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Research Article

Influence of electroencephalograph bionic electrical stimulation on neuronal activities in patients with Alzheimer's disease: A functional magnetic resonance imaging study

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Abstract

Purpose: To investigate the influence of electroencephalograph bionic electrical stimulation on neuronal activity in patients with Alzheimer's disease (AD) using resting-state blood oxygen level dependent functional MRI (BOLD-fMRI) and amplitude of low-frequency fluctuation (ALFF) and fraction ALFF (fALFF) analysis.
Methods: 42 AD patients were divided into two groups in accordance with the randomized double blind principle, every group was 21. Treatment group received electroencephalograph bionic electrical stimulation. Both groups received resting-state BOLD-fMRI scanning before and after treatment and comparing differences in ALFF and fALFF in each group by statistical methods. Correlation analysis was performed between ALFF or fALFF images and neuropsychological tests scale after treatment.
Results: Post-therapy brain regions with higher ALFF included left cerebellum posterior lobe, right cerebellum posterior lobe, left hippocampus/parahippocampus, left posterior cingulated cortex, left dorsolateral prefrontal cortex, right inferior parietal lobule in treatment group. Higher fALFF was observed in the right inferior parietal lobule. In the placebo group lower ALFF was observed in bilateral cerebellum posterior lobe and left posterior cingulated cortex. Alzheimer's Disease Assessment Scale-Cognitive section was closely correlated with ALFF in left cerebellum posterior lobe and right cerebellum posterior lobe.
Conclusion: These results indicated improved neuronal activity in some brain areas could be achieved in AD after treatment of electroencephalograph bionic electrical stimulation. The change of BOLD-fMRI signal might provide a potential imaging strategy for studying neural mechanisms of electroencephalograph bionic electrical stimulation for AD.

Keywords: Electroencephalograph bionic electrical stimulation; Alzheimer's disease; Low-frequency fluctuation; Fraction low-frequency fluctuation

1. Introduction

With the acceleration of population aging, Alzheimer's disease (AD) seriously threatens the health and quality of life in older individuals. Neurofibrillary tangles, senile plaques, neuronal loss and glial reaction were the main neuropathological changes in AD patients' brain. They always exhibit a progressive decline in cognitive function, including loss of memory, reasoning and language [1]. Most patients with AD display abnormalities on functional magnetic resonance imaging (MRI) before any alterations in structural MRI. BOLD-fMRI has fine temporal resolution and spatial resolution and has gaining wide popularity in studying neurodegenerations

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in the last decade. Logothetis et al. [2] suggested a linear correlation between approximation of BOLD-fMRI signal and neural responses. ALFF and fALFF can be used as potentially tools. Studies have identified functional MRI is sensitive to detect changes occurring in mild cognitive impairment and AD pathology compared to normal control group, and ALFF abnormalities as a potential biomarker for AD using ALFF and fALFF analytical method [3–5]. Amplitude of low-frequency fluctuation (ALFF) as a kind of potentially useful tool, have been utilized previously to analyze differences in fMRI studies investigating various regions of the brain of AD patients and may be a promising technique for studying AD [6–8]. An improved method, the fALFF could effectively reduce physiological noises associated with ALFF.

Clinically electroencephalograph bionic electrical stimulation was commonly used to treat ischemic cerebrovascular disease, such as, cerebral infraction vascular dementia, migraine and craniocerebral trauma. And there were also researches on the patients of insomnia, mild cognitive impairment and depression. The purpose of this study is to further explore the influence of EEG bionic electrical stimulation on neuronal activities in patients with AD using ALFF and fALFF analysis.

2. Materials and methods

2.1. Participants

The study was approved by the Second Affiliated Hospital of Chongqing Medical University ethics committee with written informed consent obtained from all participants. A total of 42 subjects were enrolled from the Second Affiliated Hospital of Chongqing Medical University and community of Yuzhong district. Twenty one patients were placed in treatment group stimulated with bionic electrical EEG and 21 patients were in placebo group in randomized double blind fashion. The criteria for identification and diagnosis of AD were as follows: (a) fitting the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association criteria; (b) exhibiting Mini-Mental State exam (MMSE) scores of illiteracy $\leq$17 or grade school culture degree $\leq$20 or above grade school culture degree $\leq$24, clinical dementia rating scores of $\geq$0.5, Hachinski ischemic scores of $\leq$4, Hamiton's Depression Scale scores of <7; (c) excluding patients with a history of stroke, psychiatric disease, drug abuse, severe hypertension, systematic disease and intellectual disability; (d) no other structural MRI abnormalities except for brain atrophy, deep white matter chronic small vessel ischemic changes.

2.2. Neuropsychological assessment

In the current study, the MMSE and Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) section were adopted and administered by trained neuropsychologists in standard manner before and after treatment.

2.3. Image acquisition

MRI data were obtained on a 3 T scanner (Achieva/Intera, Phillips) following routine clinical scan protocol and parameters. Foam padding and headphones were used to reduce head motion and scanner noise. The patients were instructed to keep still with their eyes closed, not to fall asleep, and not to think during the scan. To study resting state BOLD-fMRI, fast field echo–echo planar imaging pulse sequence were acquired with the following parameters: 34 axial slices, slice thickness = 4 mm, TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 240 mm × 240 mm, acquisition matrix = 64 × 64.

2.4. Electroencephalograph bionic electrical stimulation

EEG bionic electrical stimulation therapeutic instrument was from Chongqing Haikun medical instrument LTD. The main electrodes were placed in mastoid regions behind the two ears and were fixed. Each treatment was 30 min, once daily. Treatment duration was 3 months on each patient. The pulse frequency of stimulation is 1.8× (1 ± 30%) KHz, and the pulse width of stimulation is 90× (1 ± 30%) us. There was not electrical stimulation pulse applied in placebo group.

2.5. Data preprocessing

All the neuroimaging data were pre-processed using data processing assistant for resting-state fMRI (DPARSF, http://www.restfmri.net). All images of DICOM format were converted into NIFT format. The first 10 volumes of the functional images were discarded to eliminate equilibrium effects of magnetization and the patients' adaption. Pre-processing consisted of re-alignment (discarding head motion of more than 2 mm and 2) and slice timing (using the middle slice as reference). A mean image created from the realigned volumes was co-resisted with the subject's individual structural images (3D T1-weighted anatomical images). The images were spatially normalized to the template in MNI space. For each subject, Gaussian kernel of 4 mm full-width at half maximum (FWHM) was used to smooth spatially. Finally, all of the remaining images were temporally filtered (0.01–0.08 HZ) to reduce the effect of high-frequency noise and low-frequency drift. Blood oxygenation level dependent time series was first transformed to the frequency domain. The square root of the power spectrum, the ALFF was computed. fALFF was the ratio that the power of each frequency at the low-frequency range divided by that of the entire frequency range.

2.6. Statistical analyses

Independent sample *t*-test was used to compare the difference of demographic information of two groups with SPSS V.19.0. Differences of neuropsychological tests scales between before and after treatment were tested using paired *t*-test. Statistical significance was set at $P < 0.05$ for significance. The statistical analyses of MRI data were performed using

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