHAO Xiao-hu, WANG Pei-jun, GUO Qi-hao, YAN Chao-gan and HE Yong

Keywords: Alzheimer’s disease; resting-state functional MRI; amplitude of low frequency fluctuation

Background Previous studies have shown that the functional brain activity in the resting state is impaired in Alzheimer's disease (AD) patients. However, most studies focused on the relationship between different brain areas, rather than the amplitude or strength of the regional brain activity. The purpose of this study was to explore the functional brain changes in AD patients by measuring the amplitude of the blood oxygenation level dependent (BOLD) functional MRI (fMRI) signals.

Methods Twenty mild AD patients and twenty healthy elderly subjects participated in the fMRI scan. The amplitude of low frequency fluctuation (ALFF) was calculated using REST software.

Results Compared with the healthy elderly subjects, the mild AD patients showed decreased ALFF in the right posterior cingulate cortex, right ventral medial prefrontal cortex, and in the bilateral dorsal medial prefrontal cortex. No brain region with increased ALFF was found in the AD group compared with the control group.

Conclusions The reduced activity in the posterior cingulate cortex and medial prefrontal cortex observed in the present study suggest that the functional abnormalities of those areas are at an early stage of AD. The ALFF analysis may provide a useful tool in fMRI study of AD.

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder, which is characterized by global cognitive decline, including the progressive loss of memory, reasoning, and language. To date, there is still no effective treatment for AD. Considering that earlier treatment can improve disease prognosis, the early diagnosis of AD is especially important.

Structural MRI has been primarily used to differentiate AD from healthy elderly subjects, relying on volume measurements of the hippocampus and surrounding structures. However, most patients with structural MRI abnormalities often have irreversible pathological damage to the brain. Given that functional alterations might precede structural abnormalities, the blood oxygenation level dependent (BOLD) functional MRI (fMRI) may be a technique for studying AD. The commonly used task-based fMRI requires the patient to understand and perform specific cognitive tasks. Such a method is not appropriate for patients with cognitive impairment, and it cannot be widely used in clinics. In contrast, the resting-state fMRI does not require the subject to perform any task, which avoids any model design, greatly simplifies the fMRI procedure, and is especially appropriate for patients who cannot complete the neuropsychological tests or perform cognitive tasks.

The resting-state fMRI technique has also been utilized to explore the neurophysiological mechanism underlying AD. Previous studies have shown that brain functional activity in the resting state is impaired in AD patients. However, most studies focused on the relationship between different brain areas, e.g., functional connectivity methods based on region of interest (ROI) or independent component (ICA) analysis, rather than amplitude or strength of the regional brain activity. Because ROI identification is based on a priori hypothesis, ROI-based analysis is prone to user introduced bias. While ICA measures the BOLD signal synchrony, it is also difficult to pinpoint which area is responsible for the observed abnormality in the connectivity. An alternative way of measuring regional brain activity during resting state is to examine the amplitude of low frequency fluctuation (ALFF) of the BOLD signal. Biswal et al reported that the reduced low-frequency fluctuation in white matter relative to gray matter by approximately 60% suggests that ALFF is associated with field potential activity in local brain regions. In this case, the ALFF is considered to be the...
reflection of regional spontaneous neuronal activity and physiological states of the brain. In the present resting-state fMRI study, a newly reported ALFF method was used to analyze the BOLD signal of the brain. It was supposed that the resting-state fMRI technique based on ALFF analysis would allow a new insight into the neurophysiology of AD.

METHODS

Subjects
Twenty mild AD patients and twenty healthy elderly subjects participated in the study. The mild AD patients were recruited from a memory clinic at the Department of Neurology. Healthy elderly subjects were recruited from the nearby community. All subjects or their legal representatives gave written consent for participation in the study, which was approved by the Medical Research Ethics Committee of Tongji Hospital. Examinations for each subject included medical history, neurological examination, informant interview, structural MRI, and a neuropsychological assessment that included Mini-Mental State Exam (MMSE), clinical dementia rating (CDR), activity of daily living scale, Hachinski ischemic scale, and the Hamilton rating scale for depression. Patients with stroke, psychiatric diseases, drug abuse, moderate to serious hypertension and systematic diseases were ruled out. The diagnosis of AD was made on the basis of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria. All mild AD patients had a CDR scale score of 1.0. No memory complaints or neurological deficiencies were observed in the healthy elderly subjects. The demographics and neuropsychological findings of the mild AD patients and healthy elderly subjects are shown in Table 1.

Data acquisition
Functional MR images were obtained on a 1.5-T MR scanner (Marconi EDGE ECLIPSE). During scanning, all subjects were instructed to keep their eyes closed and to refrain from initiating goal-directed, attention-demanding activity. A T2 weighted, gradient-recalled echo-planar imaging sequence was obtained for functional images: echo time 40 ms, repetition time 2000 ms, slice thickness 6 mm, gap 1 mm, flip angle 90°, field of view 24 cm, and resolution 64×64 matrix.

Data preprocessing
Data of fMRI were preprocessed using Statistical Parametric Mapping (SPM2, http://www.fil.ion.ucl.ac.uk/spm/). The first 10 volumes of the functional images were discarded to equilibrate the signal and to allow participants’ adaptation to the scanning noise. For each participant, functional images were realigned using least-squares minimization without higher-order corrections for spin history and normalized to the Montreal Neurological Institute template. Images were re-sampled to 3 mm³ and smoothed with a 4 mm full-width at half maximum.

ALFF calculating
REST package (REST, http://resting-fmri.sourceforge.net) was used to calculate the ALFF with a voxel-based approach. The time courses were first converted to the frequency domain using a Fast Fourier Transform (FFT), and the power spectrum was obtained. The power spectrum obtained by FFT was square-rooted and then averaged across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. To reduce the global effects of variability across the participants, the ALFF of each voxel was divided by the global mean ALFF value within the whole-brain mask obtained previously. The global mean ALFF was calculated only within the brain, with the background and other tissues outside the brain removed.

Statistical analysis
Two-sample t-test was used to assess the differences in age, years of education, and MMSE scores between the two groups using SPSS 13.0 (SPSS Inc., USA). To investigate the ALFF difference between the two groups, a two-sample t-test was executed on the individual normalized ALFF maps. The resulting statistical map was set at a combined threshold of P <0.01 and a minimum cluster size of 500 mm³, which resulted in a corrected threshold of P<0.05.

RESULTS

Subjects’ demographic information
The demographics of mild AD patients and healthy elderly subjects, including age, sex, and education years, were matched. There was a statistically significant difference in MMSE scores between AD patients and healthy elderly subjects (t=2.86, P<0.01).

Brain areas showed decreased ALFF in mild AD patients
Compared with the healthy elderly subjects, the mild AD patients showed significantly decreased ALFF in the right posterior cingulate cortex, right ventral medial prefrontal cortex and bilateral dorsal medial prefrontal cortex (Table 2, Figure 1). No brain region with increased ALFF was found in the AD group.

### Table 1. Demographics and neuropsychological findings of healthy elderly subjects and mild AD patients

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (years)</th>
<th>Male/Female (n/n)</th>
<th>Education (years)</th>
<th>MMSE</th>
<th>CDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy elderly</td>
<td>64.7±5.62</td>
<td>10/10</td>
<td>12.2±2.47</td>
<td>28.2±1.77</td>
<td>0</td>
</tr>
<tr>
<td>Mild AD patients</td>
<td>68.8±8.65</td>
<td>9/11</td>
<td>12.0±4.11</td>
<td>20.5±2.32</td>
<td>1</td>
</tr>
</tbody>
</table>

MMSE: Mini-Mental State Exam. CDR: Clinical dementia rating. Values are means±SD. *P <0.01. There were no significant differences (P >0.05) in age, sex and education years between the two groups.
that interact with those of other interconnecting regions. Many brain regions generate their own cyclical patterns that SNA is of great physiological importance, and that R: right. B: bilateral.

Electroneurophysiological studies have shown that ALFF differences between mild AD patients and healthy elderly subjects. The blue color indicates that the mild AD patients show decreased ALFF compared with the healthy elderly subjects. Threshold was set at $P < 0.01$. PCC: posterior cingulate cortex. vMPFC: ventral medial prefrontal cortex. dMPFC: dorsal medial prefrontal cortex.

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Several methodological issues concerning the use of ALFF should be considered when interpreting these results. As in all resting-state fMRI studies, we reduced but could not eliminate the effects of physiological noise, such as cardiac pulsation, by modeling low-frequency (0.01–0.08 Hz) fluctuations of the BOLD signal, into which cardiac and respiratory noises are aliased because of the relatively low sampling rate (TR=2 seconds) for multi-slice acquisitions. Future studies should record simultaneous cardiac rate to deal with this potential problem.

In conclusion, this research applied the resting-state fMRI method to collect data and the ALFF method to analyze data. The decreased intrinsic activities in the PCC and MPFC were found to be references for distinct brain activity signatures in the mild AD patients. These abnormal activities may implicate the underlying neurophysiological mechanism in mild AD. This study provides a new method and hypothesis to study the etiology of AD, and it confirms the possibility of applying ALFF for preclinical and clinical AD studies. However, our findings of the alteration in resting-state functional activity still need to be supported by behavioral tasks. Future studies should examine the mechanism of abnormal neural activities in these brain regions in AD individuals.

REFERENCES

25. De Jager CA, Hogervorst E, Combrinck M, Badge MM.


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