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Clinical Evidence of Brain Effect Difference between True Point and False Point: A Meta-analysis Based FMRI

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Abstract

Imaging studies after acupuncture at acupoints and sham acupoints have shown significant changes in the function of specific parts of the brain, but these findings are not consistent. In this meta-analysis, we examined different studies to determine whether there are differences in brain function changes in the brain imaging findings of acupuncture at real and sham points. Pubmed, Embase, Cochrane, CNKI, VIP and Wanfang databases were used to search for acupuncture brain imaging literatures published by May 2020. Study selection, quality assessment and data extraction were carried out by two independent researchers. The whole brain function data of acupuncture points were analyzed by sdM-PSI. Thirteen studies met the inclusion criteria, including 266 subjects enrolled at acupoints including Taichong, Xingjian, Neiting, Guangming, Neiguan, Baihui, Fengchi, Sanyinjiao, Zusanli, Wai Guan, Feng Long, Zhongdu, Xiangu, 214 true acupoints, 186 false acupoints. Our analysis revealed that the brain region positively activated by acupuncture was Right fusiform gyrus, BA 30, Right inferior gyrus, Stationarity BA 48, and Right superior Temporal gyrus, BA 42. These findings suggest that the limbic system is the common difference in brain function after acupuncturing at different true and false acupoints.

Conclusion: The functional changes of limbic system are the brain regions that distinguish true and false acupoints.

Keywords: Acupoints; Brain; Acupuncture

Introduction

Traditional acupuncture and moxibustion science believes that La acupoint is a special place on the body surface where qi from viscera and meridians is injected, which is not only the reaction point of diseases, but also the operation site of acupuncture and moxibustion. La acupoint exerts effects on the body far away through meridians. This theory has been applied in the treatment of diseases for more than 2500 years. The effect of acupoints may be related to the distribution characteristics of local vascular nerve bundles, the circulation distribution of fascia and some muscles, tendons and ligaments, or the composition characteristics of these tissues at acupoints [1-3]. Studies have proved that there may be differences or changes in temperature and skin resistance between acupoints and non-acupoints under physiological or pathological conditions, stimulated or non-stimulated conditions, and biomolecules released after stimulation may be different due to the different amount of stimulation [4-9]. At the same time, the central nervous system plays an important role in the effect of acupoints [10-17]. It has been found in acupuncture analgesia studies that acupuncture induces signals in the afferent nerve, thus regulating spinal cord signal transmission and pain sensation in the brain. Moreover, acupuncture activates some brain regions, which contribute to the decline of inhibition and inactivation of several marginal regions, thus contributing to the regulation of pain emotions [18-21]. Acupuncture at a certain point can specifically activate the corresponding brain regions, and these brain regions are closely related to the efficacy of the point, indicating that acupuncture points have a relatively specific response to blood oxygen dependent level signals in the brain region. Acupuncture at a certain point can specifically activate the corresponding brain regions, and these brain regions are closely related to the efficacy of the point [22-23]. With the development of Functional Magnetic Resonance Imaging (fMRI) technology, the brain region specificity of acupoint effect has been confirmed. Some studies have proved that there are differences in brain regions activated by functional magnetic resonance imaging between acupuncture at wax points and non-wax points, indicating that there are differences in brain effects between acupuncture points and non-wax points. Then, whether there are similarities in brain functional changes after acupuncture at different true and false points can be demonstrated by brain imaging, so as to distinguish the true and false points from the brain functional changes. In this study, seed-based D-mapping with subject image arrangement (SDM-PSI) was used to conduct standard random effect meta-analysis to investigate the changes in brain activity between true and false acupuncture points in published controlled trials [24].

Data and Methods

Data retrieval

We systematically searched databases pubmed, embase and Cochrane, China National Knowledge Network (CNKI), VIP, Wanfang for literatures published from the earliest available up until May 2020. We used the following key words: acupuncture OR needling OR acupoints and MRI OR fMRI OR magnetic resonance OR Brain MRI. We included all articles of fMRI studies to investigate the effects of acupuncture on human brains with at least one group that received needle based acupuncture.

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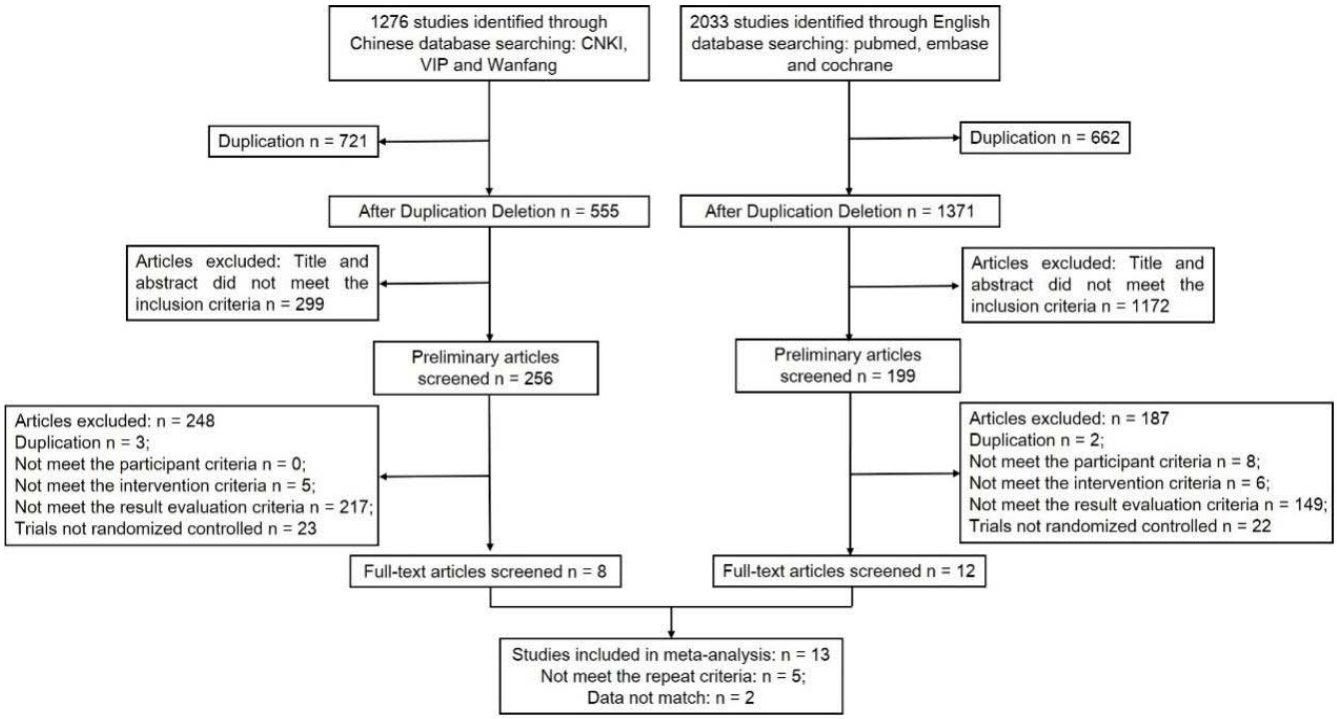

Figure 1: Literature retrieval flow chart.

Literature screening

Inclusion criteria: (1) Trials on healthy volunteers as well as patients diagnosed with certain diseases with no limitations on gender and origin; (2) People aged between 18-65 years old; (3) Trials on hand acupuncture; (4) Sham acupoints were set as controls; (5) fMRI studies based on BOLD signals were used as the outcome indicators with the MNI coordinates (x, y, z) and T-value/F-value provided; (6) At least 10 subjects were included.

Exclusion criteria: we excluded all citations that fit the following criteria (1) Reviews, systematic reviews, scientific reports, and republished researches; (2) Trials without whole brain functional imaging analysis; (3) MNI or Talairach coordinates were not available; (4) Statistics of coordinates such as T-value/F-value were not available; (5) Only the comparative analysis was performed before and after acupuncture treatments in each group; (6) Statistical analyses were carried out using software packages except SPM,

Data extraction

Extraction of basic information includes information of research object (gender, age, number of cases, physiological or pathological state), acupuncture program (acupoint, acupuncture method, manipulation) and data processing software.

Extraction of brain functional imaging data includes MNI or Talairach spatial coordinate values (statistics corresponding to x, Y and Z coordinate points (z or T values), and text files are created. According to the requirements of SDM-PSI software, all statistics of Z values are converted to T values by SDM online tools.

Statistical methods

In this study, sdM-PSI 6.21 software (https://www. Sdmproject. com) was used for voxel based meta-analysis. The statistical analysis threshold was $P<0.005$, $Z>1$, clustering degree N10, and PV 0.05 after calibration.

Quality assessment

Study selection and data extraction and summarization were independently performed in a standardized manner by two investigators (Yuxiao Mo and Shuidiao Zheng); any disagreements were resolved by a third investigator (Chuyun Chen). This meta_ analysis has been registered with the PROSPERO International Prospective Register of Systematic Reviews of the University of York (PROSPERO registration no. CRD42021187391).

Results

A total of 3309 articles were found through database search, of which 1393 duplicated publications (42.1 percent) were deleted and 1903 articles (57, 5 percent) were excluded because they did not meet the inclusion criteria. Thirteen articles (0.4%) were included in the meta-analysis (Figure 1 and Table 1). A total of 209 healthy subjects were included in the 13 trials, including 41 myopia patients and 16 ischemic stroke patients. The characteristics of these RCTS are summarized in Table 1. The acupoints involved are Taichong, Xingjian, Neitingj Guangming, Neiguan, Baihui, Fengchi, Sanyinjiao, Zusanli. Waiguan, Fenglong, Zhongdu. Xiangu, 214 acupoints 186 Pseudo acupoints. Eleven studies (84.6 percent) were conducted in China, one (7.7 percent) in the United States, and one (7.7 percent) in Germany.

Thirteen literatures were included in this study, including 4 Chinese literatures and 9 English literatures. Figure 1 shows literature retrieval screening process.

Table 1: Basic features of the included studies.

Literature	Gender (male: female)	Age (X±S)	Number of patients included in the statistics	True point: False point ratio	Research object	True Point	False Point	Manipulation	Software	coordinate
Fang [25] 2009	5:05	22-28	10	21:8	Health adult volunteers	Taichong, Xingjian, Neiting	Between metatarsal III and IV on the dorsum of the left foot	even motion	SPM99	MNI
Li [26] 2010	11:11	21.4±1.8	22	11:11	Healthy college students	Guangming	Nonmeridian-point nearby	conventional	SPM5	Talairach
Yoo [27] 2004	7:05	27.2±6.3	12	12:12	Health volunteers	Neihuan	About 1.5-2cm proximal to the PC6	rotation	SPM99	Talairach
Zhu [28] 2011	10:10	21-24	20	10:10	Health volunteers	Baihui, Fengchi, Neiguan	1.5-2cm proximal to Baihui, Fengchi and Neiguan	Supply and discharge equalization needle	SPM5	MNI
Gao [29] 2014	8:08	22.1±0.8	12	12:12	healthy	Sanyinjiao	2-3cm inwards from SP6	rotated	SPM8	MNI
Liu [30] 2010	9:09	24.2±2.9	18	18:18	healthy right-handed	Zusanli	Located 2-3cm apart from ST36	rotating	SPM5	Talairach
Qi [31] 2014	14:02	55.00±5.63, 58.50±6.95	16	8:8	Ischemic stroke patients	Waiguan	A level with Waiguan, the midpoint of the circulating route of the forearn of Shaoyang Meridian of the Hand and Taiyang Small Intensive Meridian of the Hand	twirled	SPM2	Talairach
Nierhaus[32] 2015	11:11	21-32	21	21:21	Healthy subjects	Zusanli	The same dermatome L5 as ST36: in the dermatome L2	Rotating: lift-thrusting	SPM8	Talairach
Dai Xijian [33] 2012	8:08	27.1±0.8	13	13:13	Health volunteers	Sanyinjiao	1 inch behind Sanyinjiao	Static retention needle	SPM5	MNI
Chen [34] 2010	9:06	24.5±0.6	14	14:13	Health volunteers	Zusanli	The lateral side of Zusanli point was opened by 2-3cm	twist	SPM5	MNI
Li [35] 2019	18:00	22±4.0	16	16:16	Health volunteers	Fenglong	2cm above Fenglong point on the right	Supply and discharge eqalization	SPM2	Talairach
Liu [36] 2012	21:20	25.76±3.7	41	22:19	College students with myopia	Taichong	Approximately 10 mm anterior to the classical site	twirled	SPM2	Talairach
Li [37] 2008	31:24:00	23.7±3.6	51	36:15	Healthy right-handed volunteers	Aichong, Zhongdu, Zusanli and Xiangu	Approximately 10 mm from the 2 real acupoints: nearby ST36 and LR6	Twisted, lifted, thrust	SPM2	Talairach

Basic features of the included study

Table 1.

Meta-analysis based on voxel

Peak height meta-analysis: The degree of freedom (DF) and P value of increased peak height were 11 and 0.17760063 respectively. The degree of freedom (DF) and P value of peak height decrease were 4 and 0.014636630, respectively, according to the results of heterogeneity test, the fixed effect model was selected to combine effect size and statistical inference. The 95% confidence interval for the occurrence rate of brain activation at acupuncture points and sham points was 1.101-1.671, and the mean earth standard error was 1.386±0.145. The 95% confidence interval for the occurrence rate of brain activation at acupuncture points and sham points was -2.342-0.971, and the mean earth standard error was -1.656±0.145, as shown in Table 2 and 3.

Table 2: Compared with false points, the peak height increased.

	d	SE	*z*	*P*	CI_{low}	CI_{up}
Jlfang	1.442	0.462	3.119	0.0018134	0.536	2.349
LILi	1.445	0.489	2.956	0.0031168	0.487	2.403
SSYoo	1.626	0.482	3.376	0.000735	0.682	2.57
XTZhu	1.767	0.544	3.248	0.0011613	0.701	2.834
PLiu	0.982	0.355	2.767	0.0056646	0.286	1.678
JQi	2.269	0.678	3.346	0.0008209	0.94	3.598
TNierhaus	2.622	0.43	6.094	0	1.779	3.465
XJDai	1.188	0.431	2.759	0.005802	0.344	2.033
XChen	1.196	0.423	2.827	0.0047024	0.367	2.026
XLLi	1.103	0.383	2.881	0.0039634	0.353	1.853
HLiu	1.084	0.337	3.211	0.0013212	0.422	1.745
LinLi	0.981	0.344	2.855	0.0043067	0.307	1.654
Mean	1.386	0.145	9.539	0	1.101	1.671

Table 3: Comparison between true and false points and peak height decreases.

	d	SE	*z*	*P*	CI_{low}	CI_{up}
LieGao	-3.072	0.632	-4.86	1.174E-06	-4.311	-1.833
PLiu	-1.078	0.359	-3.001	0.0026952	-1.783	-0.374
TNierhaus	-2.225	0.4	-5.563	2.6E-08	-3.009	-1.441
XChen	-1.296	0.429	-3.017	0.0025492	-2.138	-0.454
XLLi	-1.057	0.38	-2.777	0.0054798	-1.802	-0.311
Mean	-1.656	0.35	-4.734	2.199E-06	-2.342	-0.971

Threshold parameters

The Voxel threshold is in uncorrected model, (Peak height threshold) >0. 02500, threshold range Cluster size ≥1voxels.The comparison of voxel thresholds between the true and false points was shown in Table 4 and 5.

Threshold Statistics after FWE correction: After FWE correction, Peak height threshold, Peak TFCECORRECTED >0.05000, Cluster Size 1 voxel So voxel threshold ratio between true and false points, Table 6.

Heterogeneity and publication bias analysis: All studies were analyzed by SDM-PSI software heterogeneity and publication bias Metabias test, Bias: -1. 18, z: -0. 38, df: 11, p: 0. 704; 12=6. 895993, Q2=6. 589331, Funnel plot analysis is shown in Figure 2.

Discussion

Different analysis of brain activation between acupuncture at true and false points

This paper excludes the electric acupuncture, moxibustion and warm needle acupuncture methods may impact on the brain regions activated, regardless of the acupoint specificity between brain regions activated, as to research in pure acupuncture true and false cavity effect on brain regions activated in clinical research literature based on voxel meta-analysis, confirmed that the acupuncture true cavity contrast false hole part of the brain activation differences, Positive active brain regions after FWE correction were Right fusiform gyrus, BA 30, Right inferior gyrus, BA 48, and Right superior temporal Gyrus, BA 42, no negative activation.BA30 is part of the

Table 4: Brain regions with increased voxel threshold compared with sham acupoints.

MNI coordinate	SDM-Z	*P*	Voxels	Description
56,-24,16	3.934	4.172E-05	1792	Right superior temporal gyrus, BA 42
26,-38,-14	4.121	1.89E-05	1046	Right fusiform gyrus, BA 30
-30,-62,-12	3.063	0.0010971	236	Left inferior network, inferior longitudinal fasciculus
-14,-24,0	4.16	1.586E-05	192	Corpus callosum
-52,-24,24	2.934	0.0016721	138	Left superior longitudinal fasciculus III
6,-62,-38	3.172	0.0007572	129	Cerebellum, vermic lobule IX
4,-78,36	3.332	0.0004317	95	Right cuneus cortex
52,-64,-4	3.015	0.0012847	92	Right inferior temporal gyrus, BA 37
48,-62,-24	2.577	0.0049855	58	Right cerebellum, crus I
0,16,-12	2.649	0.004037	45	(undefined)
-8,-74,-40	2.527	0.0057511	37	Left cerebellum, hemispheric lobule VIIB
12,-10,40	2.871	0.002047	34	Right median cingulate / paracingulate gyri
-44,-32,-22	2.624	0.0043424	36	Left inferior temporal gyrus, BA 20
-16,-60,24	2.744	0.0030363	19	Left median network, cingulum
8,26,26	2.518	0.0059027	15	Right anterior cingulate / paracingulate gyri, BA 32
-4,-72,-6	2.142	0.0161148	5	(undefined), BA 18
24,24,52	2.11	0.0174097	3	Right superior frontal gyrus, dorsolateral, BA 8
-38,-60,-6	2.11	0.0174482	1	Left inferior network, inferior longitudinal fasciculus
-46,-36,48	2.001	0.0226926	1	Left inferior parietal (excluding supramarginal and angular) gyri, BA 2
-34,-92,0	1.991	0.0232199	1	Left middle occipital gyrus, BA 18

Table 5: Brain regions with decreased voxel threshold compared with sham acupoints.

MNI coordinate	SDM-Z	*P*	Voxels	Description
-4,44,2	-2.847	0.0022101	117	Left anterior cingulate/ paracingulate gyri, BA 10
28,-12,-16	-2.842	0.0022441	44	Right hippocampus, BA 20
56,-32,-14	-2.591	0.0047801	36	Right middle temporal gyrus, BA 20
-48,-6,-36	-2.367	0.0089625	10	Left inferior temporal gyrus, BA 20
60,-22,-6	-2.041	0.0206054	1	Right superior temporal gyrus, BA 21
6,44,-4	-2.005	0.0225039	1	Right superior frontal gyrus, medial orbital, BA 10

Table 6: Brain areas with elevated voxel value after FWE correction compared with those at sham and real points.

MNI coordinate	SDM-Z	*P*	Voxels	Description
26,-38,-14	4.121	0.001	530	Right fusiform gyrus, BA 30
52,20,18	3.609	0.001	555	Right inferior frontal gyrus, triangular part, BA 48
56,-24,16	3.934	0.001	134	Right superior temporal gyrus, BA *42 ~*

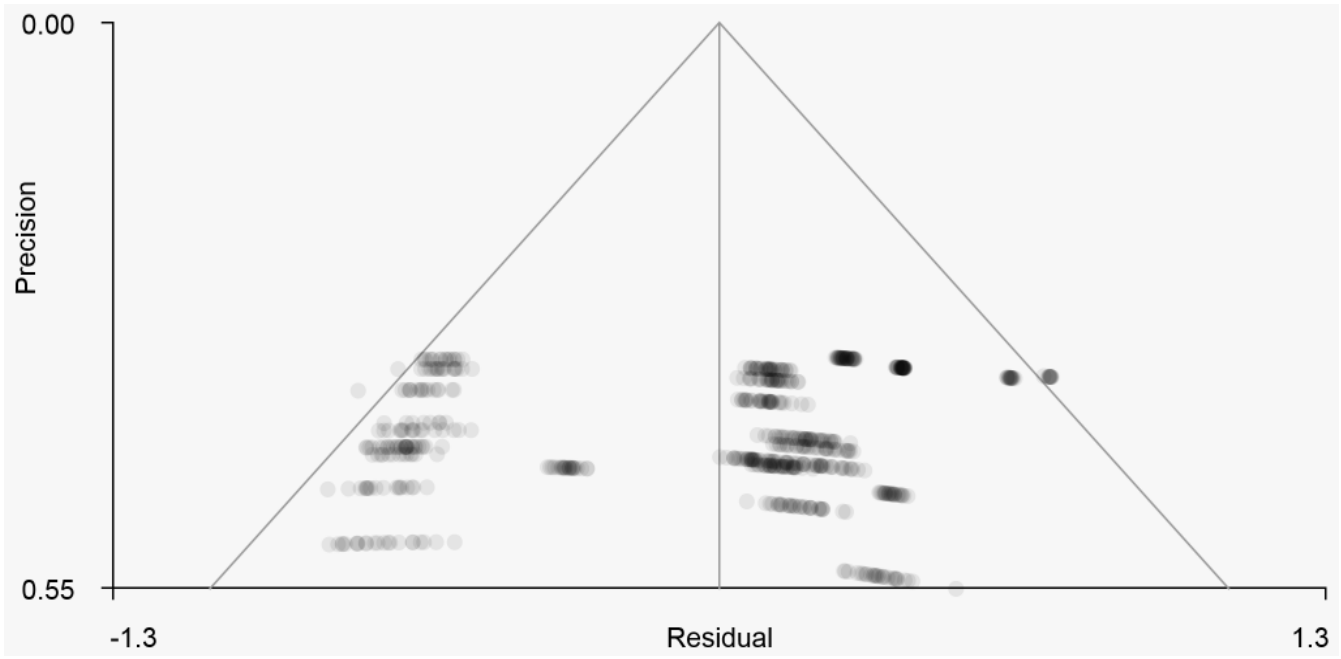

Figure 2: Funnel plot analysis.

cingulate gyrus and is responsible for responding to contingencies and is part of the memory system [39-40]. BA48, composed of the posterior parahippocampal gyrus, is closely related to the isthmus of cingulate gyrus and is involved in emotional and memory processes [41-42]. Located in the frontal lobe of the cerebral cortex between the inferior frontal sulcus and the lateral fissure, the right inferior frontal gyrus is crucial for the realization of complex behaviors. The superior temporal gyrus is located between the posterior branch of the lateral fissure and superior apparent sulcus, and is connected with the superior marginal gyrus and angular gyrus. Brain imaging and eeg studies have found that the Right superior temporal gyrus is associated with the brain mechanism of insight in creative invention [43]. The fusiform gyrus is located at the middle and bottom of the visual association cortex and is responsible for the recognition of the sub-classification of objects [44-45] = BA42 is a part of the lobe and plays a role in processing auditory information in humans and other vertebrates [46]. The triangle, a part of the inferior frontal gyrus, is located between the ascending and anterior branches of the lateral sulcus and is the central region of Brocas motor language area [47]. True acupuncture point into the literature research, including the meridian of yangming foot three mile, hong leong, Chambers, valley, jue Yin liver meridian of lr 3, leading, and lunar spleen by three vaginal intercourse, foot shaoyang bile by light, the wind pool, hand jue Yin pericardium through closed in, hand Yang outside the sanjiao (triple energizer) is the less, du meridian will, compared with points near the point, Acupuncture can specifically activate the brain areas of emotion, memory, complex behavior, creative discovery and visual, listening and language processing. The results of specific activation of true acupoints to brain regions are included in the indications and indications of wax acupoints or their meridian symptoms involved

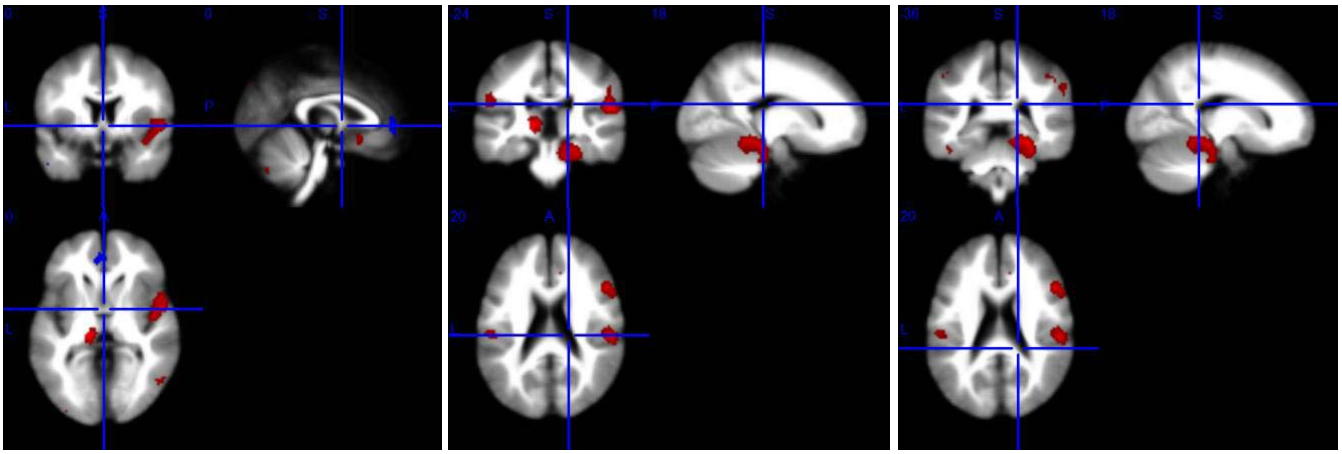

Figure 3: Activation (red) and negative activation (blue) of brain areas at sham points compared with acupuncture at real points before correction.

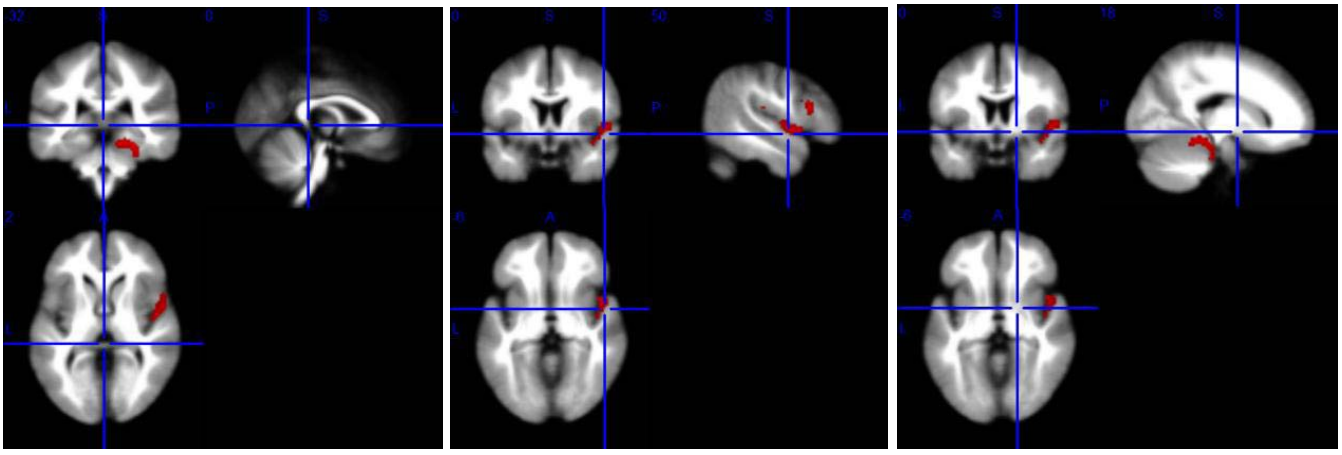

Figure 4: Activation of brain areas at real points compared with sham points after FWE correction (red).

in the article. Lingshu [48], a classic acupuncture and moxibustion, describes the indications and symptoms of foot-Yangming stomach meridian, including emotions and complex behaviors [49-50]; the indications and symptoms of acupoints Taichong, Xingjian, Guangming, Fengchi and Waiguan include eye and ear diseases [51-53]; the indications and symptoms of neiguan, Baihui and Sanyinjiao include memory, intelligence and speech diseases [54-57].

Limitations

Functional magnetic resonance imaging (FMRI) is used to study the effect mechanism of wax points, which can be carried out in living human body and provide objective basis for us to study the effect of wax points on brain. Due to the limitations of this study, insufficient evidence, and lack of homogeneous and high-quality original studies, carefully designed multi-center, large-sample randomized controlled clinical trials should be further carried out in future studies; Secondly, due to the particularity of acupuncture and moxibustion, the design of blind method is restricted to some extent, and the rigor of experimental design is still lacking; Thirdly, the acupoint is not a point but a region. If a point near the acupoint is used as a false acupoint, the acupoint effect in the false acupoint may be ignored.

Meta analysis based on voxel true acupuncture point acupuncture with fake acupuncture point of differences in activation or inhibit regions as the research object, ignore the acupoints of differences, different studies have shown that acupuncture meridians different brain regions effect, even if parts of similar function of acupuncture point is also relative specificity, Yang Jun looking reported such as acupuncture healthy li4 hole is back in si 3 hole on the right side of the forehead, inferior frontal gyrus deactivation, activation of left cingulate gyrus and left anterior central gyrus was enhanced. The specificity of the brain effect of wax points may be lost by only studying the changes of activation signals in the brain regions of true points and false points. Only one participant in the study had an ischemic stroke, one had nearsightedness, and the rest were healthy subjects. Healthy people wax point state is a resting state, different from the pathological state of acupoint sensitization, acupoint in the pathological state to "exciting", its reaction disease and treatment of malignant disease function significantly enhanced. X:Acupuncture sensitization state point with resting state in the brain regions activated or suppress differences, studies have shown that acupuncture of healthy people and patients with cervical spondylosis hanging bell, activate the show together on the back, back in his forehead, bilateral frontal cross back down, top lobule, inferior frontal gyrus, insula, back before the central, central, to return to the acupuncture healthy

people hanging The clock also activate left cingulate gyrus, in patients with cervical spondylosis, hanging bell point also activated bilateral cerebellum and occipital lobe [61].

Conclusion

Sdm-psi software based on fMRI voxel meta-analysis was used to analyze the data from different clinical studies on acupuncture at the true and false points, and the results showed that the brain regions with stronger activation degree of acupuncture at the true and false points, including Right Fusiform Gyrus, BA 30, Right inferior temporal gyrus> Stationarity and stationarity, Right inferior frontal gyrus> triangular part, BA 48, Right superior temporal gyrus, BA 42. The preliminary analysis shows that acupuncture at acupoints activates stronger brain regions, mainly in the activation of emotion, memory, complex behavior, creative invention and visual, listening and language processing functions, indicating that acupuncture at acupoints has more specific brain effects than non-acupoints. Due to the small sample size of the inclusion studies, the number of activated brain regions varies greatly in different studies, so the sample size should be appropriately expanded in future studies.

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