

Research Paper Review

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Effects of Long-Term Acupuncture Treatment on Resting-State Brain Activity in Migraine Patients: A Randomized Controlled Trial on Active Acupoints and Inactive Acupoints PLoS One 2014; 9: 6

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ABSTRACT

Background: Acupuncture has been commonly used for preventing migraine attacks and relieving pain during a migraine, although there is limited knowledge on the physiological mechanism behind this method. The objectives of this study were to compare the differences in brain activities evoked by active acupoints and inactive acupoints and to investigate the possible correlation between clinical variables and brain responses.

Methods And Results: A randomized controlled trial and resting-state functional magnetic resonance imaging (fMRI) were conducted. A total of eighty migraineurs without aura were enrolled to receive either active acupoint acupuncture or inactive acupoint acupuncture treatment for 8 weeks, and twenty patients in each group were randomly selected for the fMRI scan at the end of baseline and at the end of treatment. The neuroimaging data indicated that long-term active acupoint therapy elicited a more extensive and remarkable cerebral response compared with acupuncture at inactive acupoints. Most of the regions were involved in the pain matrix, lateral pain system, medial pain system, default mode network, and cognitive components of pain processing. Correlation analysis showed that the decrease in the visual analogue scale (VAS) was significantly related to the increased average Regional homogeneity (ReHo) values in the anterior cingulate cortex in the two groups. Moreover, the decrease in the VAS was associated with increased average ReHo values in the insula which could be detected in the active acupoint group.

Conclusions: Long-term active acupoint therapy and inactive acupoint therapy have different brain activities. We postulate that acupuncture at the active acupoint might have the potential effect of regulating some disease-affected key regions and the pain circuitry for migraine, and promote establishing psychophysical pain homeostasis.

Trial Registration: Chinese Clinical Trial Registry ChiCTR-TRC-13003635.

ANALYSIS

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Background Information

Due to their high prevalence, frequency of attacks, significant medical burden to sufferers as well as the significant impact on quality of life (QoL) and productivity, migraine headaches have been identified as a significant public health issue. While the pathophysiological mechanism of migraine has not been definitively identified, evidence from neuroimaging studies indicates that it is a disorder of the central nervous system.

A recent Cochrane review has shown acupuncture to be safe and at least as effective as prophylactic drug treatment for migraine (1). However, little is known about the physiological mechanisms behind this observed effectiveness.

The current study used a regional homogeneity (ReHo) approach to compare differences in brain activation patterns in migraine patients before and after long-term treatment with real or sham acupuncture. Higher ReHo values indicate increased local connectivity of brain tissues. The ReHo approach is data-driven and does not require any knowledge of the experimental design in order to compare fMRI data. This allows for more complete blinding and has good test-retest reliability. In addition, it detects changes or modulations induced across the entire brain by different conditions.

PERTINENT RESULTS

There were no significant differences in the groups receiving the fMRI scans at baseline.

Active Acupuncture Group

- In the active acupuncture group, significantly higher ReHo values (increased local connectivity) were seen in: the bilateral anterior cingulate cortex (ACC, or Brodmman area), insula, thalamus, supplementary motor area (SMA), superior temporal gyrus (STG), cuneus, lingual gyrus, cerebellum, and brainstem after treatment.
- Conversely, the bilateral posterior cingulate cortex, middle frontal gyrus (MFG), angular gyrus, precuneus, middle temporal gyrus (MTG), left hippocampus, inferior parietal lobule, inferior temporal gyrus, and right postcentral gyrus all showed decreased ReHo values.

Control/Inactive Acupuncture Group

• In the control/inactive *acupuncture* group, the left ACC and medial frontal gyrus showed increased ReHo values while the right middle frontal gyrus (MFG) showed decreased values.

Further Notable Results

Both the active and inactive acupuncture groups showed significant decreases in their VAS scores, frequency of migraine attacks, number of days with migraine per 4 weeks, and HIT-6 score after the 8-week treatment period. The active acupuncture group showed statistically significantly higher decreases in VAS but all other categories were comparable.

The decreases in VAS seen in the active acupuncture group were strongly correlated to the increased ReHo values seen in the anterior cingulate cortext (ACC) and insula while in the inactive acupuncture group the decrease in VAS score was related to the increased ReHo values in the ACC only. This suggests that the mechanism by which acupuncture treatment for migraine patients works is through its effect on the ACC. The ACC is involved in the medial pain system, is composed of the pain matrix, and plays a significant role in endogenous pain control.

When the current study's fMRI data was compared to data on healthy populations, it was found that individuals with migraine showed significantly decreased ReHo values, decreased amplitude of low-frequency fluctuation, and aberrant functional connectivity in the anterior cingulate cortex (ACC). This further supports the theory that the ACC is strongly involved in the effects of acupuncture treatment on migraine.

Overall, active acupuncture treatment had significant effects on the pain matrix, lateral pain system, medial pain system, default mode network, and some regions closely related to the cognitive components of pain processing. Extensive ReHo changes were seen in the bilateral thalamus, specifically in the ventral posterolateral nucleus (VPL) and ventral posteromedial nucleus (VPM) which are key intermediates in the lateral pain system and important to processing spatial and intensity aspects of noxious stimuli. In addition, effects were seen on the hippocampus, an area associated with the cognitive components of pain processing, as well as the insula, an area that participates in pain perception, emotional processing, and interoception.

CLINICAL APPLICATION & CONCLUSIONS

Both active acupuncture and inactive acupuncture treatments helped to alleviate clinical symptoms of migraine and improve the QoL in migraine patients after 8 weeks of therapy. However, acupuncture at active acupoints was greatly superior in reducing pain intensity (as measured by the VAS). Improvements with acupuncture to inactive points could be due to enhanced placebo effects based on patient expectations, longer patient-doctor interactions, and the power of touch and suggestion.

Active acupuncture treatment was also shown to play a significant role in the sensory-discriminative component of pain and the proper modulation of the emotional aspects of pain.

The results of this study support the use of acupuncture for long-term treatment of migraine. Even though both active and inactive acupuncture points were shown to be clinically useful, the larger reduction in pain when using the active acupuncture points suggests that these should be preferentially utilized instead of the inactive points. Further research should continue to illustrate the most effective point selection protocols.

STUDY METHODS

80 participants were enrolled in the study and of those, 40 were randomly selected to receive fMRIs. This included 20 from both the active acupuncture and inactive acupuncture groups. All subjects had been diagnosed with migraine without aura based on the classification criteria set by the International Headache Society (IHS). Inclusion criteria were as follows:

- 18 to 55 years of age
- Right-handedness
- A history of 2-6 migraine attacks per month during the last 3 months and during the baseline period (4 weeks before enrolment)
- Start of headaches before the age of 50
- Educated for more than 6 years
- Completion of the basic headache diary
- Not taking any prophylactic headache medicine or receiving any acupuncture treatment during the last 3 months
- No record of long-term analgesic consumption
- No contraindications to exposure to a high magnetic field

Exclusion criteria included

- Neurological diseases
- Hypertension, diabetes mellitus, hypercholesteremia, vascular/heart disease and/or major systemic conditions
- Pregnant or lactating women
- History of alcohol or drug abuse
- Participation in any neuroimaging research study in the past 6 months
- Inability to understand the doctor's instructions

The study was a single-blind, randomized controlled trial including an active acupuncture group and an inactive acupuncture group. All participants were involved in a 4-week baseline period during which they recorded details of migraine attacks (severity, frequency, and duration of headache) in a headache diary followed by an 8-week treatment period. During this time they continued to fill out their headache diary. Outcome measurement was completed at baseline, 4 and 8 weeks after randomization for all participants. In addition, 20 migraineurs in each group were randomly selected for fMRI examination at the end of baseline and the end of the treatment period. The acupuncturists could not be blinded, due to the need to know which points they were needling. The outcome assessor and patients were all blinded throughout the study.

Treatment included traditional Chinese style acupuncture performed by two specialized acupuncturists with a minimum of 5 years of training and 3 years of clinical experience. The active acupuncture group was treated with traditional and classical acupuncture points including bilateral SJ5, GB20, GB34, and GB40. The inactive acupuncture group was treated with points chosen based on anatomical locations including bilateral SJ22, PC7, GB37, and SP3 (see below). In both groups needles were inserted to approximately 2.5-3.5 cm depth and rotated at a frequency of 1-2 Hz. This was repeated 1-3 times to achieve the sensation of de-qi. Each group received 32 acupuncture sessions over 8 weeks. Sessions were performed once every other day, aiming for 4 times a week. Each treatment lasted 30 minutes.



Outcome measurements included the Visual Analogue Scale (VAS), number of days with a migraine for 4 weeks, frequency of migraines in 4 weeks (number of migraines separated by a pain free interval of 48 hours minimum), duration and severity of the headache, and the HIT-6 questionnaire to assess the severity and impact of the headache on the patient's QoL. In addition, resting-state fMRI scans were performed on 20 randomly selected patients at baseline and at the end of the treatment period to detect brain activity.

Each fMRI took 6 minutes. During this time, patients were asked to keep their eyes closed, relax, move as little as possible, and stay awake. Patients experiencing a migraine attack or within 72 hours of an attack could not be scanned and their scan would be postponed until after that particular attack had passed.

STUDY STRENGTHS / WEAKNESSES

Strengths

- Inactive acupuncture points are a validated sham control method and minimize bias from patients.
- Statistical analysis was performed by an independent statistician who was blinded to treatment allocations.

Weaknesses

- Of 80 participants, only 40 completed fMRI scans (this may have been due to budget restraints?).
- No index was available to access and quantify patient expectations during treatments sessions.

Additional References

1. Linde K, Allais G, Brinkhaus B et al. Acupuncture for migraine prophylaxis. Cochrane Database System Review 1. 2009, CD001218.

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