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Research paper

Changes of brain activity during a functional magnetic resonance imaging stroop task study: Effect of Chinese herbal formula in Alzheimer's disease

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ABSTRACT

Introduction: The functional magnetic resonance imaging (fMRI) Stroop task could be used to study brain activity changes during treatment for Alzheimer's disease(AD). The aim was to observe the brain functional activity changes during the treatment for AD patients with Yishen Huazhuo Decoction (YHD) using an fMRI Stroop task.

Methods: Thirty-five mild AD patients were randomized into either a treatment group or a control group in order to observe the brain activity before and after the treatment.

Results: Before the treatment, the activated regions were bilateral cerebellar hemispheres and bilateral frontal occipital lobe. After the treatment, the activated regions of bilateral cerebellar hemispheres and bilateral frontal occipital lobes decreased for patients in control group, but the activated regions were larger than that in treatment group, and there appeared deactivated regions in the bilateral prefrontal lobes, left orbitofrontal gyrus and right inferior parietal lobule; the activated state of bilateral anterior cingulate gyri, bilateral superior, middle, and medial frontal gyri, left middle-superior frontal gyrus, right middle-superior frontal gyrus, and bilateral posterior cingulate gyri significantly decreased after treatment compared with before treatment in control group.

Regions of higher brain functional activity changes in YHD treatment group were observed in the control group were; left anterior central gyrus, left middle-inferior frontal gyrus, bilateral medial frontal gyri, left anterior cingulate gyrus, bilateral superior frontal gyri, left middle frontal gyrus, left superior-middle frontal gyrus.

Conclusions: We used an fMRI Stroop task to investigate the brain functional activity changes during the treatment of AD patients by YHD, and we found that YHD could improve brain activity of AD patients.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease, characterized by progressive impairment of cognitive and functional ability such as difficulties with memory, language, executive functions, or perception (agnosia)[1]. Executive functions, an umbrella term for the management (regulation, control) of cognitive processes[2,3], include working memory, reasoning, task flexibility, and problem solving. The impairment of executive function is the main cause of bodily function loss. Degeneration of AD often affects the temporal lobe, parietal lobe, and parts of the frontal cortex and cingulate gyrus, which are mostly associated with cognitive areas[4,5]. No medication has been clearly shown to delay or halt the progression of AD, and pharmaceutical treatments, such as galantamine, donepezil, and memantine, offer relatively small symptomatic benefit but remain palliative in nature[6–8]. Long-term clinical practice has shown that traditional Chinese medicine (TCM) could improve cognitive symptoms of the mild and moderate AD patients to delay the progression.

Recently, imageology of AD has been developed from structure to function, and Functional magnetic resonance imaging (fMRI) Stroop task could be used to study brain functional activity changes of cognitive areas during treatment[9–12]. We developed a Chinese herbal

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formula Yishen Huazhuo Decoction (YHD) to treat AD patients and Stroop task in Chinese was used to investigate brain functional activity changes during the treatment.

2. Methods

2.1. Patients

Thirty-five patients (outpatients and inpatients) were enrolled from the Second Affiliated Hospital of Tianjin University of TCM and Tianjin Huanhu Hospital between May 2011 and June 2013. Inclusion and exclusion criteria for this study have been published [13]. All patients did not have fMRI contradictions. The participants were divided randomly into the treatment group (18) and the control group (17). During the treatment, three patients withdrew as they failed to fully complete the administration (one caught a cold, the others declined administration). Two patients refused to accept fMRI after treatment. Six patients' data of brain function (three in each group) were removed because of larger head motion (three dimensional translation > 3 mm, three dimensional rotation angle > 30°). A total of 24 cases were available for analysis of Stroop task brain functional imaging, 12 in treatment group, and 12 in control group. There were no statistically significant differences at baseline between the patients in two groups (Table 1). The study was approved by the Ethics Committee of the Second Affiliated Hospital of Tianjin University of TCM, and all informed consents were signed by patients or caregivers.

2.2. Drug administration

Participants stopped taking Chinese medicinal herbs and modern medicine for intelligence promotion, and any other medicines for AD two weeks before enrollment. Every patient in the treatment group orally took 100 ml of the Chinese herbal decoction YHD once a day half an hour after breakfast and donepezil hydrochloride (DH)-simulation (provided by Eisai China Inc. Tianjin, China)5 mg before sleep for 24 weeks. The Chinese herbal formula includes Yinyanghuo (Epimedium) 10 g, Nvzhenzi (Fructus ligustri lucidi) 10 g, Buguzhi (Psoralea fruit) 10 g, Heshouwu (Radix polygoni multiflori) 10 g, Huangqi (Radix astragali) 10 g, Chuanxiong (Ligusticum wallichi franchat) 6 g, Shichangpu (Acorus gramineus) 6 g in one unit. Each herb was provided as herbal concentrate-granules in one bag and quality controlled by the Shenzhen Sanjiu Modern Chinese Medicine limited Company (Tianjin, China). Patients in the control group took DH (provided by Eisai China Inc. Tianjin, China) orally, 5 mg a day before sleep, and YHD-simulation (provided and quality controlled by the Shenzhen Sanjiu Modern Chinese Medicine limited Company, Tianjin, China) 100 ml of the decoction half hour after breakfast for 24 weeks. During treatment, other medicines and therapies for AD were forbidden.

Table 1
Baseline characteristics of the patients.

	Treatment group	Control group	F-value	P Value
Age(years)	68.75(5.97)	69.00(5.54)	0.011	0.916[a]
Gender (female/male)	3/9	4/8		0.500[b]
Course(month)	31.5(12.09)	34.58(15.44)	0.297	0.591[a]
MMSE	23.83(3.10)	22.17(3.56)	1.495	0.234[a]
ADAS-cog	17.50(6.15)	18.93(5.55)	0.355	0.558[a]
ADL	25.08(3.75)	26.83(4.95)	0.952	0.340[a]
CDR	1	1		
Education level				
Illiteracy	1	0		0.599[b]
Primary school	0	2		
Middle school	9	7		
College	2	2		
Academic high school	0	1		

Note: [a] analysis of variance; [b] Fisher exact test.

2.3. Stroop task

The Stroop task was programmed and presented using E-Prime 2.0 software (Psychology Software Tools Inc.). Participants were initially instructed to pay attention and respond to the direction before scanning. Synchronized triggering task presenting system was used to present the stimuli and collect participants' responses. Modified block stimulus task, namely an alternating runs paradigm of baseline → task (one block) was applied. There were four blocks in total, 10 frames for baseline and 10 frames for task in each block. Collecting time for single frame was three seconds, one minute for one block, 4.5 min in total (10 experiments were randomly presented in each block stimulus task; 10 " + "" - " in different colors with the same frequency in control task). Stimulus program was Stroop task in Chinese, including congruent items (the word RED written in red, BLUE in blue, GREEN in green) and incongruent items (the word RED written in blue, BLUE in green, GREEN in red), presented in a randomized order. Control items were " + " and " - " in red, yellow, blue, and green.

2.4. Stroop task brain functional images collection

All images were taken with a Siemens Magnetom Trio Tim 3.0 T MR scanner in MRI room of Tianjin First Center Hospital. Echo planar imaging (EPI) sequence was performed, with the following parameters: TR = 3000 ms, TE = 30 ms, FOV = 230 × 230, flip angle = 11°, slice thickness = 5.0 mm, slice gap = 0.75 mm, 64 × 64 matrix, 20 slices, 90 frames, and Stroop task was processed during scanning.

After scanning, raw images were transformed with MRIcron software, while data preprocessing and results presenting were performed by REST based on Matlab 7.11.0.

2.5. Statistical analysis

Statistical Package for the Social Sciences (SPSS) v19.0 software was used. Descriptive statistics were presented for the baseline characteristics. Fisher exact test was applied to enumeration data, and independent samplest test to measurement data. REST based on Matlab 7.11.0 was performed to build the model of Stroop task data, evaluate and present results. Independent samplest test was applied to the results before treatment and activated results after treatment of the two group; paired studentt test to the activated changes before and after treatment; independent samplest test to activated changes between groups after treatment; statistical significance was taken at $p < 0.05$, cluster voxel ≥50. Xj view software was applied to confirm the anatomical location of statistical significance in the brain to the Montreal Neurological Institute (MNI) coordinate, and the results were presented using Slice Viewer of REST.

3. Results

3.1. Stroop task brain functional activity states before treatment of patients in two groups

Before treatment, the activated regions were bilateral cerebellar hemispheres and bilateral frontal occipital lobe brain functional regions, and the deactivated region was on the left orbitofrontal area (Fig. 1) when AD patients were taking Stroop task.

3.2. Stroop task brain functional activity states after treatment and activate changes before and after treatment in YHD treatment group

After treatment, the activated regions of bilateral cerebellar hemispheres and bilateral frontal occipital lobes decreased of patients in treatment group, while there appeared deactivated regions of bilateral prefrontal lobes and bilateral cingulate gyri ($p < 0.05$); activated state of right middle frontal gyrus and inferior frontal gyrus, supramarginal