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Special Topic for 973 Program

Low-frequency fluctuation amplitude analysis of resting-state fMRI for functional brain response differences between acupuncture and moxibustion at Zusanli (ST 36) in patient with functional dyspepsia

静息态 fMRI 低频振幅评价针刺与艾灸功能性消化不良患者足三里脑功能响应差异

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Abstract

Objective: To compare and analyze functional brain response characteristics by applying acupuncture or moxibustion to Zusanli (ST 36) in patients with functional dyspepsia (FD) and investigate the differences of central action mechanism resulting from acupuncture or moxibustion.

Methods: A total of eligible 24 FD cases were divided into two blood-oxygen-level dependent (BOLD) sequences for functional magnetic resonance imaging (fMRI) scan. The amplitude of low frequency fluctuation (ALFF) analyses were conducted on the data of location phase, structure phase, resting state before acupuncture/moxibustion, working state during acupuncture/moxibustion and resting state after acupuncture/moxibustion using Data Processing Assistant for Resting-State fMRI (DPARSF) software.

Results: Acupuncture and moxibustion produced significant differences in functional brain response. The working state during acupuncture/moxibustion mainly decreased ALFF values in the right supramarginal gyrus, right superior parietal lobule, right frontal gyrus, upper right occipital lobe, right precuneus and right cingulate gyrus. At the same time, it increased ALFF values in the left cerebellum, right caudate nucleus, right cerebellum and left inferior gyrus. The differences during the resting state after acupuncture/moxibustion were significantly smaller than the working state in intensity and size. It mainly resulted in decrease in ALFF values in the right postcentral gyrus and right supramarginal gyrus and increase in ALFF values in the left precuneus, orbital part of inferior frontal gyrus and right cerebellar peduncles.

Conclusion: Needling and moxibustion at Zusanli (ST 36) can produce significant differences in immediate functional brain response.

Keywords: Acupuncture Therapy; Moxibustion Therapy; Moxa Stick Moxibustion; Point, Zusanli (ST 36); Research on Acupoints; Dyspepsia; Magnetic Resonance Imaging

【摘要】目的：比较分析针刺与艾灸足三里穴治疗功能性消化不良(FD)的脑功能响应特征，探索针刺与艾灸中枢作用机制的差异。**方法：**选取符合条件的 FD 患者 24 例，分针刺、艾灸两个 BOLD 序列进行功能磁共振成像(fMRI)扫描，每个序列分为定位相、结构相、针刺/艾灸前静息态、针刺时/艾灸时任务态、针刺/艾灸后静息态，采集数据运用 DPARSF 软件进行低频振幅(ALFF)分析。**结果：**针刺与艾灸时的脑功能响应具有明显差异，针刺时/艾灸时任务态比较主要引起了右缘上回、右顶上小叶、右额中回、右枕叶上部、右楔前叶、右扣带回中部等脑区 ALFF 值降低，以及左小脑、右尾状回、右小脑、左小脑脚、左颞下回等脑区 ALFF 值的升高；针刺/艾灸后静息态的比较差异在强度和区域大小上均明显小于任务态，主要引起了右中央后回、右缘上回脑区 ALFF 值的降低,以及左楔前叶、左额下回眶部、右小脑脚脑区 ALFF 值的升高。**结论：**针刺与艾灸 FD 患者足三穴的即时脑功能响应区域有明显差异。

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【关键词】针刺疗法；灸法；艾条灸；穴，足三里；穴位研究；消化不良；磁共振成像
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Functional dyspepsia (FD) is a common gastrointestinal disorder. Its pathogenesis is unknown yet and there is no specific therapy in Western medicine[1]. Because of its low cost, good efficacy and fewer toxic/side effects, acupuncture has become a main therapy for FD. Although there are some studies regarding its action mechanism, there are fewer studies on action mechanism differences between acupuncture and moxibustion. Functional magnetic resonance imaging (fMRI) is a functional neuroimaging procedure using MRI technology that measures brain activity in a dynamic, objective and noninvasive way. It is the most reliable, direct and objective procedure to study functional brain response. It is also the most common method to study the central action mechanism of acupuncture[2]. Stimulating Zusanli (ST 36) can improve clinical symptoms of FD and alleviate the patients' anxiety and depression[3-4]. To investigate the differences in central action mechanisms between acupuncture and moxibustion, this study collected the fMRI data during the resting state, working state and after the resting state, conducted ALFF analysis using DPARSF software, and compared the functional brain response differences by applying needling and moxibustion to Zusanli (ST 36) (the most common point for FD).

1 Clinical Materials

1.1 Research objects

A total of 24 FD cases included outpatients at the Gastrointestinal Department and Acupuncture Department, the First Hospital of Hunan University of Chinese Medicine between September 2015 and April 2016 as well as volunteers from the Hunan University of Chinese Medicine. This study has been approved by the Hospital Ethics Committee. All subjects signed the informed consent and agreed to the content of the study and publication of the research data.

1.2 Diagnostic criteria

This was based on the Rome III Diagnostic Criteria for functional dyspepsia[5]. The criteria must include one or more of the following: bothersome postprandial fullness; early satiation; epigastric pain; and epigastric burning. And no evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms. Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

1.3 Inclusion criteria

Those who are right-handed and met the diagnostic criteria of FD; aged between 18 and 52 years; did not take any prokinetic drugs in the past two weeks; and signed the informed consent.

1.4 Exclusion criteria

Those who couldn't sign the informed consent; having cancer and severe heart, liver and kidney diseases or conditions involving the digestive, nervous and hemopoietic systems; having a history of mental disorder or unconsciousness; women during pregnancy, menstruation or breast-feeding; those who are aware of the location and functions of Zusanli (ST 36); having claustrophobia; having artificial pacemaker or defibrillator that are contraindicated to fMRI.

2 Research Protocol

2.1 fMRI scan

The fMRI was conducted at the Radiology Department, the First Hospital of Hunan University of Chinese Medicine using the 3.0T Philip MRI machine.

2.1.1 Preparation before fMRI scan

All patients took a 30-minute rest before the fMRI scan. The patients were well aware of the detailed procedure, acupuncture/moxibustion sites, needling sensation, duration, temperature and cautionary notes. During the scan, one upper limb of the patients was covered. The patients were asked to move the four limbs when the scan stopped, and to use a fist to signal the tolerance of moxibustion temperature or needling sensation. This helped to maintain an appropriate temperature and needling sensation as well as the patients' safety.

2.1.2 fMRI scanning procedure

The fMRI was conducted twice for each FD patient, first for acupuncture and then for moxibustion. Each scan lasted 19 min and 20 s. There was an interval of more than 1 h between the two scans. The scanning sequences were as follows: 20 s of location, 3 min of structure, 6 min of resting state, working state (acupuncture or moxibustion), and finally 10 min of resting state (Figure 1).

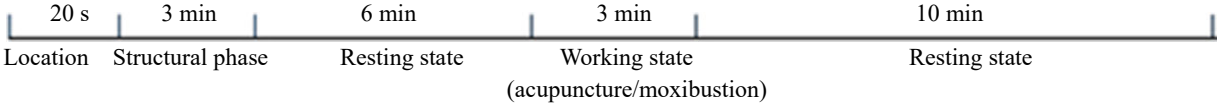

Figure 1. fMRI scanning procedure

2.1.3 Scanning parameters

T1 structure image: Repeat time (TR) 1 900 ms, echo time (TE) 9.2 ms, inverse time (TI) 750 ms, 30 slices, field of view (FOV) 240 mm × 240 mm, matrix=256 × 256, thickness=4 mm, inter-layer distance=1 mm and scanning time=3 min.

Resting state: The T1 structure image was used as the basis of anatomical location. The echo planar imaging (EPI) sequence was used to scan the resting state in the same plane as the T1 structure image. Scanning parameters were as follows: TR=2 000 ms, TE=30 ms, inverse angle (IA) = 9°, scanning layers = 25, layer thickness=5 mm, inter-layer distance=1 mm, FOV= 220 mm × 220 mm, matrix=64 × 64, and scanning time=6 min.

2.2 Intervention protocol

Points: Zusanli (ST 36) on the left side. The location of the point is based on the *Nomenclature and Location of Acupuncture Points* (GB/T 12346-2006)[6].

Materials: Disposable stainless steel filiform needles of 0.25 mm in diameter and 40 mm in length (manufactured by Suzhou Medical Instruments Co., Ltd., China) and Taiyi moxibustion sticks of 18 mm in diameter and 200 mm in length (manufactured by Nanyang Lüying Moxa Grass Biological Products Co., Ltd., China).

Both acupuncture and moxibustion were performed by a licensed acupuncturist.

2.2.1 Needling method

During the working state, the needle was inserted 0.8-1.2 cun perpendicularly after routine sterilization, followed by twirling manipulation (amplitude: 90-180 °; frequency: 60-90 times/min) until the presence of needling sensation (signaled by the patients' fist). The acupuncturist manipulated every 10 s to maintain the needling sensation. The repeated procedure lasted 3 min.

2.2.2 Moxibustion method

During the working state, the mild moxibustion was performed by keeping the ignited moxa stick 3-4 cm away from the point. The practitioner adjusted the distance according to the patients' signal. The moxibustion procedure lasted 3 min.

2.3 fMRI data processing

2.3.1 Data pre-processing

The data pre-processing and statistical analysis were done using the Data Processing Assistant for Resting-state fMRI (DPARSF) software (http://restfmri.net/forum/index.PhP) developed by the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University in MATLAB (MathWorks Inc., USA). The first 10 volumes of each time series were discarded, and the remained 170 time points were analyzed. Research subjects who had less than 1.5 mm 3-D head translation and less than 1.5° 3-D rotation were recruited for pre-processing. The pre-processing procedure included slice-timing, realignment, spatial normalization, and removal of the linear trend of time courses to calculate energy and its root mean square.

2.3.2 Amplitude of low frequency fluctuation

The amplitude of low-frequency fluctuation (ALFF) was analyzed using the DPARSF software. The main calculation and procedure were as follows: The filtered time series were converted to a frequency domain using a Fast Fourier Transform. The area under the peak was calculated to symbolize the signal energy. Its extraction symbolizes the amplitude of signal fluctuation, i.e., the intensity of blood oxygenation level dependent (BOLD) signal changes. The ALFF of each voxel was divided by the global ALFF value to get the mean ALFF (mALFF). The BOLD signal amplitude allowed for direct observation of BOLD signal changes during the resting state, i.e., the spontaneous activity level of individual voxels during the resting state and neural activity intensity of voxels in a low frequency range (0.01-0.08 Hz) from energy metabolism. The physiological significance of these spontaneous neuronal activities can be understood as a rhythmic motion pattern produced through information exchange between interconnected brain areas[7-8]. Increased ALFF signal means strongly activated brain areas, otherwise poorly activated areas. In addition, the ALFF calculation avoided errors due to dependence on model and assumed time dependence.

3 Research Results

3.1 Baseline data

Of the 24 FD cases, there were 12 males and 12 females. The average age was (24.0±3.4) years old. The mean duration was (30.3±8.1) months. The average FD symptom score was (7.38±2.42) points. During the experiment, 1 case could not tolerate the noise, 1 case had incomplete data, and 4 cases had more than 1.5 mm of head motion. The data of the rest 18 cases were statistically analyzed.

3.2 fMRI findings during acupuncture and moxibustion

As for the functional brain activity differences during acupuncture and moxibustion, the ALFF decreases manifested in the right supramarginal gyrus, right superior parietal lobule, left middle frontal gyrus, right middle frontal gyrus, right upper occipital lobe, triangle part of the left inferior frontal gyrus, right precuneus, right superior frontal gyrus, right middle cingulate gyrus, right middle temporal gyrus and right calcarine sulcus, and the ALFF increases manifested in the left cerebellum, right caudate gyrus, right cerebellum, left cerebellar peduncle, right cerebellar peduncle, left caudate gyrus and left inferior temporal gyrus. The DPARSF software, two-sample *t*-test and GRF correction

were used to analyze the fMRI findings during acupuncture and moxibustion. The results showed significant differences (all $P<0.05$) in above-mentioned brain areas (Table 1 and Figure 2).

Table 1. Findings of functional brain activity differences during acupuncture and moxibustion

Brain area	Broadman area (BA)	Mini coordinates			Voxel value	T value[1)]
		X	Y	Z		
Cerebelum_8_L	--	−28	−57	−44	71	4.3393
Caudate_R	BA25_R	12	19	3	48	3.9473
Cerebelum_8_R	--	24	−63	−50	175	3.7178
Cerebelum_Crus2_L	--	−3	−72	−36	32	3.5402
Cerebelum_Crus1_R	BA19_R	48	−67	−21	17	3.5237
Caudate_L (aal)	--	−15	19	3	39	3.3753
Temporal_Inf_L	BA36_L	−36	−4	−32	17	3.1292
Supra Marginal_R	BA40_R	60	−36	33	16	−2.7015
Parietal_Sup_R (aal)	BA5_R	21	−52	60	25	−2.7361
Frontal_Mid_L	BA46_L	−36	39	33	25	−2.9108
Frontal_Mid_R	BA46_R	27	46	33	21	−3.0966
Occipital_Sup_R	BA7_R	26	−72	48	27	−3.1979
Frontal_Inf_Tri_L (aal)	BA48_L	−46	28	20	18	−3.3107
Precuneus-R	--	11	−51	39	21	−3.6334
Frontal_Sup_R	BA8_R	25	20	46	49	−4.0484
Cingulum_Mid_R (aal)	BA23_R	3	−32	36	41	−4.1484
Temporal_Mid_R	BA39_R	52	−67	22	34	−4.3365
Calcarine_R	BA23_R	5	−61	20	175	−4.7254

Note: 1) T value indicates the activation (feedback) of the relative brain area, positive value indicates positive activation (feedback), negative value indicates negative activation (feedback)

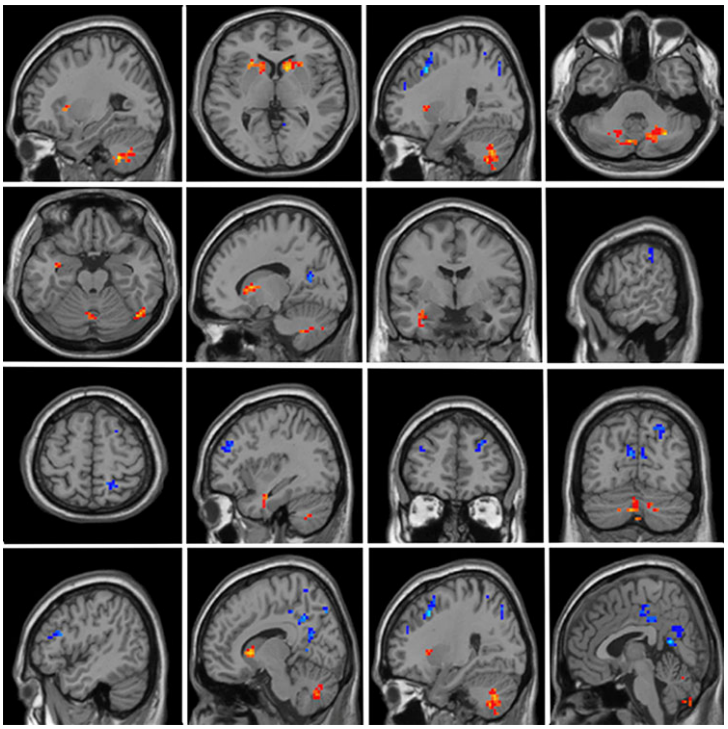

Figure 2. Findings of functional brain response differences during acupuncture and moxibustion

3.3 Functional brain response characteristics during the resting state after acupuncture and moxibustion

As for the functional brain response differences during the resting state after acupuncture and moxibustion, the ALFF decreases manifested in the right postcentral gyrus and right supramarginal gyrus, and the ALFF increases manifested in the left precuneus, the orbital part of the left inferior frontal gyrus and right cerebellar peduncle. The above differences were of statistical significances (all $P < 0.05$), (Table 2 and Figure 3).

Table 2. Comparison between functional brain responses during the resting states after acupuncture and moxibustion

Brain area	Broadman area (BA)	Mini coordinates			Voxel value	T value[1)]
		X	Y	Z		
Precuneus_L	BA23_L	−3	−57	19	11	2.8144
Frontal_Inf_Orb_L	BA47_L	−42	51	−12	12	2.6271
Cerebelum_Crus1_R	--	32	−69	−35	10	2.6035
Postcentral_R	BA2_R	42	−30	45	12	−2.8302
Supra-Marginal_R	BA48_R	51	−42	33	12	−3.0015

Note: 1) T value indicates the activation (feedback) of the relative brain area, positive value indicates positive activation (feedback), negative value indicates negative activation (feedback)

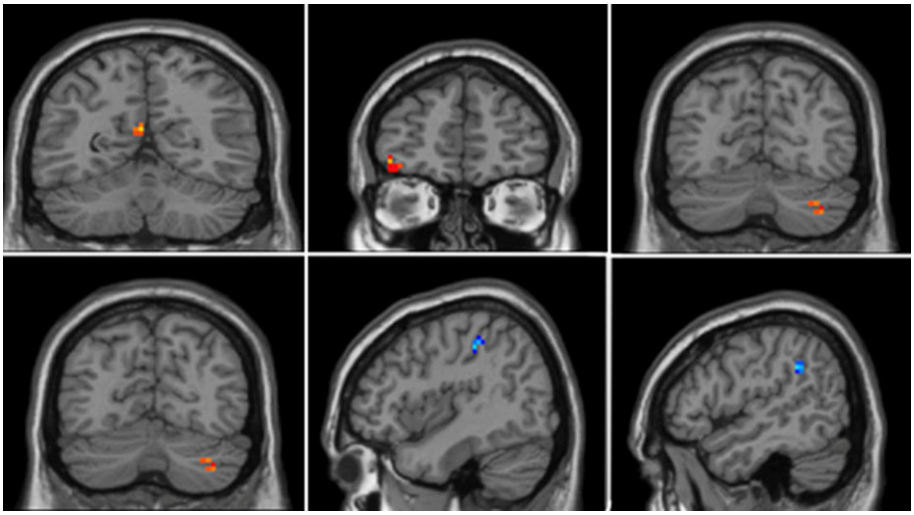

Figure 3. Functional brain response differences during rest states after acupuncture and moxibustion

4 Discussion

This study has shown that the differences of ALFF value between acupuncture and moxibustion manifested in the right parietal lobe (right supramarginal gyrus, right precuneus, and right superior parietal lobule), prefrontal lobe (left middle frontal gyrus, right middle frontal gyrus, the triangle part of the left inferior frontal gyrus and right superior frontal gyrus), right upper occipital lobe, right limbic lobe (right calcarine sulcus and right middle cingulate gyrus) and right middle temporal gyrus. Functional brain activity differences mainly showed in the right cerebral hemisphere. FD is closely associated with psychosocial factors such as a history of abuse, anxiety and depression[9-10]. The prefrontal lobe is related to perception, emotion and cognition and correlated to psychosocial assessment scale[11]. The right precuneus and cingulate gyrus are involved in personal behaviors in social context and correspondence with internal organs[12]. This indicates that social context and psychological factors may play a role in FD occurrence through regulating functions of the prefrontal lobe, precuneus and cingulate gyrus[13]. The prefrontal lobe is the key brain area that regulates pain in the midline and involves in pain processing[14]. In addition, it is correlated with changes in proximal gastric pressure and good compliance of proximal stomach[11]. The right middle cingulate gyrus and right calcarine sulcus are important parts of the limbic system, which is known as the visceral brain. They are associated with gastric motility and pain perception and involved in regulation of emotion, memory and behaviors[15]. The middle cingulate cortex directly receives the input signal of amygdaloid nucleus. It is involved in pain process and nociception and closely associated with visceral

stimuli[16]. The glucose metabolism in the cingulate cortex of FD patients is significantly higher than that in normal population[17]. According to the research findings, compared with moxibustion, the immediate central action produced by needling Zusanli (ST 36) mainly manifests in regulating the right cerebral hemisphere, specifically the prefrontal lobe, limbic lobe and parietal lobe. As for mechanism, needling Zusanli (ST 36) may inhibit brain areas such as the prefrontal lobe and right precuneus, reduce psychological and environmental effect on FD and thus alleviate FD symptoms by inhibiting the prefrontal lobe and limbic lobe and regulating gastric motility and interfering with stomach pain process[18]. Moxibustion, on the other hand, inhibits functional brain activities in the left and right cerebellum, left and right caudate nucleus, left and right cerebellar peduncle and left inferior gyrus, especially the left cerebral hemisphere and cerebellum. The cerebellum and cerebellar peduncle are connected with the middle brain and medulla oblongata via fibers. They regulate gastric sensation and motility directly or indirectly[19]. The caudate nucleus is a key component of the basal ganglia and involved in the process of gastric sensation[20]. It is also associated with visceral impulse and pain management[21]. Its low-frequency amplitude value is positively correlated to the duration of FD[12]. Compared with acupuncture, the immediate central action of moxibustion can be explained by inhibiting the left cerebral hemisphere, specifically the cerebellum and caudate nucleus. It interferes with the brain process of gastric pain and satiation and thus alleviates FD symptoms. Just like the working state during acupuncture that deactivates the right brain area, the resting state after acupuncture deactivates the right postcentral gyrus and right supramarginal gyrus. As the sensory center, the right postcentral gyrus can directly regulate gastric sensation. Compared with the resting state after moxibustion, acupuncture alleviates FD symptoms by inhibiting the sensory center to interfere with the process of gastric pain and satiation. Just like the working state during moxibustion that mainly inhibits the left cerebral hemisphere, the resting state after moxibustion mainly inhibits the left precuneus, the orbital part of the left inferior frontal gyrus and right cerebellar peduncle. The orbitofrontal cortex of the left inferior frontal gyrus is associated with homeostasis including the visceral reaction, food intake, and visceral pain[22]. The prefrontal lobe is closely associated with higher mental functions such as emotion and cognition[23]. The prefrontal lobe collects and processes the information on emotions and external factors. The left precuneus is responsible for matching these information with internal organs[13]. The prefrontal lobe is directly involved in the perception and pain processing. The right cerebellar peduncle is the relay station between the cerebellum and middle brain/medulla oblongata. Since these are the key areas related to visceral sensation and motor regulation, the resting state after moxibustion can inhibit the above-mentioned areas and reduce the effect of psychological factors on FD. By inhibiting the cerebellar peduncle, moxibustion helps to decrease information exchange between the cerebellum and middle brain/medulla oblongata, reduce the input and output of gastric pain/discomfort and thus alleviate FD symptoms.

The comparison between resting states during and after acupuncture and moxibustion has suggested that the deactivated brain areas are mostly in the right cerebral hemisphere and activated brain areas in the left cerebral hemisphere. Furthermore, the working states produced a more significant difference in activation intensity and area than the resting state. Acupuncture mainly works on brain areas that are associated with psychological and environmental factors in FD patients. The post-acupuncture effect mainly manifests in brain areas that affect gastric motility and pain. Moxibustion mainly works on brain areas that are related to gastric pain and satiation. The post-moxibustion effect mainly manifests in functional brain activities that are associated with mental or psychological factors.

Conflict of Interest

The authors declared that there was no potential conflict of interest in this article.

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Statement of Informed Consent

Informed consent was obtained from all individual participants included in this study.

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