fMRI Study of Effect on Brain Activity According to Stimulation Method at LI11, ST36: Painful Pressure and Acupuncture Stimulation of Same Acupoints

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Abstract

Objectives: The objective of this study was to assess differences in brain responses between pressure and acupuncture stimulation at the same acupoint using functional magnetic resonance imaging (fMRI).

Subjects: A total of 10 healthy right-handed volunteers were studied.

Design: fMRI was performed with two different paradigms; namely, pressure and acupuncture stimulation at acupuncture points LI11 and ST36 on the left. fMRI data were analyzed using SPM2.

Results: In comparison with the left LI11 pressure stimulation, both sides of the parahippocampal gyrus, cerebellum, left side of thalamus, and right side of posterior cingulate regions were more activated by the left LI11 acupuncture stimulation. In comparison with the left ST36 pressure stimulation, the secondary motor cortex, limbic system (cingulate gyrus, posterior cingulate), primary visual cortex, pons, and medulla regions were more activated by left ST36 acupuncture stimulation. In comparison with the left ST36 pressure stimulation, both side of BA 4 and BA 6 were more activated by the LI11 pressure stimulation. In comparison with the left LI11 acupuncture stimulation, left BA 6, BA 8, and anterior cingulate cortex (ACC) were more activated by the left ST36 acupuncture stimulation.

Conclusions: In conclusion, brain signal activation patterns according to the stimulation methods and acupoints were observed to differ. Acupuncture stimulation activated more regions than pressure at the same acupoint. In particular, acupuncture stimulation activated the limbic system, such as the parahippocampal gyrus and ACC.

Introduction

ACUPUNCTURE IS A fundamental and core medical treatment in Oriental medicine. The principle of various effects of acupuncture is meridian pathways or the qi-blood circulation system that goes through the whole body and connects the five viscera and the six entails, tissue, and organs. People use meridian pathways to treat diseases, and it has been shown that acupuncture on the limbs can stimulate the brain as well as the limbs.

Functional magnetic resonance imaging (fMRI) has been used to image areas of the brain related to specific functions such as language, visuoperception, memory, sensory, motor, and so on. It has furnished fresh information about actions and mechanisms of brain neuropil structures, so it is an advanced methodology to understand brain functions. Recently, clinical applications of fMRI have been increased due to several advantages: fine resolution, no risk of radiation, and repeated image acquisition. fMRI studies have been utilized to investigate brain activations by acupuncture stimulations. There have been several studies comparing multiple acupoints or different methods of stimulations such as tactile acupuncture and electroacupuncture.

Thus, various research and clinical studies are progressing and many effects are being reported. However, to the best of our knowledge, no fMRI studies have been published on fMRI activations in response to acupuncture and pressure stimulations at the same acupoint. Clinically, taping
or massage therapies accompanied by pressure on acupoints are often carried out instead of acupuncture therapy. The objective of this study was to investigate brain activity patterns during stimulations of both acupuncture and pressure at the same acupoint, and whether massage therapies or pressure stimulation on acupoint has the same effect as compared with acupuncture treatment. We specifically evaluated fMRI activations associated with painful pressure and acupuncture stimulations of the Large intestine 11 acupoint (LI11) of the upper limbs and the Stomach 36 acupoint (ST36) of the lower limbs on the left, which are used very often and are included in the Seven Points of cerebrovascular accident (CVA), seven acupoints used frequently for stroke according to the acupuncture literature. We observed different brain activation patterns according to stimulation methods and acupoints.

Materials and Methods

Subjects

Ten (10) healthy right-handed volunteers aged 55–65 years (5 each male and female, average age 59.5 years) were recruited and consented to the study. Volunteers suffering from neurological, mental or internal problems, drug abuse, alcohol abuse, or those with a history of cerebrovascular diseases were excluded. No volunteers exhibited reasons for disqualification from MRI. The protocol (number KHNMC-2007–012) was approved by the Institutional Review Board of the Kyung Hee University, and informed consents were obtained.

fMRI task design

The points of left LI11 and left ST36 were marked with a pen. The intensity of pressure stimulation by a cotton tip was to a degree that volunteers felt pain. The needle was inserted 1.5–2.0 cm deep vertically and the rotation rate was 2 Hz consistently. De qi was to be achieved through needle manipulation. All procedures were done by the same Oriental medical doctor with a headphone to hear the operator’s signal. LI11 pressure, ST36 pressure, LI11 acupuncture, and ST36 acupuncture stimulations were taken in order. After pressure stimulations, there was 4 minutes’ rest before the acupuncture stimulations were carried out. After 30 seconds of rest, an acupuncture needle was inserted, rotated consistently, and pulled out. There were three insertions and three removals of the needle (Fig. 1). For the acupuncture stimulation, disposable, stainless steel needles (diameter = 0.25 mm, length = 40 mm) (Dongbang Acupuncture & Moxibustion Company, Seoul, Korea) were used. After the scan, we checked whether or not subjects felt pain by pressure and de qi by acupuncture stimulation.

fMRI image acquisitions

A subject was positioned supine, with the head in the eight-channel head coil to adapt to the surroundings after 30 minutes of rest. The head was fixed by a sponge and the subject was not supposed to move or open their eyes during the MRI scans. The MRI bore was lit dark and there was no sound other than the sounds from the MRI machine. All images were acquired by a well-trained professional operator. A 3.0-Tesla MRI system (Phillips Achieva, Best, the Netherlands) was used. Transverse blood oxygenation level dependent (BOLD) MRI images were acquired with a gradient-echo echo-planar imaging sequence. The corresponding imaging parameters were: TR (repetition time) = 3000 ms, TE (echo time) = 35 ms, flip angle = 90°, field of view (FOV) = 230 × 230 mm, slice thickness = 4 mm without interslice gap, number of slices = 37, matrix size = 64×64, and voxel resolution = 2.88 mm×2.91 mm×4.00 mm. In addition, anatomical images were acquired with a two-dimensional T1-weighted turbo spin echo sequence (TR = 1297 ms, TE = 10 ms, flip angle = 90°), FOV = 230×230 mm, slice thickness = 3 mm, matrix size = 256×256, voxel resolution = 0.9 mm×1.20 mm×3.00 mm, and transverse orientation) and a three-dimensional T1-weighted gradient echo sequence (TR = 9.9 ms, TE = 4.6 ms, flip angle = 8°, FOV = 240×240 mm, slice thickness = 1 mm, matrix size = 240×240, voxel resolution = 1.00 mm×1.00 mm×1.00 mm, and sagittal orientation).

Data analyses

Statistical Parametric Mapping 2 (SPM2, Wellcome Department of Cognitive Neurology, London, UK) was used for postprocessing of fMRI data. Motion of the head during the fMRI acquisition was calculated by rotation and translation on X, Y, and Z coordinates and realigned automatically using three-dimensional (3D) motion correction to minimize the movement-related variance of the volunteer. Anatomical MR images and fMRI images went through coregistration. Anatomical 3D MR images were standardized using standard anatomical space devised by Talairach and Tournoux22 and fMRI images were standardized with the same process as the anatomical images.23 The spatially normalized images volumes were smoothed to raise the power of discrimination among noises of MR signal changes classified by voxels produced by hemodynamic response and to set match statistical model offered by SPM.24,25 The full-width half maximum of the Gaussian filter was set to 8×8×10 mm.

In statistical analysis, we did a comparative analysis of brain activation induced by pressure or acupuncture stimulation. One sample t test (p = 0.0001 without multiple compensation, voxel ≥ 20) was carried out to compare the BOLD fMRI signal activation before and after stimulation using individual t-contrast maps. Then, for group analysis, one-way analysis of variance within-subjects was carried out.
**Results**

**Brain activation differences between the two stimulation methods (group analysis)**

We treated this as 2 * 2 factorial designs.

When we combined acupuncture and pressure stimulation data at the second level, acupuncture showed more activation than pressure stimulation. On the left side, precuneus, thalamus, and uvula of vermis regions were activated. On the right side, culmen and midbrain regions were activated (Table 1).

At the left LI11 acupoint, more areas were activated with the acupuncture stimulation than with the pressure stimulation. The parahippocampal gyrus, culmen, and uvula of vermis regions were activated. On the left side, the subgyral, thalamus, extranuclear, inferior semilunar lobule, and midbrain regions were activated. On the right side, the culmen and midbrain regions were activated.

\[ P_{value} \text{ adjustment control and threshold was “none 0.001.”} \]

We treated this as 2 * 2 factorial designs.
regions were activated. On the right side, lingual gyrus, posterior cingulate (BA 29, 30), fastigium, and declive regions were activated (Table 2, Fig. 2).

At the left ST36 acupoint, more areas were also activated with the acupuncture stimulation than with the pressure stimulation. On the left side, the precentral gyrus, postcentral gyrus (BA 1), cingulate gyrus, and posterior cingulate (BA 31) regions were activated. On the right side, cuneus, lingual gyrus, cingulate gyrus (BA 24), culmen, fastigium, and pons regions were activated (Table 3, Fig. 3).

Brain activation differences between the two acupoints (group analysis)

When we combined LI11 and ST36 stimulation data at the second level, ST36 showed more activation than LI11 stimulation. Medial frontal gyrus and postcentral gyrus regions were activated on the right side (Table 4).

With the pressure stimulation, more areas were activated at the left LI11 than at the left ST36. On the right side, the precentral gyrus (BA 4, 6) region was activated (Table 5, Fig. 4).

With the acupuncture stimulation, more areas were activated at the left ST36 acupoint than at the left LI11. On the left side, the claustrum, insula, and cingulate gyrus (BA 24) regions were activated. On the right side, the cingulate gyrus region was activated (Table 6, Fig. 5).

There were no deactivations. Pressure stimulation showed no significant activation or deactivation compared to acupuncture. At the left LI11 or ST36 pressure stimulation, there was no significant activation or deactivation compared with acupuncture stimulation. Also, LI11 stimulation showed no significant activation or deactivation than ST36 stimulation. ST36 pressure stimulation showed no significant activation or deactivation than LI11 pressure stimulation, either. And LI11 acupuncture stimulation showed no significant activation or deactivation than ST36 acupuncture stimulation.

Finally, the interaction showed that acupuncture or ST36 has greater responses than pressure stimulation or LI11 (Table 7).

Discussion

There have been many acupuncture studies using fMRI to investigate the effect of acupuncture after stimulating a specific acupoints,8,9 to compare the differences of brain activations after stimulating multiple acupoints,10,11 and to observe differences of brain activations with different stimulation methods such as tactile or electroacupuncture.12–16

In this study, we investigated brain activation patterns using the two different stimulation methods, painful pressure and acupuncture, at the same acupoint, the left LI11 and the left ST36, respectively. We discuss activated areas classified into cerebrum, cerebellum, and brain stem.26

In comparison between the left LI11 painful pressure and acupuncture stimulation, the left side of parahippocampal gyrus, thalamus and cerebellum were more activated by

| Table 2. Activated Areas Where Acupuncture Showed More Signal Activation Than Pressure in Comparison Between the Pressure and the Acupuncture Stimulation at the Left LI11 Acupoint |
|-----------------|--------|--------|--------|--------|
| Brain regions included in cluster | BA     | KE     | Coordinates | Z     |
| Cerebrum        |        |        | x y z      |       |
| Limbic lobe     | L      | Parahippocampal gyrus | 28 | 227 | 18, 28, 6 | 3.86 |
| Sublobar        | L      | Thalamus |        | 227 | 8, 16, 6 | 3.98 |
| Cerebellum      | R      | Declive | 384 | 6, 56, 14 | 4.04 |

Table 3. Activated Areas Where Acupuncture Showed More Signal Activation Than Pressure in Comparison Between the Pressure and the Acupuncture Stimulation at the Left ST36

<table>
<thead>
<tr>
<th>Brain regions included in cluster</th>
<th>BA</th>
<th>KE</th>
<th>Coordinates</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum</td>
<td></td>
<td></td>
<td>x y z</td>
<td></td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>L</td>
<td>Precentral gyrus</td>
<td>548</td>
<td>30, 28, 6</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>L</td>
<td>Postcentral gyrus</td>
<td>548</td>
<td>40, 26, 60</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>R</td>
<td>Cuneus</td>
<td>1055</td>
<td>14, 80, 12</td>
</tr>
<tr>
<td>Limbic lobe</td>
<td>L</td>
<td>Lingual gyrus</td>
<td>1055</td>
<td>6, 74, 0</td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>488</td>
<td>4, 22, 42</td>
<td>3.84</td>
<td></td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>31</td>
<td>4, 66, 14</td>
<td>3.64</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>Culmen</td>
<td>789</td>
<td>18, 54, 24</td>
</tr>
<tr>
<td>Anterior lobe</td>
<td>R</td>
<td>Fastigium</td>
<td>789</td>
<td>6, 52, 22</td>
</tr>
<tr>
<td>Brain stem</td>
<td>R</td>
<td>Pons</td>
<td>789</td>
<td>10, 34, 30</td>
</tr>
</tbody>
</table>

P_corrected (cluster level) ≥ 0.05, cluster size ≥ 50 voxels. L, left; R, right; BA, Brodmann area; KE, expected voxels per cluster; Z, peak Z-value.
acupuncture than by painful pressure stimulation. The thalamus transfers every sensory division and input from the cerebellum, basal ganglia, limbic system, and reticular formation to the cerebral cortex. The parahippocampal gyrus plays an important role in memory, and the cerebellum takes part in regulation of motor function. In this connection, we can find the clinical significance of LI11 acupuncture stimulation.

In comparison between the left ST36 painful pressure and acupuncture stimulation, limbic system (BA 24, 31), and cerebellum regions were more activated by acupuncture than by painful pressure stimulation. ST36 pressure stimulation did not activate this area, either. We can observe the clinical significance of ST36 acupuncture stimulation, not shown by painful pressure stimulation.

In comparison between the left LI11 and the left ST36 painful pressure stimulation, BA 4 and 6 were more activated by LI11 stimulation than by ST36. BA 4 is the primary motor area (M I). When the primary motor cortex is stimulated electrically, a specific muscle of the contralateral contracts in accordance with the stimulated area. Considering BA 4 activated by the left LI11 stimulation, this acupoint is supposed to have an influence of ipsilateral movement. The primary motor cortex coordinates muscle that is necessary for correct movement of distal muscle, which, when injured, does not paralyze the muscle permanently, but recovers gradually. Therefore, it is supposed that stimulation of this area supports recovery of motor disturbance. The premotor area corresponds with BA 6a in the cerebral lateral surface, and receives afferent fibers mainly from the sensory association cortex. This area is known to be concerned with movement accompanied by sensory input, and it reacted to considerable electrical stimulation. Also, the supplementary motor area corresponds with BA 6a in the cerebral medial surface, and receives afferent fibers mainly from the basal ganglia, primary motor area, and premotor area. It is connected with the opposed part, and stimulation of this area activates upper motor neurons. This area also supports composite motor programs, and activates lower motor neurons through the pyramidal tract. In this study, this area was activated by LI11 pressure stimulation, so it is supposed that this area is connected with the opposite through corpus callosum, and activation of this area supports recovery of motor disturbance.

In comparison between the left LI11 and the left ST36 acupuncture stimulation, the cingulate gyrus (BA 24), insula, and claustrum were more activated by ST36 acupuncture stimulation than LI11. Therefore, it is supposed that ST36 acupuncture could have an effect on rational recognition and autonomic nerve function.

In this study, LI11 pressure stimulation activated the left side of the anterior lobe and a part of the posterior lobe of the cerebellum. Brain areas with significantly increased signal activation by LI11 or ST36 acupuncture stimulation were similar to the spinocerebellar tract. Therefore, it is supposed that acupuncture stimulation is transferred through the spinocerebellar tract as deep sensibility, and this is different from a sense of touch or pressure sensation transmission. It is supposed that pathways of painful pressure and acupuncture stimulation are different.

LI11 acupuncture stimulation activated the right side of the cerebellum and ST36 acupuncture stimulation activated the right side of the cerebellum and pons. Nerve tracts, namely, ascending tracts, descending tracts, and composite bundles are located in the tegmentum, which constitutes most of the brain stem. The posterior white column–medial lemniscal pathway of the ascending cortical system transfers discriminative touch, vibration-flutter, and position sensation. The spinothalamic tract transfers thermesthesia and

### Table 4. Activated Areas by Painful Pressure and Acupuncture at the Left ST36 Showed More Signal Activation Than the Left LI11

<table>
<thead>
<tr>
<th>Brain regions included in cluster</th>
<th>BA</th>
<th>KE</th>
<th>Coordinates x y z</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum &lt;br&gt; Frontal lobe</td>
<td>R</td>
<td>Medial frontal gyrus</td>
<td>6</td>
<td>290</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>R</td>
<td>Postcentral gyrus</td>
<td>3</td>
<td>290</td>
</tr>
</tbody>
</table>

$p_{\text{corrected}}$ (cluster level) $\geq 0.05$, cluster size $\geq 50$ voxels.

L, left; R, right; BA, Brodmann area; KE, expected voxels per cluster; Z, peak Z-value.

### Table 5. Activated Areas by Painful Pressure with a Cotton Tip at the Left LI11 Showed More Signal Activation Than the Left ST36

<table>
<thead>
<tr>
<th>Brain regions included in cluster</th>
<th>BA</th>
<th>KE</th>
<th>Coordinates x y z</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum &lt;br&gt; Frontal lobe</td>
<td>R</td>
<td>Precentral gyrus</td>
<td>6</td>
<td>244</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>32, –22, 62</td>
</tr>
</tbody>
</table>

$p_{\text{corrected}}$ (cluster level) $\geq 0.05$, cluster size $\geq 50$ voxels.

L, left; R, right; BA, Brodmann area; KE, expected voxels per cluster; Z, peak Z-value.

**FIG. 4.** Activated areas by painful pressure with a cotton tip at the left LI11 showed more signal activation than the left ST36 (height threshold: $p = 0.001$, voxel $\geq 20$). A: Precentral gyrus (R). R, right.
indiscriminative touch sensation. The trigeminothalamic tract transfers touch, temperature, and position sensation accepted from the face. Therefore, it is supposed that LI11 or ST36 acupuncture stimulation is transferred to the midbrain, pons, or medulla through the above nerve tracts and as a result, it has an effect on the function of the relevant brain area. For example, contralateral hemiplegia, facial palsy, and ataxia are clinical syndromes of pons, and related to the efficacy of LI11 or ST36.

In this study, LI11 and ST36 acupuncture stimulation activated the parahippocampal gyrus or cingulate gyrus. The anterior cingulate cortex (ACC, BA 24, 32), a fibrous bundle that transfers neural signals between the right and left sides of the cerebrum hemisphere, plays an important role in rational cognitive functions and autonomic functions such as blood pressure, heart rate, and feeling control. Also, the ACC receives a lot of input from intralaminar thalamic nuclei, main targets of spinoreticulothalamic tracts that are some of the nerve tracts to transfer the sense of pain, and as a result it triggers a pain response. Accordingly, we can confirm sense transmission of acupuncture stimulation. It is supposed that LI11 or ST36 acupuncture stimulation has an important significance to change autonomic function, and acupuncture and painful pressure stimulation are different because painful pressure stimulation did not activate the limbic system. In this study, the limbic system was activated by acupuncture, but in different studies the limbic system was deactivated, so this is open to dispute. It seems that brain activation or deactivation is related to the sympathetic or parasympathetic nerve. At any rate, this result suggests that acupuncture stimulation has an effect on autonomic nerve regulation, and further research is needed regarding activation or deactivation of autonomic nerves.

This process was done by 1 Oriental medical doctor, so the intensity of painful pressure or acupuncture stimulation would seem to be consistent, but it is supposed that there is a different degree of response according to volunteers. However, the purpose of this study is to see the difference between the two stimulation methods, and the result of group analysis showed a significant difference, so comparison between the two stimulation methods is possible and significant.

A limitation of this study is that the result had no regard for individual differences in pain threshold. Though 1 Oriental medical doctor carried out regular stimulation, the intensity of stimulation and de qi of each volunteer may be different. Moreover, intensity of stimulation and de qi on two acupoints may be different in the same volunteer. Furthermore, 10 subjects may be somewhat small for an fMRI study in healthy volunteers, but we observed signal changes using mainly the paired t test, so we believe it is not that big a problem.14,18,27 Also we cannot exclude the possibility of order effects.

In conclusion, the painful pressure and acupuncture stimulation on LI11 or ST36 have different effects on brain activity. Even on the same acupoint, the effect was different according to stimulation methods.

Acknowledgments

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Table 6. Activated Areas by an Acupuncture Needle at the Left ST36 Showed More Signal Activation Than the Left LI11

<table>
<thead>
<tr>
<th>Brain regions included in cluster</th>
<th>BA</th>
<th>KE</th>
<th>Coordinates x y z</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum Frontal gyrus L Subgyral</td>
<td>182</td>
<td>-40,22,22</td>
<td>3.44</td>
<td></td>
</tr>
<tr>
<td>Sublobar L Claustrum Insula</td>
<td>182</td>
<td>-34,8,6</td>
<td>5.05</td>
<td></td>
</tr>
<tr>
<td>Limbic lobe L Cingulate gyrus</td>
<td>24</td>
<td>-8,6,44</td>
<td>4.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1485</td>
<td>4,6,40</td>
<td>4.00</td>
<td></td>
</tr>
</tbody>
</table>

P_corrected (cluster level) > 0.05, cluster size ≥ 50 voxels.

L, left; R, right; BA, Brodmann area; KE, expected voxels per cluster; Z, peak Z-value.

Table 7. Activated Areas Where Acupuncture or ST36 Showed More Signal Activation Than Pressure or LI11 (Interaction Between Four Conditions)

<table>
<thead>
<tr>
<th>Brain regions included in cluster</th>
<th>Coordinates x y z</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrum Frontal lobe Precentral gyrus</td>
<td>6</td>
<td>177, 30, -16,62</td>
</tr>
<tr>
<td>Limbic lobe Cingulate gyrus</td>
<td>24</td>
<td>274, 4,38</td>
</tr>
</tbody>
</table>

P_corrected (cluster level) > 0.05, cluster size ≥ 50 voxels.

L, left; R, right; BA, Brodmann area; KE, expected voxels per cluster; Z, peak Z-value.
Disclosure Statement

All the authors declare that no competing financial interests exist.

References


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