



A study of the brain functional network of Deqi via acupuncturing stimulation at BL40 by rs-fMRI

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ARTICLE INFO

Article history:

Received 26 December 2014

Received in revised form

25 December 2015

Accepted 8 January 2016

Available online 14 January 2016

Keywords:

Acupuncture

Deqi

PCC

Default mode network

Pain matrix

fMRI

ABSTRACT

Objective: Acupuncture is a therapeutic treatment defined as the insertion of needles into the body at specific points (i.e., acupoints). The acupuncture sensation of Deqi is an important component of acupuncture, but the functional brain responses of Deqi have not been entirely supported by the results of functional magnetic resonance imaging (fMRI) studies. The aims of this study were to test the conditions that would generate a Deqi sensation and to investigate the effect of Deqi and the response of acupuncture at different depths and intensities on brain fMRI blood oxygen level-dependent (BOLD) signals.

Design/setting: Healthy subjects ($n=16$) completed two resting-state fMRI (rs-fMRI) scans, once during shallow needling (2 mm) and once during deep needling (10–20 mm) pseudorandomly, at the acupoint BL40.

Results: When undergoing shallow needling, 16 subjects had a mild stabbing pain sensation, and no one had a composite Deqi sensation; when undergoing deep needling, 14 subjects had a composite Deqi sensation, and only 2 subjects had a sharp pain feeling. Composite deep needling of Deqi sensation modulated neural activity at multiple levels of the brain and cerebellum, decreased functional connectivity in the default mode networks (DMN) and the pain matrix networks, and increased connectivity in the right posterior cerebellar lobe, left parahippocampal gyrus, thalamus, and supplementary motor area ($P<0.05$, false discovery rate [FDR] <0.05). When subjects underwent shallow needling, the brain network increased functional connectivity in the right side (precentral gyrus, superior frontal gyrus, cerebellar tonsil) and both side thalamus; moreover, the right side of the medial prefrontal cortex had a decreased functional connection ($P<0.05$, FDR <0.05).

Conclusions: The hemodynamic response of deep needling of Deqi sensation hypothesis whereby deep needling could affect a variety of deep tissues and never fibers was supported as acupuncture modulates the limbic-paralimbic-neocortical network to produce its Deqi effects. The similarity of LPNN and DMN suggests that deep needling may mobilize an important intrinsic brain network for its multiple modulation effects.

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1. Introduction

Acupuncture is a form of alternative medicine that has been commonly used to relieve symptoms in the Chinese medical system for more than 2000 years.¹ The acupuncture stimulation of Deqi is considered by most acupuncturists to be an important part of acupuncture that includes aching, pressure, soreness, fullness, distension, numbness, tingling, local warm or cool sensations,

and pain.^{2–4} A body of clinical and experimental evidence indicates that most acupuncture effects are mediated by the release of neurotransmitters, such as opioids, or mediated by the adenosine A1 receptor.^{5,6} However, the effects of Deqi in the brain network remain unclear.

Advances in noninvasive brain imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have facilitated the direct study of the human brain and have been widely used in the study of sensory, cognitive, and acupuncture treatments.^{7–9} In addition, fMRI has been increasingly used to assess the dynamic response patterns of the brain to acupuncture stimuli.^{10–12}

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Using fMRI is a new way to study the acupuncture stimulation to quantify brain network changes.^{13,14} Reports from resting-state fMRI (rs-fMRI) have shown a unique effect achieved by acupuncture stimulation. Research on Zusanli and Hegu acupoints has shown negative activity in the limbic system and attention network,^{2,15,16} but the impact of acupuncture stimulation of Deqi on the default mode network (DMN) and pain matrix remains unclear.

The posterior cingulate (PCC) is the hub of the DMN and pain matrix and comes into close contact with the cerebral cortex, making it an important area for examination of the brain network.¹⁷ In this study, acupuncture was performed at BL40 (Weizhong). In traditional Chinese medicine, BL40 (Weizhong acupoint) is considered to be one of the four most important acupoints, and it is proven to have unique efficacy in the treatment of low back pain and other diseases.¹⁸

Our aim in the present investigation was to compare the impact of needling with and without composite Deqi sensations by grouping fMRI datasets into those in which participants experienced composite Deqi sensations and those with only pain sensations with needling manipulation at BL40 (Weizhong). Since Deqi is culturally defined, rather than scientifically defined,¹⁹ as a term for subjective sensations, we focused more on shallow needling and deep needling and their respective fMRI responses while including the Deqi sensation elements alongside. Most importantly, we explored the effect of Deqi and the response to acupuncture at different depths and intensities by observing brain region changes.

2. Subjects and methods

2.1. Subjects

This study included 16 healthy subjects recruited by advertising in Zhujiang Hospital. The subjects had a similar residence (southern region, Guangzhou, Guangdong Province, China), age (21–30 years old, average 24.6 ± 2.3 years), education (15–20 years, average 16.8 ± 1.8 years), and gender (8 men and 8 women). All subjects were right-handed. Inclusion criteria included: (1) some knowledge of acupuncture due to cultural exposure; (2) never received acupuncture treatment; (3) body mass index range for standard $\pm 10\%$; (4) no psychiatric illnesses or medical illnesses (i.e., multiple sclerosis, epilepsy); (5) no pain (including dysmenorrhea) or drug (i.e., anti-pyretics, sleeping pills) experience within the last month; and (6) self-rating anxiety scale and self-rating depression scale scores < 50 (lower than 50 represents “normal”). The general exclusion criteria were organic brain disease, a history of skull or brain damage, substance dependency, severe neurological illnesses, metallic components in the body, claustrophobia, and analgesic medication (during the last four weeks). All experiments and protocols were approved by the Ethics Committee of Zhujiang Hospital affiliated to Southern Medical University, China.²⁰ According to the dictates of the State Council of China, each subject provided written informed consent after receiving detailed instructions on the experimental procedures and after the precautions were fully explained.

BL40 is anatomically located at the midpoint of the transverse crease of the popliteal fossa, and therefore each subject's knee was leaned on a mattress to keep the lower limbs in a valgus position for therapeutic stimuli (Fig. 1).

2.2. Methods

Sixteen healthy subjects (8 men and 8 women; aged 24.6 ± 2.3 years) were included in the study. The experiment was performed in the Department of Radiology of Zhujiang Hospital, Southern Medical University, China, from July 2013 to March 2014.

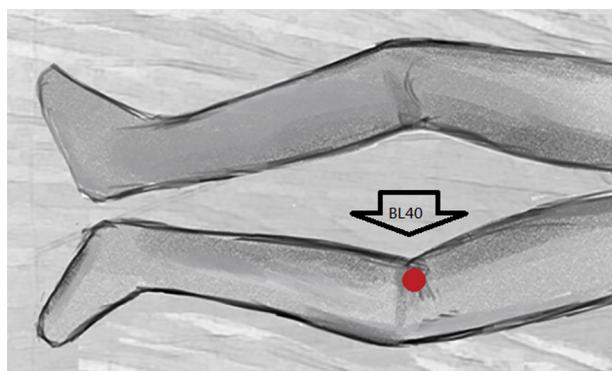


Fig. 1. The location of BL40 and the posture of the subjects when needling at the point.

Anatomical scans of the brain were collected prior to stimulation imaging. Initially, the subjects were subjected to a baseline rs-fMRI scan for 5 min. Then, two rs-fMRI scans (each for 5 min) were performed on the brain of every subject, one for shallow needling and one for deep needling pseudorandomly. In order to maximize washout of the sustained effects induced by the former therapeutic stimulation, the time interval between the two scans was 10 min (Fig. 2). At the end of the fMRI scan, the subjects were questioned regarding the sensations they experienced during stimulation and whether they were anxious or relaxed during the procedure. They could not see their lower extremities from their supine position in the enclosed scanner. Shallow needling and deep needling were performed with sterile disposable graduated pure silver needles at left BL40 (Weizhong point). Manual acupuncture needling was performed at the acupuncture point left BL40 (Weizhong) by an experienced acupuncturist. We used sterile, disposable, graduated, and non-magnetic pure silver needles (25 mm long and 0.40 mm diameter) manufactured by Beijing Zhongyan Taihe Medicine Co., Ltd., Beijing, China. The insertion depth of the shallow needle into the skin was 2 mm; According to fat thickness, the insertion depth of the deep needling was 10–20 mm, as commonly used in China. This approximates a technique used in clinical practice.²¹ (Fig. 1). To obtain a subjective acupuncture sensation, namely Deqi sensation, the needle was rotated backward and forward with even motion at a rate of 60/min (1 Hz) with an amplitude around 180°. This approximates a technique used in traditional Chinese medicine.

Considering that stimulation may cause subjective bias towards the scan, all subjects were asked to keep their eyes and ears closed in order to prevent them from discriminating the therapeutic stimulation. Moreover, all subjects were purposely misguided that they would receive two different forms of needling.

2.3. Data collection and analysis

2.3.1. Psychophysical data collection and analysis

At the end of the scan, subjects were asked questions from the Park questionnaire about the needle sensations they experienced of the two types of needling.²² Participants rated the intensity of each sensation on an ordinal scale: “none” (0), “slight” (1), “moderate” (2), or “strong” (3).²³ For each fMRI dataset and for each sensation, we multiplied the participants’ sensation score (0–3) by the expert weighting (0–8) for the seven Deqi sensations (aching, dull, heavy, numb, radiating, spreading, and tingling) and nine pain sensations (burning, hot, hurting, pinching, prickling, sharp, shocking, stinging, and tender).²⁴ The data from those subjects who had experienced “Deqi” were from the experimental group, and those from who had not experienced “Deqi” were from the control group for analyses. SPSS 18.0 software (SPSS, Chicago, IL, USA) was used to calculate descriptive statistics (mean \pm SD) for Deqi score, pain

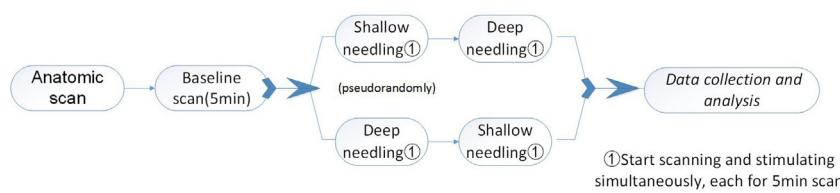


Fig. 2. The experimental paradigm for the subjects.

score, and other data. The score of Deqi sensation or pain sensation was compared by the one-sample *T*-test ($p < 0.05$), and for other data differences between deep needling and shallow needling, we used the two-sample *T*-test ($p < 0.05$).

2.3.2. Imaging

Brain imaging was conducted on a 3.0 T Philips Achieva MRI System (Royal Philips Electronics, Eindhoven, Netherlands) with an eight-channel head array coil equipped for echo planar imaging. Imaging encompassed the entire brain, including the cerebellum and brainstem. The resting-state functional data were acquired by a T2*-weighted gradient echo sequence (repetition time/echo time = 2000/40 ms, flip angle = 90°, 3.4 × 3.4 mm in-plane resolution, 150 time points, for a total of 300 s). Structural images were collected prior to functional imaging by means of a T1-weighted fast spin echo sequence (repetition time/echo time = 500/14 ms, flip angle = 90°, 0.859 × 0.859 mm in-plane resolution, slice thickness = 1 mm).

2.3.3. fMRI data analysis

2.3.3.1. Preprocessing of experimental functional MRI data. fMRI datasets were classified, on the basis of the psychophysical subjects' reports of needling scores, into those that were associated with Deqi sensations and those with only pain sensations in shallow needling. The fMRI image data were preprocessed and analyzed using the Data Processing Assistant for Resting-State fMRI (DPARSF, <http://www.restfmri.net>) by routines in MATLAB R2010a. The blood oxygen level-dependent (BOLD) time series preprocessing steps included removal of the first 10 volumes, slice-time correction, motion correction, intensity normalization, spatial smoothing, and linear high-pass temporal filtering. The first 10 volumes of each scan were discarded to eliminate any non-equilibrium effects of magnetization and to allow subjects to become familiar with the scanning environment. The motion time courses were used to select subjects' head movements of < 2 mm in translation and 2° in rotation, which were used for further analysis (no subjects were excluded). Each individual's functional images were normalized using the symmetric echo-planar imaging templates and resampled at a resolution of 3 mm × 3 mm × 3 mm. The normalized functional images were smoothed spatially using a Gaussian kernel of full-width half-maximum 6 mm. Finally, voxel-wise linear trend removal and temporal high-pass filtering (0.01 Hz < f < 0.08 Hz) were applied.

2.3.3.2. Seed regions of interest for functional connectivity analysis. Data selection of PCC for the region of interest (ROI) ($6 \times 6 \times 6 \text{ mm}^3$) was based on the results of a previous MRI study.²⁵ Montreal Neurological Institute (MNI) brain region coordinates were selected as the central voxel ROI ($x = -7, y = 54, z = 32$). A function (functional connection) of DPARSF software was used. The individual time course of activity from the ROIs relative to the standard echo-planar imaging template for PCC was extracted, and six motion correction parameters and their global gray matter, white matter, and cerebrospinal fluid were removed. By analyzing Pearson correlation coefficients of the seed point and whole-brain voxel time series and using the Fisher's Z-transformation of correlation coefficients into z

values for standardization, brain functionality images for each subject were ultimately obtained. Random-effects analysis was used to create intragroup statistical parametric mapping (SPM8, <http://www.fil.ion.ucl.ac.uk>) for the ROIs and to explore the brain network change in different needling feeling. After correction for multiple comparisons using the false discovery rate (FDR) < 0.05 and applying a minimum cluster size of 10 contiguous voxels, regions that were positively correlated with the seed ROI were identified at the cluster level ($P < 0.05$). The intrinsic brain connectivity differences 1 between the condition of Deqi sensation and baseline; 2 between the condition of pain sensation and baseline were calculated by two-tailed paired *t*-tests ($P < 0.05$), corrected for multiple comparisons (FDR) < 0.05 . The resulting images were shown by a rest (<http://restfmri.net/forum/rest>) and Brainnet viewer (<http://www.nitrc.org/projects/bnv>).

3. Results

3.1. Psychophysical responses

When undergoing shallow needling, 16 subjects had a mild stabbing pain feeling, no one had a composite Deqi feeling; when undergoing deep needling, 14 subjects had a composite Deqi feeling, and 2 subjects only had a sharp pain feeling, so there were 14 subjects with deep needling in the experimental group, and 16 subjects with shallow needling in the control group. The score of Deqi sensation is 4.8 ± 1.1 , and the score of pain sensation is 2.3 ± 0.9 . There were no significant differences in the intensity of subjects' anxiety evoked by shallow needling and deep needling ($p > 0.05$).

3.2. Hemodynamic responses

In the experimental group, compared with the baseline, the result showed decreased functional connections in the DMN, including the cingulate cortex, prefrontal cortex, temporal lobe, anterior angular gyrus, and hippocampus, and in pain matrix, including the second somatosensory area (S2), insula (IC), cingulate gyrus, temporal lobe, frontal lobe, globus pallidus, putamen, caudate nucleus, and left cerebellar lobe. The increased functional connection areas were limited and included the right cerebellar tonsil, left brain parahippocampal gyrus (PHpc), thalamus, and supplementary motor area (SMA). Most changes appeared on both sides, with the decreased functional connection appearing most often on the right and the increased functional connection appearing most often on the left ($P < 0.05$, FDR < 0.05 , Table 1, Fig. 3).

In control group, compared with the baseline, the result showed that some brain areas, including right side (precentral gyrus, superior frontal gyrus, cerebellar tonsil) and both side thalamus had an increased functional connection, right side medial prefrontal cortex had an decreased functional connection ($P < 0.05$, FDR < 0.05 , Table 2, Fig. 4).

4. Discussion

In this study, we found that only deep needling could cause a Deqi sensation, and it produced a widely decreased functional con-

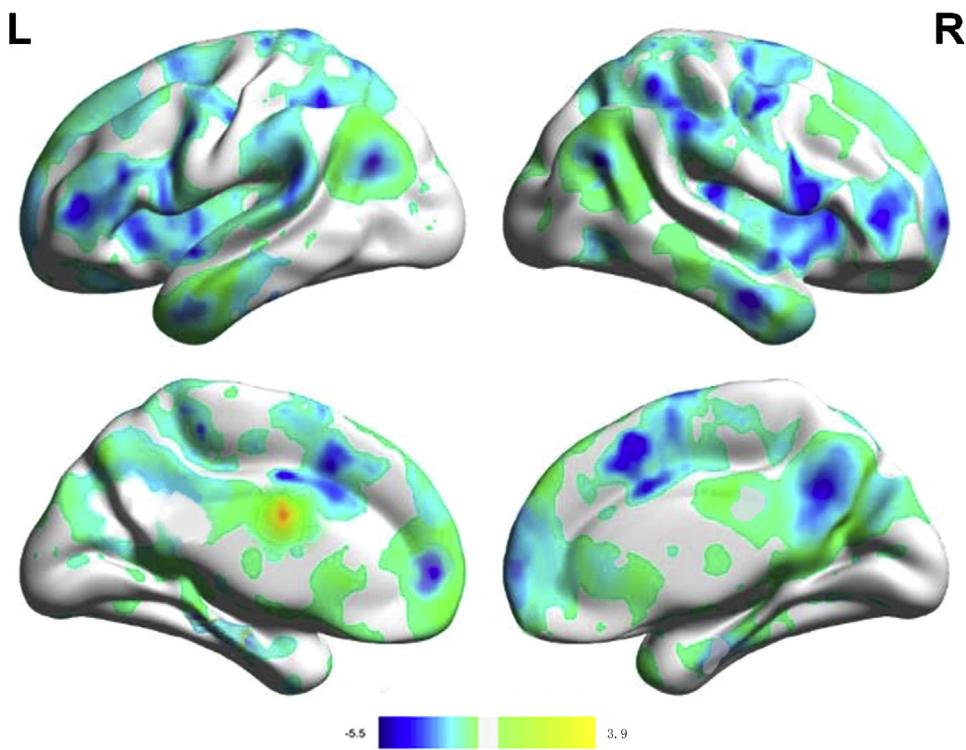


Fig. 3. The brain functional connection increased and decreased surface view in cortical and subcortical brain structures in the experimental group ($P < 0.05$, FDR < 0.05).

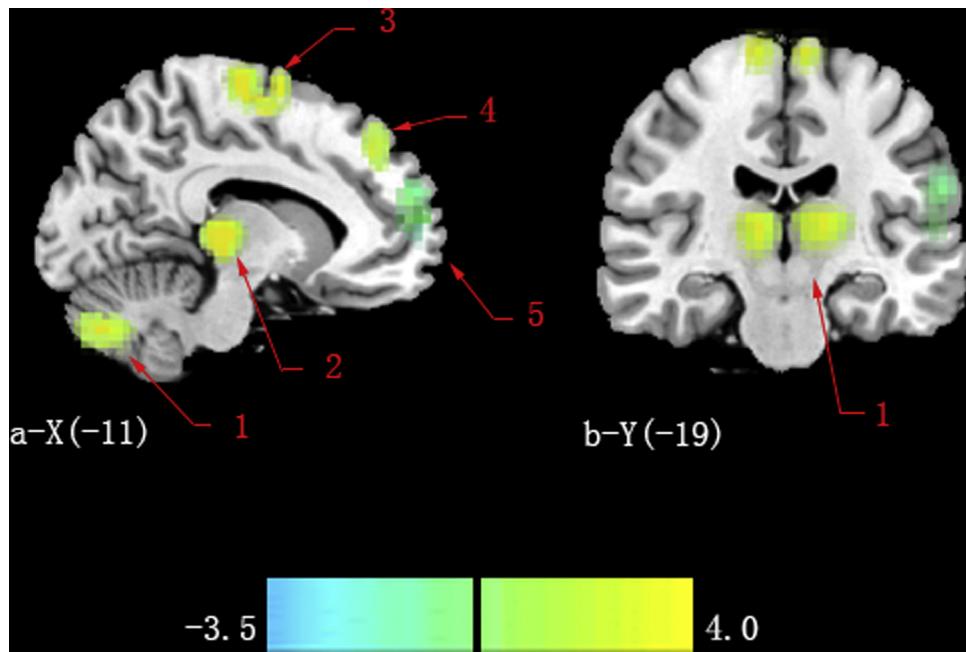


Fig. 4. The brain functional connection increased and decreased in cortical and subcortical brain structures in control group ($P < 0.05$, FDR < 0.05). P. a: (1) cerebellar tonsil, (2) Thalamus, (3) precentral gyrus, (4) superior frontal gyrus, (5) medial prefrontal cortex; P. b: (1) Thalamus.

nection in the brain network, revealing an effect of Deqi. At the same time, because most subjects with deep needling could obtain a Deqi sensation, we can surmise that the Deqi sensation is a part of the effect of deep needling based on experiments and culture. However, it would be more scientific to discuss from the deep needling perspective.

Some previous studies have showed that the acupoint is a three-dimensional structure which is based on connective tissue and contains many nerve endings, blood vessels and cells. When deep

issues have a deep needling stimulation, the connective tissue is closely intertwined with the needle, then transfers the stimulation to other cells, such as plasma cells and fibroblasts.^{26,27} Compared with the shallow needling, the complex Deqi sensation and the score of Deqi sensation during deep needling showed that it had a stronger and broader impact than shallow needling. With winding, deep needling could influence more deep tissues and nerver endings, to get a complex Deqi sensation.

Table 1

The brain functional connection changed in the experimental group ($P \leq 0.05$, FDR ≤ 0.05).

	BA	X	Y	Z	Peak Z-score	Cluster Size
R-IC	13	46	-19	19	-4.75	401
L-IC	13	-41	-15	18	-4.66	317
R-S2		59	-24	20	-4.81	128
L-ACC		32	-7	-30	-3.01	42
R-inferior frontal gyrus	45	48	42	3	-5.01	139
R-inferior frontal gyrus	45	36	33	-18	-4.54	54
R-superior frontal gyrus	6	20	20	58	-4.65	66
L-superior frontal gyrus	6	-19	6	45	-4.54	37
L-Angular gyrus	39	-47	-75	36	-5.38	156
L-posterior cerbellar lobe		-33	-33	-36	-3.89	23
L-Orbital gyrus		-12	51	45	-4.67	305
L-thalamus	19	3	-57	22	3.17	57
R-middle temporal gyrus	39	66	12	-9	-3.89	33
L-middle temporal gyrus	39	-27	-30	-6	-4.11	58
R-superior temporal gyrus	39	57	-63	18	-4.65	207
R-inferior parietal lobule	40	54	-69	27	-4.57	213
R-FP	10	-7	-33	10	-4.12	87
L-PHpc		-21	-36	-12	2.97	45
R-MPFC		-2	47	-4	-4.02	99
Lenticular nucleus		47	3	24	-4.36	107
R-Hpc		-22	12	-20	-4.41	127
R-caudate	20	0	21	0	-4.13	99
R-globus pallidus	45	42	42	-6	-4.54	119
L-FP	10	6	-50	5	-3.99	66
R-thalamus	19	-6	-27	-3	3.65	26
Brain stem		-9	-33	-39	-3.97	34
R-cerebellar tonsil		9	-48	-51	3.11	98
L-SMA	6	10	20	55	3.78	33

Abbreviations: FDR, false discovery rate; MNI, Montreal Neurological Institute. The negative values of Peak (−) represent the decrease functional connection, and the positive values of Peak (+) represent the increase functional connection. FP: Frontal pole; IC: insular; S2: second somatosensory area; ACC: anterior cingulate cortex; FP: frontal pole; PHpc: parahippocampal gyrus; MPFC: medial prefrontal frontal cortex; Hpc: hippocampus; SMA: supplementary motor area.

Some studies have reported that sensations of numbness, pressure, aching, and fullness are conducted by myelinated nerve fiber types II and III (A β , A γ , A δ), with a faster conducting rate, whereas temperature, soreness, and pain are conducted by slower-conducting type III A δ or type IV (C) fibers.^{28,29} In our study, the results showed that only during deep needling could the subjects report a clear feeling of Deqi at the acupoint. This verified the previous conclusion that the deep needling sensation could generate a greater stimulation of the deep sensory nerve fibers, which produce more types of feelings and produce a positive BOLD response in the brain network through fiber types II and III.

Furthermore, our results showed some features of deep needling based on the fMRI response. In the sensory conduction path, S1 received sensory information from muscle spindle and baroreceptor, then transferred the sensory information to S2 and the insular.^{30–32} The result showed a decreased functional connection of this conduction path, which suggested the deep needling could affect that sensory conduction of deep tissues, and create an extensive stimulation for deep tissues. In addition, compared

with shallow needling, the sensory network (such as S2, thalamus, and PHp) had a widely functional connection which changed during deep needling, also supporting the conclusion that deep needling had a stronger and broader impact than shallow needling. The widely decreased functional connection of brain network also showed a feature of Deqi sensation.

4.1. Hemodynamic responses

During deep needling, functional connection increased in the cortical sensorimotor network, including the S1, SMA, thalamus, and PHp, similar to a previous study on body touch and fMRI studies on acupoints.¹⁵ The thalamus is the most important sensory integration center,^{33,34} and it is highly correlated with pain.^{35,36} Because deep needling is a form of stimulation, it will generate mild pain stimulation in the body which increases the functional connection in the thalamus. In addition, compared with shallow needling, some functional connections of the brain areas increased, such as SMA and PHpc, revealing a unique phenomenon for deep needling,³⁷ providing foundation for the differences in deep needling of Deqi sensation and shallow needling for future fMRI research.

4.2. Functional connection of PCC

The PCC is commonly identified as a critical node in the DMN and pain matrix. fMRI and PET studies of humans have demonstrated that the DMN is involved with the PCC, linking regions of the bilateral MPFC, hippocampus, posterior thalamus, inferior parietal cortex (IPC) and precuneus.^{38,39} The results showed that, during deep needling, PCC had a widely decreased functional connection with most brain areas of the DMN and pain matrix, and the results suggest that, the reduced function of PCC in the DMN and pain matrix would indirectly cause the function of DMN and pain matrix to decrease. A number of studies have suggested that the PCC plays an essential role in spatial orientation, self-appraisal and internal monitoring as well as memory processing^{38–41}. With deep needling, the decreased functional connection of PCC would reduce the internal control and the speed of memory processing, revealing an effect of deep needling on the brain network.

4.3. Functional connection of the DMN

The experimental results of deep needling showed a decreased functional connection in the DMN, similar to the results of a previous study.⁴² The DMN has two apparently opposite functions: a spontaneous cognition function and the function of monitoring the environment (sentinel hypothesis).^{43,44} These results suggest that the deep needling achieved by acupuncture widely inhibited the functional activities of the DMN, weakening both the spontaneous cognition function and the function of monitoring the environment. In addition, it reduced self-evaluation and alerts for environmental awareness, eventually leading to reduced episodic memory and alertness, all of which would play an important role in the effect of deep needling. Meanwhile, the deep needling of Deqi sensation showed a much lower functional connection in the DMN, which was a special phenomenon of the brain network with acupuncture and provides a starting point for future research on deep needling.

4.4. Functional connection of the pain matrix

The brain areas with activity in the pain networks have been defined as the pain matrix.^{45,46} Some areas of the pain matrix play an important role in the generation and transmission of feeling. For instance, the insular cortex and anterior cingulate are involved in the emotional component.³⁷ With deep needling, the

Table 2

The brain functional connection changed in the control group ($P \leq 0.05$, FDR ≤ 0.05).

	BA	X	Y	Z	Peak Z-score	Cluster size
R-precentral gyrus	44	45	5	10	3.75	81
R-superior frontal gyrus	8	3	33	50	3.25	45
R-cerebellar tonsil		-32	-60	-44	3.71	52
R-Thalamus		23	-19	17	3.63	77
L-Thalamus		-10	-23	8	3.48	34
R-medial prefrontal cortex	8	21	27	55	-3.43	32

Abbreviations: FDR, false discovery rate; MNI, Montreal Neurological Institute. The negative values of Peak (−) represent the decrease functional connection, and the positive values of Peak (+) represent the increase functional connection.

decreased functional connection has widespread inhibition for the pain matrix, reducing the functional connection with each brain area and slowing the transmission of sensations through the network, showing an effect of Deqi. The intensity and scope of the insular activation significantly increased in the pain condition,⁴⁷ indicating its important role in the identification of feeling,⁴⁸ and its extensive connections with the limbic system, including the cingulate gyrus and hippocampus.^{49,50} The decreased functional connection during deep needling reduces the ability of the insular to identify feeling and reduces connections with the limbic system, slowing the speed of feeling transmission.

Although the subjects in this study were not pain patients, needle stimulation could produce mild pain,¹⁸ coupled with the BL40 point. Thus, the deep needling caused changes not only in the functional connection in the DMN, but also in the pain matrix.

4.5. Related brain function network

In a previous experiment, the negative activity of limbic-paralimbic-neocortical network (LPNN) was the notable feature of deep needling.¹⁵ The DMN has a high degree of overlap with LPNN in the brain networks impacted by deep needling.^{42,51} Our research has shown that the DMN overlapped with LPNN in the brain function, with a widely decreased functional connection. On the one hand, we hypothesize that the DMN may be the core of the brain function network for acupuncture regulating LPNN. On the other hand, the decreased functional connection between LPNN and the pain matrix, reduced transmission of feeling between the two networks, and regulation between the pain matrix and LPNN will play an important role in the effect of deep needling on the brain network. Therefore, we hypothesized that the DMN and pain matrix work with LPNN to adjust the brain network, which may explain why the brain function network changed with the Deqi sensation during deep needling.

5. Conclusion

The hemodynamic response of deep needling of Deqi sensation hypothesis whereby deep needling could affect a variety of deep tissues and never fibers was supported as acupuncture modulates the limbic-paralimbic-neocortical network to produce its Deqi effects. The similarity of LPNN and DMN suggests that deep needling may mobilize an important intrinsic brain network for its multiple modulation effects.

Conflict of interest

The authors have no conflict of interest.

Experimental site

All MRI scanning was conducted at the MRI Clinical Imaging Department at Zhujiang Hospital (Guangzhou, China).

Funding

This work was supported by National Natural Science Foundation of China (NNSFC), China; Contract grant number: 81473769, Natural Science Foundation of Guangdong Province, China; Contract grant number: 2014A030313335.

Acknowledgments

We thank Yang JM from the Department of Neurology, Zhujiang Hospital, Southern Medical University in China for assistance. We thank all subjects for the assistance in the scanning.

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