

# Research advances in the brain mechanisms of acupuncture effects based on the BOLD-fMRI technology

## 基于 BOLD-fMRI 技术的针刺效应的脑机制研究进展

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### Abstract

By summarizing the recent literatures on brain mechanisms with acupuncture intervention based on blood oxygenation level-dependent (BOLD)-functional magnetic resonance imaging (fMRI), the BOLD-fMRI examination and analysis methods, the points to be acupunctured, the corresponding meridian activation regions, the specific intensity range, functions and indications of the acupoints, the manifestation of 'bi-directional regulation' characteristics, fMRI performance of chronergy, laterality and needling qi of acupuncture were reviewed to provide the ideas for future research in this area.

**Keywords:** Acupuncture-moxibustion Therapy; Acupuncture Therapy; Magnetic Resonance Imaging; Research on Acupoints; Review

**【摘要】** 通过总结近年来针刺干预血氧水平依赖的功能性磁共振成像(BOLD-fMRI)脑机制研究的相关文献,对BOLD-fMRI检查及分析方法、施针穴位及对应经脉激活区域、针刺的穴位特异性的强度范围及功能主治、“双向调节”特性的体现、针刺效应的时效性、偏侧性及得气的fMRI表现进行综述,并提出该领域以后的研究思路。

**【关键词】** 针灸疗法; 针刺疗法; 磁共振成像; 穴位研究; 综述

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Acupuncture-moxibustion is an important discipline that uses acupuncture, moxibustion and other therapeutic tools to act on certain special parts of the human body (meridians and acupoints) for preventing and treating diseases. Acupuncture-moxibustion has been widely used worldwide due to its wide-range indications, quick effect, easy operation, low cost, safety and many other advantages, but the basic scientific principles of the clinical effects have not been fully clarified<sup>[1]</sup>.

The vigorous development of modern science has promoted the combination of acupuncture and medical imaging. Blood oxygenation level dependent (BOLD)-functional magnetic resonance imaging (fMRI) is a fMRI technology, which can non-invasively detect the brain anatomical structure and the functional characteristics, and combine the neuroimaging and clinical manifestation to facilitate the study on the neural

mechanism of diseases, thus to objectively and visually reflect the pattern of the brain activity response in acupuncture, to provide new information and ideas for studying the neural mechanism of acupuncture<sup>[2]</sup>.

### 1 Common Methods for BOLD-fMRI Studies on the Acupuncture Effect

Since Cho ZH, *et al*<sup>[3]</sup> pioneered the application of fMRI technology to study the mechanism of acupuncture, fMRI has been widely used in researches on the specificity of acupoints, the role of acupoints along the meridian, and the related influencing factors, and has become one of the most effective methods to explore the substance of acupuncture<sup>[4]</sup>.

In the imaging studies of the acupuncture effects, due to the characteristics of intuitively reflecting the functional activities of specific areas of the brain, BOLD-fMRI can directly locate the cerebral cortex of the patient, target the changes in the cerebral cortex function and the effects of acupuncture<sup>[2]</sup>, and analyze the correspondence between the changes in cerebral

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cortex function and acupuncture effects from multiple angles and at advanced levels, providing ideas for clinical diagnosis and treatment monitoring<sup>[5-6]</sup>. The use of different analytical methods according to different research focus will help to fully understand the effect of acupuncture and make the research results more accurate, objective, and intuitive, thus more convenient for modern medical theories to explain the brain mechanism of acupuncture effects<sup>[7]</sup>.

Due to the advantages and disadvantages of different fMRI data analysis methods, the corresponding analysis method is usually selected according to the study focus<sup>[7]</sup>. At present, the commonly used research methods include resting-state fMRI and task-based fMRI. The resting-state fMRI requires the subject to stay as still as possible during the scan to reduce the body movement, and to collect the fMRI images for a certain period of time, which reflects the spontaneous activity of the BOLD signal and is closer to the physiological state with a simple and operable application. Task-based fMRI is designed to perform a specific task and to record the neural response of the cerebral cortex and the change of the BOLD signal in the corresponding area within a certain period of time<sup>[8]</sup>. Sometimes, the incomparability of the experimental results can be caused due to the special experimental design and the complicated execution differences in the subject training<sup>[8]</sup>. There will be spontaneous activities in the low-frequency range of the brain in the resting state, as well as inherent functional connections in different brain regions<sup>[9]</sup>. The main data research methods involved in acupuncture effect network research include<sup>[10]</sup>: independent component analysis (ICA), regional homogeneity (ReHo), amplitude of low frequency fluctuations (ALFF), voxel-mirrored homotopic connectivity (VMHC)<sup>[11-12]</sup> and other resting-state fMRI brain image analysis<sup>[13]</sup>. In recent years, the focus of fMRI analysis has gradually shifted to the multivariate pattern analysis (MVPA) and the univariate pattern analysis (UVPA). The MVPA and UVPA combined with the functional connectivity analysis methods show the improvement in the research methods in exploring the resting-state functional connectivity within and between the brain networks of patients, which has confirmed that in-depth studies on brain regulatory mechanisms of acupuncture have been conducted<sup>[13]</sup>.

## 2 Research Progress of BOLD-fMRI on Brain Functional Mechanism of Acupuncture Effect

### 2.1 Acupuncture effect of single acupoint

#### 2.1.1 Study on the effect of acupuncture at Hegu (LI 4)

The fMRI analysis of acupuncture at Hegu (LI 4) showed that the consistent activation region was located in the encephalic region including the anterior

central gyrus, the posterior central gyrus, the cerebellum and the limbic system. The anterior central gyrus and the posterior central gyrus correspond to the brain regions of the hand, face and mouth, while the hypothalamus and the limbic system correspond to the central regulatory pathway of acupuncture analgesia. Hegu (LI 4) has a two-way regulatory effect, exerting its effect through the excitement or inhibition of multiple encephalic regions<sup>[13]</sup>. On one hand, these phenomena are in line with the traditional Chinese medicine (TCM) theory that 'Hegu (LI 4) is used to treat the head and the face diseases'; on the other hand, they are in line with the basic theory of acupuncture-moxibustion regulation. Acupuncture at bilateral Hegu (LI 4) both causes the signal changes in the right insula lobe and cingulate gyrus, which activates the contralateral posterior central gyrus and the insula lobe, as well as the homolateral anterior central gyrus and the insula lobe; acupuncture at the right Hegu (LI 4) activates the bilateral anterior central gyrus and the posterior central gyrus, which reflects the unequal phenomenon of the central stimulation effect and the difference in the intermediate links caused by the stimulation, indicating the laterality of the right brain function<sup>[14]</sup>. A study on the therapeutic mechanism of acupuncture at Hegu (LI 4) for facial paralysis suggested a possible association with increased synaptic activity in complex motor coordination and sensorimotor integration<sup>[15]</sup>.

#### 2.1.2 Study on the effect of acupuncture at Taixi (KI 3)

Acupuncture at Taixi (KI 3) positively activates the brain areas such as brainstem and thalamus, and negatively activates the brain areas such as the periventricular and subcortical structures of the limbic system; acupuncture acts on the blood pressure regulation points in this brain area and nearby to raise or lower the blood pressure by changing the peripheral resistance through vasoconstriction and vasodilatation. The most important part of the diversified mechanism of regulating blood pressure by Taixi (KI 3) should be the central function<sup>[5]</sup>. The signal in the positively activated brain area is more significantly increased under the action of acupuncture than in the resting state<sup>[16]</sup>.

#### 2.1.3 Study on the effect of acupuncture at Waiguan (TE 5)

The negatively activated brain regions, by real acupuncture at Waiguan (TE 5) in the healthy people, include the left top lobulus parietalis superior, the lobulus parietalis inferior, the precuneus, the superior frontal gyrus, the anterior central gyrus and the posterior central gyrus; the negatively activated brain regions, by real acupuncture at Waiguan (TE 5) in the pathological conditions such as ischemic stroke, include the left gyrus frontalis medialis, the gyrus centralis posterior and the gyrus temporalis medius, the right posterior central gyrus and the anterior central gyrus.

Acupuncture at Waiguan (TE 5) simultaneously positively activates and negatively activates the bilateral posterior central gyrus and the left lobulus parietalis inferior. The indications of Waiguan (TE 5) include cold, headache, fever, and tinnitus. The negative activation of the functional dominant area of Waiguan (TE 5) is seen under the real acupuncture<sup>[17]</sup>. The activated brain areas by acupuncture at Waiguan (TE 5) are positively correlated with the indications of Waiguan (TE 5); part of the negatively activated brain area is not task-dependent, while the rest is still related to the indications of Waiguan (TE 5). Therefore, the therapeutic effect is closely related to the positive activation and the negative activation of the brain center<sup>[18]</sup>. In addition, the conventional acupuncture activates the brain area more intensively than the superficial skin acupuncture, which specifically activates the right cerebellum<sup>[19]</sup>.

#### 2.1.4 Study on the effect of acupuncture at Zusanli (ST 36)

The limbic system is related to the regulation of visceral activities, emotions, behaviors, learning and memory. Acupuncture at Zusanli (ST 36) activates the limbic system brain regions such as the temporal lobe, the gyrus hippocampi, the cingulate gyrus, the hypothalamus, the insular lobe and the occipital lobe. Zusanli (ST 36) shows a strong immediate aftereffect of acupuncture. Electroacupuncture at Zusanli (ST 36) and Guanyuan (CV 4) shows a common brain activation feature, that is, both of them have a significant negative activation effect on the limbic lobe-neocortical pathway. This phenomenon is also present in acupoints such as Taichong (LR 3), Guangming (GB 37) and Hegu (LI 4). Acupuncture at Guanyuan (CV 4) specifically activates the right superior temporal gyrus, the left somatosensory area II, and the cerebellar vermis, which is speculated to be related to the acupoint-specific central nervous system regulation<sup>[20]</sup>.

#### 2.1.5 Study on the effect of acupuncture at Jiexi (ST 41)

The positively activated brain regions by acupuncture at Jiexi (ST 41) include the left anterior adenohypophysis, the brainstem, the midbrain and the temporal lobe. The activated brain regions correspond to its clinical efficacy, and its BOLD signal can reflect the time variability of the acupuncture stimulation. Some brain areas such as the right frontal lobe and the left occipital lobe produce both positive and negative activations with acupuncture at the Jiexi (ST 41). The BOLD signal reflect more than a simple increase or decrease, but can confirm the complex regulatory mechanism of the acupoints<sup>[21]</sup>. The accuracy of the experimental data may also be affected by the post-acupuncture effect (the therapeutic effect will continue for about 20 min after acupuncture treatment) on the baseline signal level.

#### 2.1.6 Study on the effect of acupuncture at Rangu (KI 2)

Acupuncture at Rangu (KI 2) positively activates the brain areas include the left posterior lobe of cerebellum, the right temporal lobe, the brain stem and the midbrain<sup>[22]</sup>; it negatively activates the brain regions including the left inferior temporal gyrus, the fusiform gyrus (BA20), the right limbic lobe, and the hippocampal gyrus. Similar to stimulating Jiexi (ST 41), its BOLD signal can also reflect the time variability of acupuncture stimulation, with different activation modes during the initial and the continuing stages.

### 2.2 Studies on the brain functional mechanism of acupuncture at multiple acupoints

#### 2.2.1 Study on the combined acupuncture effect of Dazhong (KI 4) and Taixi (KI 3)

Clinically, the Yuan-Primary and Luo-Connecting points are often used together to enhance the efficacy, and the activated brain areas are not simply a superposition, but specific areas.

Compared with acupuncture at Dazhong (KI 4) or Taixi (KI 3) alone, by acupuncture at Dazhong (KI 4) and Taixi (KI 3), the positively activated brain regions include the left frontal lobe, the anterior central gyrus, the gyrus frontalis inferior, and the right insular lobe; negatively activated brain regions include the left midbrain, the right limbic lobe, the gyrus hippocampi; there are co-activated brain areas-the bilateral frontal lobes; the overlapping brain areas include the left gyrus hippocampi, the right insular lobe, and the anterior lobe of cerebellum; the specifically activated brain areas include the left anterior central gyrus, the midbrain, the right thalamus, and the parietal lobe. It is speculated that the brain activation area caused by the combined use of Yuan-Primary point and Luo-Connecting point should be related to the clinical efficacy<sup>[10]</sup>.

#### 2.2.2 Study on the acupuncture effect of acupoint group containing Waiguan (TE 5)

Waiguan (TE 5) combined with Yanglingquan (GB 34) belongs to the acupoint combination of the meridians that share the same name: Hand Shaoyang Meridian and Foot Shaoyang Meridian. Acupuncture at Waiguan (TE 5) activates the right cerebellum in a wide range, and the two acupoints together specifically activate the regions of the left parietal lobe, the left occipital lobe and the bilateral basal ganglia, with more concentrative and high-intensive activation of the right cerebellum.

The acupoint combination of the Hand Shaoyang Meridian and Foot Shaoyang Meridian can strengthen the treatment of motor, sensory and balance disorders, which has provided a reference for studying the regularity of the acupoint combination of the meridians that share the same name, and analyzing the basis of the acupoint combination of the meridians that share the same name from the perspective of brain function imaging<sup>[23]</sup>.

### 2.2.3 Study on the combined acupuncture effect of Taixi (KI 3) and Feiyang (BL 58)

Acupuncture at Taixi (KI 3) and Feiyang (BL 58) in healthy people positively activates the brain areas including the left anterior lobe of cerebellum, the posterior lobe of cerebellum, the gyrus frontalis medialis, the middle frontal gyrus, and the right posterior lobe of cerebellum. Acupuncture at single acupoint shows negative activation phenomenon. But acupuncture at both Taixi (KI 3) and Feiyang (BL 58) does not show significant negative activation in brain areas; the overlapped brain areas are the left posterior lobe of cerebellum, the right gyrus temporalis superior, and the right middle frontal gyrus, and the activation intensity of these brain areas are higher than that of the single acupoint. The specific brain areas include the left gyrus frontalis medialis, the paracentral lobules, and the right inferior parietal lobules, which are related to the function and indication of Taixi (KI 3) and Feiyang (BL 58). Acupuncture at a single acupoint also has specific brain areas. Acupuncture at the two acupoints activates the brain area with higher intensity and wider range. It is not only a simple superposition of the single acupoint, but the reorganization to form more complex brain changes, which should be related to the complexity of the acupuncture mechanism<sup>[24]</sup>.

### 2.2.4 Study on the combined acupuncture effect of Hegu (LI 4) and Taichong (LR 3)

Acupuncture at Hegu (LI 4) combined with Taichong (LR 3) versus acupuncture at Hegu (LI 4) or Taichong (LR 3) alone, they trigger the common brain activation regions, including the frontal lobe, the occipital lobe, and the temporal lobe. However, it is not a simple addition of the activation areas of the individual acupuncture at the two acupoints, but the redistribution of the functional brain activation areas following the hemodynamic changes produced by the central regulatory mechanisms<sup>[15, 25]</sup>.

### 2.2.5 Study on the combined acupuncture effect of the Five Shu-Transmitting points of the Stomach Meridian

At present, most researches focus on studying the single acupoint specificity or the clinical efficacy of the external and internal acupoint combination<sup>[26-27]</sup>. Cao DN, *et al*<sup>[28]</sup> performed fMRI examination after acupuncture at the Five Shu-Transmitting points of the Stomach Meridian, and found the activated brain regions including the midbrain, the brainstem, the left thalamus and the right temporal parietal lobe; as well as the negatively activated brain regions such as the left frontal lobe, the left anterior central gyrus (BA32) and the bilateral anterior cingulate gyrus (BA10).

Research on the correlation among the circulation, clinical efficacy and activation areas in the brain of the

Stomach Meridian of Foot Yangming showed that acupuncture at the Stomach Meridian of Foot Yangming could affect the limbic system, the language, the smell and the cognitive memory, and had a certain correlation with the circulation of meridians and clinical functions, but the activation of these brain areas only partially explained the functions of meridians. It has been confirmed through animal experiments that acupuncture at the acupoints of the Stomach Meridian has a bidirectional benign effect on the nerve-endocrine-immune network. It remains to be proved whether there are precise positioning differences, the nature of the activated pixels, and the specific pixel size differences in the similarly activated brain regions of different meridians.

### 2.2.6 Study on the combined acupuncture effect of Guangming (GB 37) and Yanglingquan (GB 34)

The ipsilateral occipital visual cortex has obvious excitatory areas, and the average BOLD signal intensity of the post-acupuncture excitement in the occipital visual cortex is increased significantly with acupuncture at Guangming (GB 37) and Yanglingquan (GB 34)<sup>[29]</sup>. In addition, excitation of brain tissue is also seen in the frontal lobe, temporal lobe, basal ganglia and pons varolii. The increased signal intensity in the corresponding brain regions shown by fMRI after acupuncture at the acupoints has provided a theoretical basis for the neurophysiological excitation in the corresponding brain regions<sup>[30]</sup>.

### 2.3 Study on the brain functional mechanism of acupuncture at non-acupoint regions

By detecting the amplitude of the low-frequency fluctuation (ALFF) change plots in both Sanyinjiao (SP 6) and non-acupoint brain regions of the sleep-deprived patients, Dai XJ, *et al*<sup>[31]</sup> found that needle retention caused ALFF signal changes in several functional brain regions, which could be expressed in the Decision Model and Notation (DMN) related brain regions. In the non-acupoint area with the same innervation as Sanyinjiao (SP 6), the range and intensity of brain region changes caused by Sanyinjiao (SP 6) were stronger than those of the non-acupoint area, and the non-acupoint area was more of an adverse stimulus. It is speculated that this difference may be related to the existence of meridians. It was found that the stimulation intensity of acupoint-specific brain regions was obvious, while the activation range of non-acupoint regions was non-specific and weak determined by the ALFF and DMN plots after acupuncture at the acupoints or non-acupoint areas (for many diseases, including sleep deprivation, etc.).

Acupuncture at Hegu (LI 4), Jiexi (ST 41), Taixi (KI 3), Rangu (KI 2), Zusanli (ST 36), Sanyinjiao (SP 6) and other acupoints followed by BOLD-fMRI assessment shows that each acupoint has its corresponding brain region,

that is, the acupoint specificity in the brain area can be shown on BOLD-fMRI. Studies have shown that acupuncture at different acupoints may activate different brain regions, and acupuncture at a few acupoints may also have overlapped brain regions. The clinical efficacy of these brain regions is closely related to the specificities of the acupoints, with different signal changes in BOLD-fMRI and complicated mechanism. It is not only the single acupoint stimulation performance, but sometimes it can redistribute the activation area through improving blood flow, or strengthening the motor, sensory and balance function dominated by the meridians that share the same name, and increasing the two-way regulatory effect. Acupuncture together with the real-time task-based brain signal observation, and comparing the main function of the acupoint can find, in most cases, the overlapped brain regions representing the regulatory role of the mechanism action point (the therapeutic effect point).

BOLD-fMRI, using the different forms such as the resting-state and task-based, the different analysis methods such as ALFF and ReHo, and the changes in local or entire brain regions under disease conditions as a basis, plays an active exploratory role to study the brain mechanism of acupuncture treatment. It confirms the specificity and complexity of the brain mechanism of acupuncture and moxibustion by actively exploring the role<sup>[32]</sup>.

The specific activation performance of fMRI is closely related to the acupuncture method, whether to achieve a needling response, and the immediate effect of acupuncture, for example, the needling manipulation and a stronger stimulation method will produce a strengthening effect on the fMRI signal<sup>[33]</sup>. By comparing the real acupuncture group with the shallow acupuncture group, it is found that the real acupuncture group has stronger connection strength among the hippocampus, the caudate nucleus and the orbital prefrontal cortex at the corresponding activation site. The real acupuncture group has a stronger sense of acupuncture than the shallow acupuncture group<sup>[34]</sup>, and the interaction of the brain network is enhanced. However, acupuncture at non-acupoint areas has less specificity, weaker intensity, and more adverse stimulation.

#### 2.4 The role of BOLD-fMRI in studying the brain mechanism of acupuncture at the meridians

Zhang F, *et al*<sup>[10]</sup> used BOLD-fMRI technology to observe the effect of simultaneous acupuncture at Dazhong (KI 4) and Taixi (KI 3) belonging to the Kidney Meridian of Foot Shaoyin. The results showed that the acupuncture effect between the acupoints in each group not only had overlapping brain activation areas, but also existed specific brain activation regions. The ALFF method was used to study the fMRI of acupuncture at the Lung Meridian of Hand Taiyin, and

found a significantly changed intrinsic activity of the cerebral cortex (activation and inhibition appeared separately), with especially significantly enhanced ALFF in the right gyrus subcallosum and the gyrus frontalis inferior.

Acupuncture at the Yuan-Primary point and the Luo-Connecting point belonging to the Bladder Meridian activates the right superior temporal gyrus (BA22) and the bilateral fusiform gyrus. This area is the auditory cortex with the central-Wernicke's area, which is related to the semantic understanding of; the left and right fusiform gyri are closely related to the fine face recognition and human perception learning. In the theory of acupuncture and moxibustion, the Bladder Meridian enters the brain from the top, and is directly connected to the brain. The functional activation of these two brain regions corresponds to that 'the real memory is based on the sea of essence', which reflects the direct connection between the Bladder Meridian and the brain.

### 3 Summary

In summary, the meridian acupoint effect of acupuncture and moxibustion is manifested in multiple organs and systems of the human body. The cortical signal excitation regions and intensities of resting-state fMRI at human acupoints and meridians to which they belong are different. There is often specific and overlapping brain activation regions, and it is often consistent with the functional principal of the acupoint. The neurological mechanism of functional brain region activation triggered by acupuncture at combined acupoints, acupuncture at Yuan-Primary point and Luo-Connecting point and meridians is not a simple functional region-point correspondence, but rather a complex process in which multiple brain regions are involved and acting together. The process is even related to the activation of the brain function network corresponding to the motor function of the human body, and also corresponds to the functional region of the point, which is theoretically consistent with the synergistic effect of acupuncture.

BOLD-fMRI is the basic research model in the high-quality literature on the mechanism of acupuncture. However, the current researches on BOLD-fMRI for the brain mechanism of acupuncture and moxibustion are relatively of single-method, high literature repetition rate and poor accuracy; besides, the research objects are mainly healthy people, the diseases involved are mainly neurological ones, and the research contents mostly focus on the acupoint specificity, furthermore, there are few studies on the combination of acupoints and the laws of meridians, and no strong logical basis has been developed at this stage to explain the mechanism of acupuncture. For example, what are the

regularities in brain activation changes stimulated by acupuncture at different acupoint combinations and different meridians compared to acupuncture at a single acupoint? What are the inherent specific connections and meanings between these regularities with the embodiment of TCM theory in acupuncture and moxibustion? And what is the regulatory effect relevance of acupuncture? In addition, an emphasis on the consistency between design and the treatment protocols, as well as establishing a baseline of brain activity will help to judge and exclude the influence of factors such as environment and emotions in the clinical trials. Besides, various devices should be adopted to analyze the specific mechanism of brain function changes after acupuncture. The above factors will all be the key points in future research.

#### Conflict of Interest

The authors declare that there is no conflict of interest in this article.

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