Effect of Acupuncture Given at the HT 7, ST 36, ST 40 and KI 3 Acupoints on Various Parts of the Brains of Alzheimer’s Disease Patients

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ABSTRACT:
In this study, we explore various regions of the brains of Alzheimer’s Disease (AD) patients before and after acupuncture treatment of acupoints in the brain in order to determine the effect, if any, of acupuncture on AD. Twenty-six patients with clinically-diagnosed AD underwent functional magnetic resonance imaging (fMRI) while undergoing acupuncture at the four acupoints of Shenmen (HT 7), Zusanli (ST 36), Fenglong (ST 40) and Taixi (KI 3). fMRI Block design paradigm was chosen by electroacupuncture interval stimulation, and the data of fMRI were analyzed by Statistical Parametric Mapping (SPM 99). The result demonstrated that there were right main hemisphere activations (temporal lobe, such as hippocampal gyrus, insula, and some area of parietal lobe) and left activated regions (temporal lobe, parietal lobule, some regions of cerebellum). The activated regions induced by these acupoints were consistent with impaired areas in brain for AD patients, which were closely correlated with the cognitive function (memory, reason, language, executive, etc.). The present study provided the strong evidence that acupuncture had a potential effect on AD, and in partial revealed the mechanism.

Key Word: Alzheimer’s Disease; Functional Magnetic Resonance Imaging; Acupuncture; Mechanism.

Introduction

Alzheimer’s disease is a chronic degenerative disease of the brain, which causes cognitive
impairment, and behavior or personality abnormality. A good effect of acupuncture on AD had been reported, but its mechanism is not clear [1,2]. Functional magnetic resonance imaging (fMRI) combines function, images and anatomy, and is an effective method to study the function of human brain. The fMRI is noninvasive with a high time resolution in vivo, and has been widely used to study on AD [3] or acupuncture [4]. It can reflect the change of brain function in acupuncture process. Therefore, fMRI appears to have superiority on study of acupuncture. According to the theories of, tonifying kidney and invigorate the spleen, dissipating phlegm for resuscitation in traditional Chinese medicine (TCM), we selected Shenmen (HT 7), Fenglong (ST 40), Taixi (KI 3) and Zusanli (ST 36) acupoints [5], and to explore their effects on AD patients and the mechanism by fMRI.

Materials and Methods

Subjects
Twenty-six patients with mild to moderate AD came from the out-patient department of neurology in Xuan Wu Hospital. In 26 patients, there were 16 men and 10 women (mean age = 71.6 yrs, mean course of disease = 3.2 yrs, mean education = 7.8 yrs, all right handed). The mild or moderate AD was diagnosed according to the criterion of the National Institute of Neurological and Communicative Disorders and Strokes-Alzheimer’s Disease and Related Disorders Association Work Group Criteria (NINCDS-ADRDA). The patients were excluded with other diseases by the physical examination and the imageology, and not treated with acupuncture. All subjects signed a written informed consent and the experiment protocol was approved by the Research Ethical Committee.

Electro-stimulation Instrument
Electro-stimulation instrument (Shanghai HuaYi Medical Instrument Factory, G6805-□, Batch No: GB200102, Shanghai, China), 0.30×50mm silver acupuncture needle (China Great Wall Medical Instrument Factory, Batch No: 20010168, Suzhou, China).

Paradigm and Block Design
The Block Design (the separation of experimental conditions into distinct blocks, so that each condition is presented for an extended period of time) was adopted with the electro-acupuncture stimulation for the fMRI scanning. Shenmen (HT 7), Fenglong (ST 40), Taixi (KI 3) and Zusanli (ST 36) acupoints on subjects left side were selected (Fig. 1).

Fig 1. The schematic diagram of acupoints (ST36: 3 cun below Dubi, one finger-breadth from the anterior crest of the tibia. ST40: 8 cun superior and anterior to the external malleolus, one finger-breadth from the anterior crest of the tibia. HT7: at the ulnar end of the transverse
crease of the wrist, in the depression on the radial side of the tendon of m. flexor carpiulnaris. 
**K13** : in the depression between the prominence of the medial malleolus and heel tendon.)

All acupoints were sterilized and inserted with sliver acupuncture needle. The acupoints were 
perpendicularly punctured, with a depth of 5mm for Shenmen (HT 7) and Taixi (K1 3), and 
15mm for Zusanli (ST 36) [6] and Fenglong (ST 40).

When the patients had a DeQI sensation (DeQI refers to the patient’s sensation of soreness, 
numbness of a distending feeling around the point when the needle is inserted to a certain 
depth. At the same time, the operator may feel tightness around the needle.), the needle was 
connected to the electro-acupuncture instrument.

![Image of Electro-stimulation Instrument and MRI](image)

**Fig 2.** The schematic diagram of fMRI for electro-acupuncture

The first group electrode: Shenmen (HT 7) was connected to the positive electrode and 
Zusanli (ST 36) to the negative electrode. The second group electrode: Fenglong (ST 40) to 
the positive electrode and Taixi (K1 3) to the negative electrode (Fig. 2). The stimulating 
parameters of the waveform of the electrical instrument: the impulse wave, 2.7Hz frequency, 
1mA current (Fig 3) [7]. The Block Design for the fMRI scanning comprised 6 times of 
stimulating (30s) and resting (30s), which were alternately undertaken for a session to every 
patient (Fig. 4).

![Image of a waveform](image)

**Fig 3.** The waveform of the electrical instrument (The photograph of output waveform of 
electro-stimulation instrument showed by the oscilloscope. f: 2.7Hz; V: 0.1V; A: 1mA; 500Ω).
Magnetic Resonance Imaging acquired
During stimulating and resting, the patients were scanned after they quietly rested 30 minutes. The fMRI scanning was performed at a 1.5 Tesla MRI system (Philips, 1.5T Achieva, Netherlands). The protocols as follows: (1) T1-weighted images were acquired using a Spin Echo (SE) sequence with 160 axial slices, 1mm thickness, FOA (flip of angle) = 90°, TR (repetition time) = 7.3 seconds, TE (echo time) = 3.3 seconds, acquisition matrix = 64×64. (2) A blood oxygenation level-dependent (BOLD) contrast functional images were acquired by an echo-planar imaging (EPI) sequence. The major acquisition parameters of this sequence were 32 axial slices, slice thickness = 4.0mm, FOA = 90°, TR = 3000 millisecond, TE = 30 millisecond, acquisition matrix = 64×64, interval gap = 0mm. The scanning lasted continuously 6 minutes and 3840 pieces of images were acquired at last.

Imaging processing
Statistical Parametric Mapping software 99 (SPM 99, Welcome Department of Cognitive Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/) was used for imaging data processing and statistical analysis. First, anatomical images were transformed into Talairach space and realigned with the functional images. Secondly, all images were normalized to elevate the signal and to reduce noise ratio. The statistical threshold was set at $P < 0.001$, corrected for comparison, voxels $>50$, to acquire the cerebral activated images. The Talairach coordinates (brain standard stereotactic coordinate system) and volumes of transactivation domains were acquired and BA areas were located by the Talairach Daemon (nearest gray matter) and Talspace software. At last, the average functional images were superimposed to the anatomical images.

Statistical analysis
The Clinical Report Form was made before the test. All data was analyzed with by the SPSS 11.5 for Windows (SPSS Inc. Chicago, USA). The measurement data was demonstrated on the $\pm s$. The numeration data was analyzed by the chi square test. The statistical threshold was set at $p<0.05$ corrected. The BOLD data was analyzed by the one sample t-test.

Results
When stimulation was given by electro-acupuncture, compared to resting phase levels, it was mainly showed that the cerebral temporal lobe, parietal lobe, cerebellar hemisphere and limbic lobe were activated.

The activated regions
Right: superior temporal gyrus, middle temporal gyrus, fusiform gyrus, hippocampal gyrus, clivus of the cerebellar posterior lobe and the anterior lobe top, claustrum and insula, and posterior central gyrus.

Left: superior temporal gyrus, middle temporal gyrus, transverse temporal gyrus, hippocampus, insula, middle occipital gyrus, and superior parietal lobule (Tab 1 & Fig 5).

Fig. 5: The schematic diagram of brain anatomic regions. The areas marked in different colourations show different functional domains of brain.
Fig 6. The activated regions for acupuncture. The red regions represent the activated regions, which are closely correlated with memory, attention, language, reason, executive, etc.

<table>
<thead>
<tr>
<th>The activated regions</th>
<th>Brodmann’s area (BA)</th>
<th>Cluster size (mm³)</th>
<th>Talairach coordinate</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-top of anterior cerebellum lobe</td>
<td>BA37</td>
<td>16</td>
<td>46 -48 -16</td>
</tr>
<tr>
<td>R-vermis of cerebellum</td>
<td>BA34</td>
<td>11</td>
<td>12  -4 -16</td>
</tr>
<tr>
<td>R-clivis of cerebella</td>
<td>BA28</td>
<td>84</td>
<td>16 -16 -8</td>
</tr>
<tr>
<td>L-hippocampus</td>
<td>L-hippocampus</td>
<td>12</td>
<td>L-hippocampus</td>
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<tr>
<td>L-thalamus</td>
<td>L-thalamus</td>
<td>14</td>
<td>L-thalamus</td>
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<tr>
<td>L-insula</td>
<td>L-insula</td>
<td>4</td>
<td>L-insula</td>
</tr>
<tr>
<td>R-superior temporal gyrus</td>
<td>BA21</td>
<td>12</td>
<td>56 8 0</td>
</tr>
<tr>
<td>R-middle tempore gyrus</td>
<td>BA22</td>
<td>10</td>
<td>-40 -14 2</td>
</tr>
<tr>
<td>L-middle occipital gyrus</td>
<td>BA18</td>
<td>12</td>
<td>12 -68 -22</td>
</tr>
<tr>
<td>L-middle temporal gyrus</td>
<td>BA21</td>
<td>54</td>
<td>10</td>
</tr>
<tr>
<td>L-superior temporal gyrus</td>
<td>BA42</td>
<td>12</td>
<td>-58 -30 10</td>
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<tr>
<td>R-insula</td>
<td>R-insula</td>
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<td>R-insula</td>
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<tr>
<td>R-middle temporal gyrus</td>
<td>BA39</td>
<td>18</td>
<td>33 50 -52 14</td>
</tr>
<tr>
<td>L-transverse temporal gyrus</td>
<td>BA41</td>
<td>12</td>
<td>18 -42 -30 12</td>
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<td>L-superior temporal gyrus</td>
<td>L-superior temporal gyrus</td>
<td>157</td>
<td>14</td>
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<tr>
<td>R-middle occipital gyrus</td>
<td>R-middle occipital gyrus</td>
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<td>R-insula</td>
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<td>R-middle tempore gyrus</td>
<td>BA39</td>
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<td>13 34 -4 14</td>
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<tr>
<td>R-middle tempore gyrus</td>
<td>BA39</td>
<td>12</td>
<td>10 44 -64 18</td>
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<tr>
<td>L-superior parietal lobule</td>
<td>BA40</td>
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<td>L-superior parietal lobule</td>
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<td>L-middle occipital gyrus</td>
<td>L-middle occipital gyrus</td>
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<td>L-middle temporal gyrus</td>
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<tr>
<td>L-superior parietal lobule</td>
<td>L-superior parietal lobule</td>
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<td>15</td>
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</table>

Note: BA=Brodmann’s area; L, left; R, right; voxels >10; Cluster size refers to the size of the sum activated region x, y, z, size of three dimension axis of coordinate in brain. $p < 0.001$ uncorrected.

Discussion

A typical symptom for AD includes a gradual decline in cognitive, intellectual, functional and social abilities, such as memory, attention, language function, and visual-spatial processing. While AD patient progressively destroys the ability to reason, remember, imagine and learn, and executive functions, it is difficult for them to finish a simple task. As we know in AD, tangles and plaque eventually take over healthy brain tissue, devastating the area of the brain.
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associated with intellectual function, and progressively destroying the ability to reason, remember, imagine and learn. In early stage, neurofibrillary tangles and senile plaques occur in medial temporal lobe (MTL) such as entorhinal cortex, hippocampus [8], subiculum hippocampus, amygdala, etc. With the progress of AD, it gradually affects the new cortex and eventually destroys the sensory cortex [9]. According to TCM treatment principles: “Tonifying kidney and invigorate the spleen, dissipating phlegm for resuscitation”, we selected a group of acupoints including Shenmen (HT 7), Zusanli (ST 36), and Fenglong (ST 40), and Taixi (KI 3) on AD, and found the activated regions in the brain. Our experimental result showed main activated regions were: temporal lobe (superior temporal gyrus, middle temporal gyrus, transverse temporal gyrus, and fusiform gyrus), the limbic lobe (hippocampal gyrus), the cerebellum (clivus of the cerebellar posterior lobe and the anterior lobe top), claustrum and lobus insularis. The superior temporal gyrus plays an important role in handling information of hearing and voices, and its left is more important [10]. The left inferior temporal gyrus also plays an important role in words. But language is largely created in left fronto-center and inferior temporal gyrus 46 BA. The part of the cortex in the front of the left language areas within the temporal lobe are related to the language signal and the concept knowledge [11]. Many of Alzheimer's disease fMRI studies focused on analysis of patients with medial temporal lobe activation. The medial temporal lobe includes the hippocampus and subiculum hippocampus, where senile plaques and neurofibrillary tangles are mainly deposited in AD. The regions activated by our experiment in temporal lobe are related with language, voice recognition, auditory information coding and storage. Our result supplied an evidence for potential use of acupuncture for the treatment of AD.

The damage of the limbic system usually leads to a memory storage disorder. If the damage in the left hippocampus, a selective memory defects on language information usually occurs. However, the injury to same areas of the right side will lead to nonverbal memory impairment, such as learning and spatial information. If medial temporal lobe is damaged, it will lead to extensively forgotten syndrome of words. The right limbic lobe and gyrus hippocampus (BA 34) and left limbic lobe and hippocampus (BA 28) activated by the acupuncture are areas which closely related to the functions of coding language, memories, learning and recalling the space content. These provide an experiment basis, and explains in partial why acupuncture can recuperate the memory function for AD.

This group of acupoints also activated the clivus of the right posterior cerebellar lobe (voxels number 106) and the anterior lobe top (voxels 37). Recently there are many studies about the cerebellar cognitive function from the neural anatomy, physiology, clinical neuro-psychological tests, functional brain imaging and so on. The results have confirmed that the cerebellum is not only responsible for motor function, but also responsible for feeling, memory, learning, emotional, linguistic and other cognitive activities. In general, the cerebellum can precisely adjust and integrates the information from cerebra. In addition, cerebellar lesions can cause the loss of motor coordination, and lead to the language, memory and emotional dysfunction [12]. In our experiment, patient's left acupoints were punctured, but their clivus of the right cerebellar posterior lobe and the anterior lobe top were significantly activated. These activated regions have coincidence with cognitive ability of the cerebellar. The results showed that the effect of acupuncture on AD involved in extensive areas, not only cerebra cortex, but also cerebella.

There are a lot of reports about acupuncture on AD up to now. We have used these acupoints to treat the AD patients for many years. The acupuncture could actually improve the senior cognitive function for AD patients, such as memory, attention, language function, visual-spatial processing. As how acupuncture acts in the brain, the present test show that selected acupoints could activate some areas in the brain, which are correlated with reason, memory,
imagine and learn, executive functions, providing a clue to understanding the mechanism of acupuncture on AD.

Reference

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