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RESEARCH ARTICLE

Acupuncture for ischemic stroke: cerebellar activation may be a central mechanism following *Deqi*

Miao-keng Li[1, #], Yu-jie Li[2, #], Gui-feng Zhang[3], Jun-qi Chen[4, *], Ji-ping Zhang[1], Ji Qi[1], Yong Huang[1, *], Xin-sheng Lai[5], Chun-zhi Tang[5]

1 School of Chinese Medicine, Southern Medical University, Guangzhou, Guangdong Province, China
2 First Clinical Medical School, Southern Medical University, Guangzhou, Guangdong Province, China
3 Zhaoqing Medical College, Zhaoqing, Guangdong Province, China
4 Department of Rehabilitation Medicine, the Third Affiliated Hospital of Southern Medical University, Guangzhou, Guangdong Province, China
5 College of Acupuncture and Massage, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong Province, China

***Correspondence to:**
Yong Huang, M.D. or Jun-qi Chen, M.D., nfhy@fimmu.com or meixibao@126.com.

 # These authors contributed equally to this work.

orcid:
0000-0002-6425-0733 (Yong Huang)
0000-0001-6847-0891 (Jun-qi Chen)

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Abstract

The needling sensation of *Deqi* during acupuncture is a key factor of influencing acupuncture outcome. Recent studies have mainly focused on the brain function effects of *Deqi* in a physiological state. Functional magnetic resonance imaging (fMRI) on the effects of acupuncture at *Waiguan* (SJ5) in pathological and physiological states is controversial. In this study, 12 patients with ischemic stroke received acupuncture at *Waiguan* (SJ5) and simultaneously underwent fMRI scanning of the brain, with imaging data of the activated areas obtained. Based on the patient's sensation, imaging data were allocated to either the *Deqi* group or non-*Deqi* group. In the *Deqi* group, the activated/deactivated areas were the left superior temporal gyrus (BA39)/right anterior lobe of the cerebellum and left thalamus. In the non-*Deqi* group, the activated areas included the medial frontal gyrus of the right frontal lobe (BA11), right limbic lobe (BA30, 35), and left frontal lobe (BA47), while the only deactivated area was the right parietal lobe (BA40). Compared with the non-*Deqi* group, the *Deqi* group exhibited marked activation of the right anterior lobe of the cerebellum and right limbic lobe (BA30). These findings confirm that the clinical effect of *Deqi* during acupuncture is based on brain functional changes. Cerebellar activation may be one of the central mechanisms of acupuncture in the treatment of ischemic stroke.

Key Words: *nerve regeneration; traditional Chinese medicine; acupuncture; functional magnetic resonance imaging; ischemic stroke; Brodmann area; Waiguan (SJ5) acupoint; Deqi; non-Deqi; 973 Program; neural regeneration*

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Introduction

The needling sensation of *Deqi* refers to the feeling experienced by both the practitioner (*i.e.*, a hollow sensation immediately after insertion of the needle, and a tight and heavy feeling during twirling and vertical lifting/thrusting of the needle) and patient (*e.g.*, soreness, numbness, distention, and heaviness) during acupuncture (Lu, 2007). Twinge does not belong to the category of *Deqi* (Kong et al., 2007). The feeling of *Deqi* is mainly distention, numbness, conduction, and soreness, while the combined feeling of *Deqi* is severe pain and numbness, aching and numbness, and heavy soreness (Guo et al., 2014).

Meridian-brain theory is a hot topic in the study of mechanisms underlying acupuncture. Many researchers have investigated aspects of meridian acupuncture by imaging cerebral function. However, most studies have only examined the feeling experienced by the practitioner during acupuncture, and neglected that experienced by the patient, which may affect the test results. The effect of a patient's feeling on activated areas has been verified in many studies. In normal individuals, acupuncture at *Zusanli* (ST36) activates more brain areas with the feeling of *Deqi* than without the feeling of *Deqi* (Zhang, 2011b). Furthermore, acupuncture of normal individuals at the right *Waiguan* (SJ5) predominantly activated the left temporal lobe and superior temporal gyrus in the *Deqi* group (Zhang, 2011a).

Certain brain areas are deactivated with the feeling of *Deqi* during acupuncture. Hui et al. (2009) found that the limbic-paralimbic-neocortical network (including the medial prefrontal, medial parietal, and medial temporal lobes) is deactivated after *Deqi* during acupuncture at *Hegu* (LI4), *Zusanli*, and *Taichong* (LR3) in healthy volunteers. Similarly, Fang et al. (2012) found that the limbic system is deactivated after *Deqi* during acupuncture at the right *Taichong*, which is consistent with previous studies (Bai et al., 2009; Liu et al., 2011). Nevertheless, whether correlation between *Deqi* and

deactivation of the limbic system can explain the mechanisms underlying acupuncture remains poorly understood (Asghar et al., 2010). The above studies recruited normal subjects, and whether the results are relevant to patients undergoing different pathological conditions deserves further investigation.

Acupuncture is an effective approach to treat stroke sequelae (Qi et al., 2014). Numerous studies have confirmed that acupuncture can promote recovery of neurological function in stroke patients (Long and Wu, 2012; Zhao et al., 2012; Cheng and Chen, 2014). Thus, ischemic stroke patients are commonly used to compare acupuncture effects under physiological and pathological states. Chen et al. (2003) used imaging to compare cerebral function following acupuncture at the right *Waiguan* in patients with left hemispheric ischemic stroke and normal subjects. They found that in normal subjects, activation of brain areas was associated with insomnia and other functions, while in patients, activation of brain areas was associated with sensory, visual, and motor functions. These studies suggest that meridian acupuncture has different effects on functional magnetic resonance imaging (fMRI) under pathological and physiological states.

There is a lack of imaging studies on cerebral function after *Deqi* during acupuncture for a pathological state. Here, to primarily investigate the central mechanism of *Deqi* during acupuncture in the treatment of ischemic stroke, we used fMRI to compare cerebral areas in the absence and presence of *Deqi* in a pathological state.

Subjects and Methods

Subjects

A total of 12 patients with ischemic stroke from the First Affiliated Hospital of Guangzhou University of Chinese Medicine in China were enrolled in this study, including 10 males and 2 females, aged 47–65 years old. They had a disease course of 1–12 months.

Inclusion criteria

Ischemic stroke patients (1) were in accordance with the diagnostic criteria of the Cardiovascular Health Study (Price et al., 1993); (2) had foci mainly in the left basal ganglia, right hemiataxia (upper extremity strength and/or lower extremity strength, China Stroke Scale score ≥ 4), and sensory disturbance; (3) managed the acute phase in a stable condition; (4) had a regular diet, without smoking, alcohol, tea or coffee, and a normal sleep and body structure; (5) accepted basic western medicine treatments, and their treatment protocols were not altered at 1 month before the experiment; (6) aged 40–65 years old; (7) were right handed.

Exclusion criteria

Patients (1) had a disease course > 1 year; (2) received acupuncture within 1 month before the test; (3) had severe heart, liver, or kidney disease, or a tumor; (4) had severe aphasia or a history of dementia and claustrophobia, which may impact upon communication and operation during the experiment; (5) were pregnant or breastfeeding women; (6) had metal materials (such as a coronary stent) in the body; (7) had experienced hemophilia.

The protocols were approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine in China (approval No. [2008]024), and registered in the Chinese Clinical Trial Registry (registration No. ChiCTR- NRC-00000255).

Acupuncture treatment

Acupuncture at the right *Waiguan* was performed in ischemic stroke patients. In accordance with the Name and Location of Acupoints (GB/T12346-2006), *Waiguan* is located on the dorsal aspect of the forearm, on the line connecting *Yangchi* (SJ4) and the tip of the elbow, 2 cun above the transverse crease of the wrist (the distance between the transverse line in the flat olecranon elbow and the transverse striation in the palmar wrist was 12 cun) between the ulna and radius. The physician held the needle cannula (Dongbang AcuPrime, Exeter, UK) with his left hand and the right index finger tapped the silver acupuncture needle (0.30 mm × 40 mm; Zhongyan Taihe, Beijing, China). The needle cannula was removed and the needle vertically punctured at 15 ± 2 mm in depth. When the physician had a tight and heavy feeling, he used a uniform reinforcing-reducing method and twirled the needle at an angle of ± 180°, at a frequency of 60 times/min. The acupuncture process was designed using a block method with twirling and non-twirling stimulation alternated in 30-second blocks, and a total stimulation time of 6 minutes (**Figure 1**).

fMRI

Each subject rested on a bed for 5 minutes. fMRI scanning was performed using a 3.0 T MRI scanner (GE, Bethesda, MD, USA) and a standard head coil. Anatomical images were collected using a T1-weighted three-dimensional (3D) gradient echo-pulse fast spin sequence for 2 minutes 42 seconds before acupuncture. The precise parameters were: axial view T1 fluid-attenuated-inversion-recovery scan: repetition time 2, 300 ms; echo time 21 ms; time of inversion 920 ms; slice thickness 6.0 mm; gap 1.0 mm for 20 layers for 2 minutes and 45 seconds; field of view 240 mm × 180 mm; matrix 320 × 256; number of excitations 2; echo train length 9; and band width 50. Acupuncture was performed at the right *Waiguan* for 66 minutes and 30 seconds. Simultaneously, blood oxygenation level-dependent functional images were collected using a single provocation echo-planar imaging sequence with a gradient echo/echo-planar imaging/90 (90° pulse) for 6 minutes 30 seconds as follows: repetition time 3, 000 ms; echo time 20 ms; flip angle 90°; field of view 24 cm × 24 cm; slice thickness 6 mm; gap 1.0 mm; matrix 96 × 96; number of excitations 1; and phase per location 130, 2, 600 phases for 6 minutes 30 seconds. 3D scanning was followed by an axial view 3D T1 fast-spoiled gradient echo/20 T1 450 for 6 minutes and 2 seconds. The detailed parameters were: repetition time 7.6 ms; echo time 3.3 ms, field of view 24 cm × 18 cm; flip angle 20;

Table 1 Comparison of the patients' general data from both groups

Group	Sex (*n*)		Age (year)		Disease course (month)		Chinese Stroke Scale (score)		History of hypertensive disease (*n*)	History of type 2 diabetes mellitus (*n*)
	Male	Female	mean±SD	Min–Max	mean±SD	Min–Max	mean±SD	Min–Max		
Deqi (*n* = 5)	4	1	56.80±5.02	49–62	5.20±3.71	1–10	17.20±4.02	15–27	5	1
Non-*Deqi* (*n* = 5)	5	0	55.40±5.50	47–65	5.40±3.05	1–12	18.15±4.63	16–25	4	1

No significant differences were observed between the two groups ($P > 0.05$).

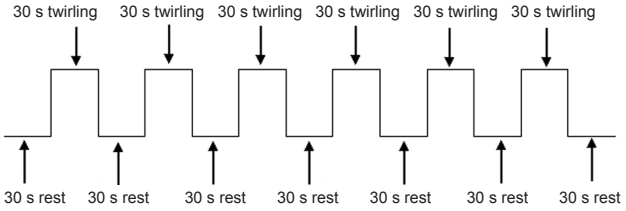

Figure 1 Acupuncture stimulus procedure at *Waiguan* (SJ5).
S: Second.

Table 3 Brain regions activated during acupuncture at *Waiguan* (SJ5) in the non-*Deqi* group

	Brodmann area	*T*	Talairach coordinate (mm)		
			X	*Y*	*Z*
Right limbic lobe parahippocampal gyrus	35	17.9765	21	–9	–24
Left frontal lobe sub-gyral	47	40.5633	–21	18	–12
Right frontal lobe medial frontal gyrus	11	9.1927	12	57	–15
Right limbic lobe posterior cingulate	30	16.1773	18	–60	9
Right parietal lobe supramargina gyrus	40	–8.8515	57	–54	36

With *T* values, a positive number represents activation and negative number represents deactivation. Large absolute *T* values indicate strong activation (*n* = 5 per group).

Table 2 Brain regions activated in the *Deqi* group during acupuncture at *Waiguan* (SJ5)

	Brodmann area	*T* value	Talairach coordinate (mm)		
			X	*Y*	*Z*
Left superior temporal gyrus	39	15.0733	–57	–54	15
Right anterior lobe of cerebellum	–	–11.6987	6	–45	–30
Left thalamus	–	–11.7420	–3	–3	9

With *T* values, a positive number represents activation and negative number represents deactivation. The large absolute T value in the left superior temporal gyrus indicates strong activation (*n* = 5 per group).

Table 4 Difference of activated brain regions in stroke patients in the *Deqi* and non-*Deqi* groups

	Brodmann area	*T* value	Talairach coordinate (mm)		
			X	*Y*	*Z*
Right/limbic lobe posterior cingulate	30	6.3670	15	–63	9
Right cerebellum anterior lobe	–	7.8092	6	–45	–30

With *T* values, a positive number represents activation and negative number represents deactivation. Large absolute *T* values indicate strong activation (*n* = 5 per group).

bandwidth 25; matrix 256 × 256; number of excitations 1; and slice thickness 1.2–0.6 mm, for 248 layers in 6 minutes 2 seconds.

Quantization of acupuncture sensation and experimental groups

An acupuncture sensation scale was designed, which incorporated five types of feeling during acupuncture: soreness, numbness, distention, heaviness, and twinge. Each feeling was analyzed using a Visual Analogue Scale (Kou et al., 2007). A 10 cm horizontal line was drawn on the paper. One end of the horizontal line represented insensitive (0) and the other end unbearable (10). Subjects filled in the self-designed scale immediately after scanning. Subjects experiencing soreness, numbness, distention, and heaviness were included in the *Deqi* group, and those without any feeling were included in the non-*Deqi* group. Subjects that experienced twinge were not included.

Data processing

Data were processed using statistical parametric mapping 8 software (downloaded from http://www.fil.ion.ac.uk/) on the platform of MATLAB 6.5 (MathWorks, Nedik, MA, USA). Slight head movements were corrected. To obtain high-resolution images, anatomical images were registered to functional images using the mean* file. After registration, anatomical images were divided and images normalized to the standard brain template of the Montreal Neurological Institute space (http://www.fil.ion.ac.uk/).

Statistical analysis

Analysis of general data: all the data were analyzed using SPSS 19.0 software (SPSS, Chicago, IL, USA). Measurement data are expressed as the mean ± SD. Numerical data were presented as percentages. Measurement data between groups were compared using two-sample *t*-tests. Numeration data between groups were compared using Fisher's exact test. *P*

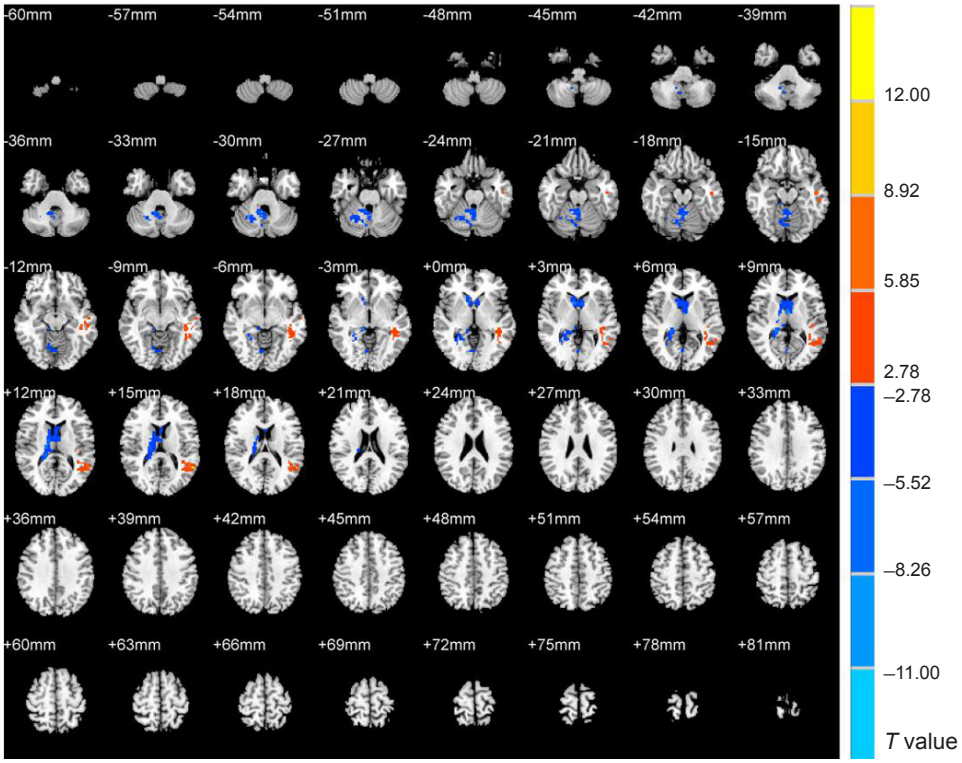

Figure 2 Brain regions activated during acupuncture at *Waiguan* (SJ5) in the *Deqi* group.
The left superior temporal gyrus (BA39) was activated, while the right anterior lobe of the cerebellum and left thalamus were deactivated. Activation: Nervous activity increased above baseline level with increased blood oxygen levels (red). Deactivation: Nervous activity decreased below baseline level with decreased blood oxygen levels (blue).

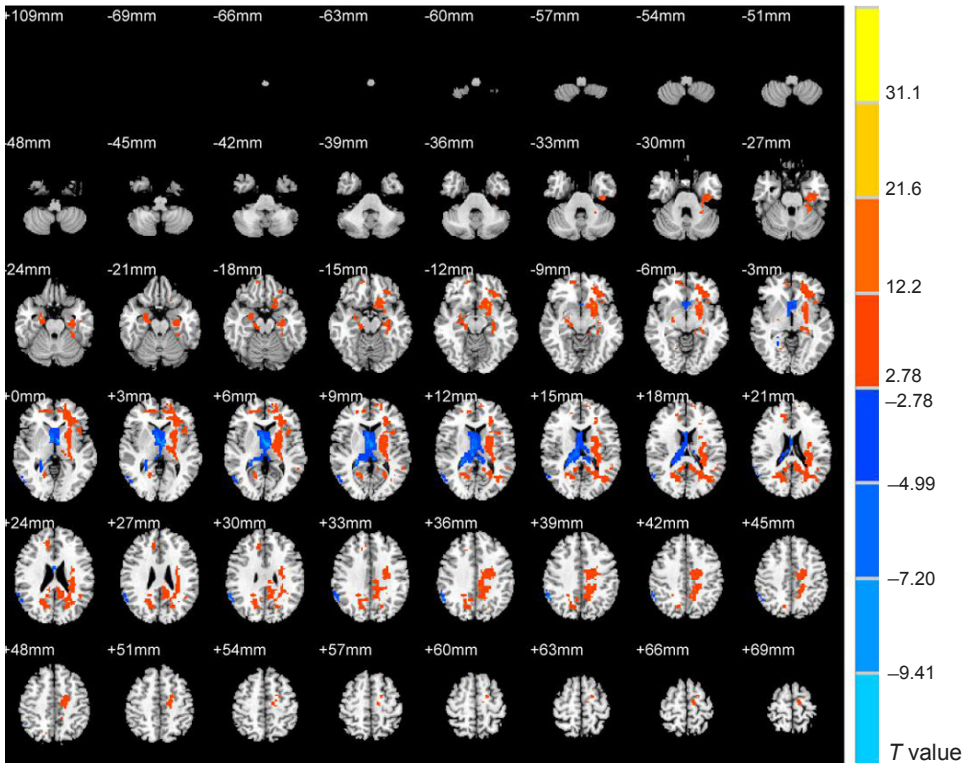

Figure 3 Brain regions activated during acupuncture at *Waiguan* (SJ5) in the non-*Deqi* group.
The right medial gyrus frontalis (BA11), right limbic lobe (BA30, BA35), and left frontal lobe (BA47) were activated, and the right parietal lobe (BA40) deactivated. Activation: Nervous activity increased above baseline level with increased blood oxygen levels (red). Deactivation: Nervous activity decreased below baseline level with decreased blood oxygen levels (blue).

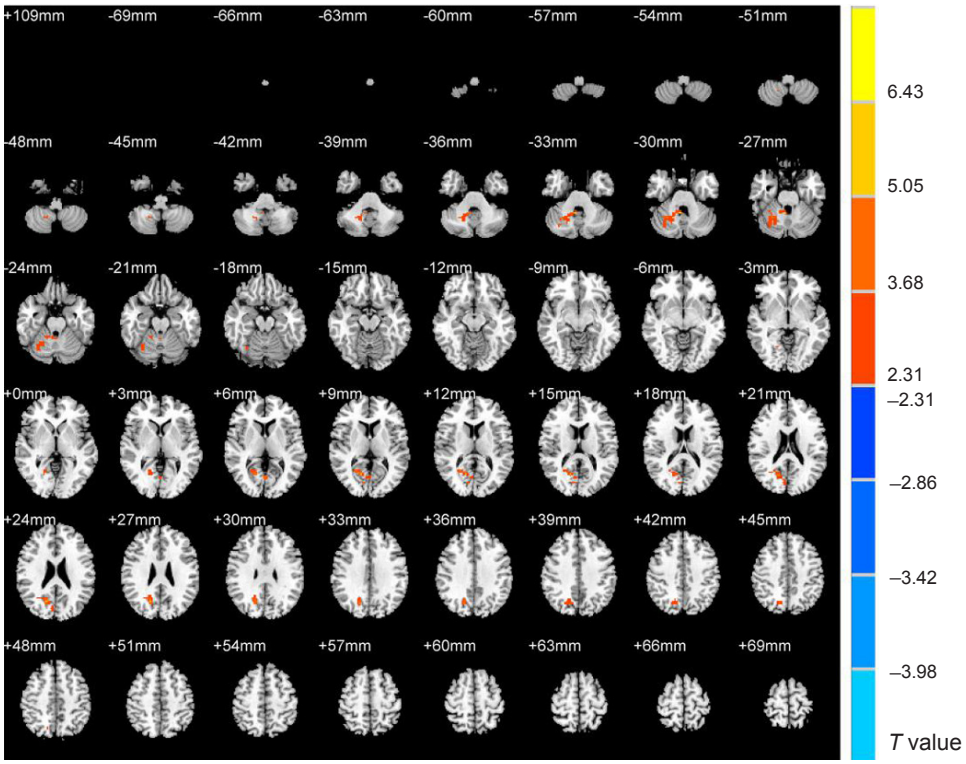

Figure 4 Difference of brain regions activated during acupuncture at *Waiguan* (SJ5) in the *Deqi* and non-*Deqi* groups.
Compared with the non-*Deqi* group, the right anterior lobe of the cerebellum and right limbic lobe (BA30) were significantly activated in the *Deqi* group. Activation: Nervous activity increased above baseline level with increased blood oxygen levels (red). Deactivation: Nervous activity decreased below the baseline level with decreased blood oxygen levels (blue).

values ≤ 0.05 were considered statistically significant.

Analysis of imaging data: (1) all the data were analyzed voxel by voxel using a generalized linear model. The *T* value of each voxel was calculated using a two-sample *t*-test, with statistical parametric mapping based on the *T* value ($P \leq 0.05$, uncorrected; $K > 85$). Alterations in brain regions during stimulation and control conditions were identified and superimposed on the standard brain image model derived from anatomical images of each subject. (2) The activated and deactivated con file output of models for the *Deqi* and non-*Deqi* groups were then analyzed using a two-independent samples *t*-test. The rest of the analysis was the same as in (1).

Central coordinates of statistical parameters determined using the statistical parametric mapping software package were reproduced and inputted to Talairach Client (download from http://www.talairach.org/client.html) to obtain the Brodmann area (BA) range of functional brain areas and anatomical location (Noppernc y and Price, 2003), which were corrected by a physician from the Department of Neurological Medicine according to anatomical knowledge and clinical experience.

Results

Comparison of patients' general data

A total of 12 ischemic stroke patients were included in this study. During acupuncture, five subjects experienced soreness, numbness, distention, and heaviness, and were included in the *Deqi* group. Five subjects without any feeling were included in the non-*Deqi* group. Two subjects experienced twinge and were excluded. No significant differences in general data were observed between the two groups ($P > 0.05$; **Table 1**).

Acupuncture at *Waiguan* (TE5) affected brain areas in ischemic stroke patients

After acupuncture, activation of the left superior temporal gyrus (BA39) was detected (**Figure 2**). Simultaneously, in the *Deqi* group, inhibition of the right anterior lobe of the cerebellum and left thalamus (**Table 2**) was detected. Activation of the right medial gyrus frontalis (BA11), right limbic lobe (BA30, BA35), and left frontal lobe (BA47) were also observed (**Figure 3**). In the non-*Deqi* group, simultaneous inhibition of the right parietal lobe (BA40) was detected (**Table 3**). Compared with the non-*Deqi* group, the right anterior lobe of the cerebellum and right limbic lobe (BA30) were significantly activated in the *Deqi* group ($P < 0.05$, $K > 85$; **Table 4**, **Figure 4**).

Discussion

The presence of *Deqi* and its time of occurrence are important factors for the clinical efficacy of acupuncture. *Deqi* refers to the feelings of both physicians and patients, although the effects of *Deqi* on central mechanisms have not yet been reported. In this study, we used fMRI to investigate the effect of a patient's feelings on cerebral function after acupuncture

at *Waiguan* in ischemic stroke patients.

In the *Deqi* group, the activated/deactivated brain regions were the left superior temporal gyrus (BA39)/right anterior lobe of the cerebellum and left thalamus. Using positron emission tomography, Zhang et al. (2011a) found that BA7, BA13, BA20, BA22, BA39, BA42, and BA45 were activated after acupuncture at the right *Waiguan* in healthy volunteers. Additionally, Chen et al. (2012) confirmed using single-photon emission computed tomography that BA6, BA8, BA19, BA21, BA28, BA33, BA35, BA37, and BA47 are markedly activated in a *Deqi* group compared with a non-*Deqi* group after acupuncture at *Waiguan* in normal subjects. Compared with normal individuals, less brain regions are activated in the pathological state. BA39 (right anterior lobe of the cerebellum and left thalamus) does not belong to the limbic system, and is not consistent with previous findings that *Deqi* during acupuncture is negatively correlated with deactivation of the limbic system (Bai et al., 2009; Hui et al., 2009; Liu et al., 2011; Fang et al., 2012). This difference may be associated with the patient's status and differing acupoints.

We found that the activated brain regions were mainly in the left hemisphere in the *Deqi* group (**Figure 2**), which probably correlates with brain tissue remodeling. Brain plasticity is the adaptive capacity of the brain, and the brain can change its structure and function to adapt to an altered environment, a key theoretical basis for treatments of the central nervous system (Green et al., 2003; Rossini et al., 2003). Nervous system plasticity is implemented by plasticity of neuronal synapses and motor relearning. Plasticity of neuronal synapses includes changes in the synaptic threshold, axonal sprouting, latent pathway, and ion channels. Motor relearning is performed by partial compensation in intact brain regions. Acupuncture is an effective method to stimulate the central nervous system and increase the efficiency of synapse formation and promote functional recovery. Sensory feedback during acupuncture contributes to relearning of the original function (Liu et al., 2012). Consequently, we assume that *Deqi* during acupuncture is a condition that can produce brain activation.

Following acupuncture at the right *Waiguan*, activation in the medial gyrus frontalis of the right frontal lobe (BA11), posterior cingulate of the right limbic lobe (BA30), hippocampal gyrus of the right limbic lobe (BA35), and left frontal lobe (BA47) was detected, as well as inhibition of the right parietal lobe (BA40) in the non-*Deqi* group. Interestingly, the activated/deactivated brain regions are not in the motor and sensory brain regions. BA11 has a cognitive function and is associated with thoughts and emotions. BA30 belongs to the memory system, and BA35 is involved in hippocampal function. BA40 is involved in fine-motor coordination, and BA47 in language processing (Sun, 2001). Acupuncture with the absence of *Deqi* also induces activation of brain regions. Using fMRI, Zhang (2011b) verified that acupuncture at the right *Zusanli* (ST36) in a non-*Deqi* group of healthy individuals activates the temporal lobe, hypothalamus, hippocampal gyrus, and cingulate gyrus. These findings indicate that the tight and heavy feeling experienced by physicians' is likely associated with activation of brain regions. Therefore during clinical operations, acupuncturists may be able to provide knowledge on brain activation.

We found that the activated brain regions were mainly in the right hemisphere in the *Deqi* group (**Figure 4**), including the posterior cingulate (BA30) and anterior lobe of the cerebellum. The posterior cingulate belongs to the limbic lobe and is associated with visceral regulation, emotional response, and memory, which is consistent with the acupuncture effects at *Waiguan*. Acupuncture at *Waiguan* in patients with cerebral infarction activates the cerebellum. Using positron emission tomography, Liu et al. (2013) observed changes in glucose metabolism in the brain of seven patients with cerebral infarction after acupuncture at *Waiguan*, and confirmed that the activated brain regions in bilateral hemispheres (superior temporal gyrus and right inferior frontal gyrus) were focused on the uninjured side. The activated cerebellar regions were focused on the left cerebellar hemisphere, and included the culmen of the anterior lobe of the left cerebellum and tonsil of the posterior lobe of the bilateral cerebellum. Chen et al. (2013) reported that the tonsil of the posterior lobe of the cerebellum was activated after acupuncture at *Waiguan* in 10 stroke patients.

The cerebellum is involved in motor function such as maintaining balance, controlling muscle tension, and coordinating motion. In recent years, various clinical neuropsychological evaluations and imaging studies have demonstrated that the cerebellum may be associated with the cerebral cortex and regulate cognitive function *via* a "cerebrum-cerebellum" loop. Cho et al. (2012) investigated cerebral metabolism using repetitive transcranial magnetic stimulation and ^{18}F-fluorodeoxyglucose and positron emission tomography to study neuronal activity in the cerebellum of 12 right-handed healthy volunteers. When the left cerebellum was stimulated, they found enhanced glucose metabolism in cognitive- and language-related brain regions such as the left inferior frontal gyrus and bilateral superior temporal gyrus. Simultaneously, metabolism in the dentate body of the left cerebellum and pons was also enhanced, suggesting that repetitive transcranial magnetic stimulation in the left cerebellum not only excites the target area, but also brain regions related to movement, speech, cognition, and emotion. Taken together, acupuncture causes soreness, numbness, distention, and heaviness, and leads to cerebellar activation, which potentially regulates motor and language functions *via* a "cerebrum-cerebellum" loop. This may be a central mechanism of *Deqi* during acupuncture for ischemic stroke.

In summary, a tight and heavy feeling experienced by the physician is the basis of *Deqi*, while soreness, numbness, distention, and heaviness experienced by the stroke patient during acupuncture are important components of *Deqi*. However, the activated brain regions are not more extensive in the *Deqi* group than in the non-*Deqi* group, which may possibly be due to the small sample and lack of acupoint compatibility. Further investigation with a larger sample and a longer period of observation with acupoint compatibility is needed.

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Conflicts of interest: *None declared.*

Plagiarism check: *This paper was screened twice using Cross-Check to verify originality before publication.*

Peer review: *This paper was double-blinded and stringently reviewed by international expert reviewers.*

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