FUNCTIONAL GI DISORDERS

Influence of Acupuncture Treatment on Cerebral Activity in Functional Dyspepsia Patients and Its Relationship With Efficacy

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OBJECTIVES: **Acupuncture is a commonly used therapy for treating functional dyspepsia (FD), although the mechanism remains unclear. The objectives of this study were to investigate the differences in cerebral glycometabolism changes evoked by acupuncture and sham acupuncture and to explore the possible correlations between brain responses and clinical efficacy.**

METHODS: **In all, 72 FD patients were randomly assigned to receive either acupuncture or sham acupuncture treatment for 4 weeks. Ten patients in each group were randomly selected for fluorine-18 fluorodeoxyglucose positron emission tomography computed tomography scans to detect cerebral glycometabolism changes. The Nepean Dyspepsia Index (NDI) and Symptom Index of Dyspepsia (SID) were used to evaluate the therapeutic effect.**

RESULTS: **(i) The clinical data showed that after treatment the decrease in SID score in the acupuncture group was significantly greater than that in the sham acupuncture group ($P<0.05$). The increase in NDI score between the two groups did not differ ($P>0.05$), and only the improvement in NDI score in the acupuncture group was clinically significant. (ii) The neuroimaging data indicated that after treatment the acupuncture group showed extensive deactivation in cerebral activities compared with the sham acupuncture group. In the acupuncture group, the deactivations of the brainstem, anterior cingulate cortex (ACC), insula, thalamus, and hypothalamus were nearly all related to the decrease in SID score and the increase in NDI score ($P<0.05$, corrected). In the sham acupuncture group, the deactivations of the brainstem and thalamus tended to be associated with the increase in NDI score ($P<0.1$, corrected).**

CONCLUSIONS: **Acupuncture and sham acupuncture have relatively different clinical efficacy and brain responses. Acupuncture treatment more significantly improves the symptoms and quality of life of FD patients. The more remarkable modulation on the homeostatic afferent network, including the insula, ACC, and hypothalamus, might be the specific mechanism of acupuncture.**

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INTRODUCTION

Functional dyspepsia (FD) is a major functional gastrointestinal disorder characterized by symptoms originating from the gastroduodenal region in the absence of underlying organic disease that would readily explain the symptoms (1). According to the 2006 Rome III criteria, FD includes two subgroups: postprandial distress syndrome and epigastric pain syndrome. The former is marked by nonpainful symptoms including abdominal fullness and early satiety; the later is marked by epigastric pain and a burning sensation (2). FD has become an important public

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health-care and social issue because of its high prevalence (3), unclear pathology, unsatisfactory treatment options (4), large medical burden (5), and serious reduction in quality of life (QOL) (6). Hence, both patients and practitioners desire effective alternative therapies.

In China and some other Asian countries, acupuncture, a major medical resource, has been used to treat gastrointestinal symptoms for several millennia. In Western countries, acupuncture is being increasingly accepted as an alternative treatment for functional gastrointestinal disorders (7,8). During the past decade, a considerable number of clinical and experimental studies have indicated that acupuncture is able to relieve gastric symptoms such as belch, abdominal distension, and stomachache and to alter gastrointestinal motility functions (9–12), as well as that acupuncture points on the stomach meridian were the most effective sites for gastric disorders (11,12). However, it is not fully understood how needling at acupuncture points works and how real acupuncture differs from sham acupuncture.

Many studies have demonstrated that most of the clinical benefits of acupuncture are mediated by the central nervous system (13,14), but the specific effects of acupuncture on the human brain remain uncertain. With the development of neuroimaging techniques, the use of positron emission tomography (PET) and functional magnetic resonance imaging to explore the central mechanism of acupuncture has been an active area of research. However, most current studies are centered on the healthy state or organic diseases, and little work has been undertaken with regard to functional disorders, which is where the advantages of acupuncture treatment lie.

In a previous study, we found that FD patients showed an extensive increasing cerebral glycometabolism, especially in the homeostatic afferent processing network, compared with healthy subjects. The anterior cingulate cortex (ACC), insula, and thalamus/hypothalamus might be the regions most closely related to the severity of FD (15). We hypothesize that successful acupuncture therapy will reduce the increase in cerebral glycometabolism and regulate the activity of these key regions. Our previous work also suggested that affecting cerebral activity might be the mechanism through which short-term manual acupuncture treatment relieves FD (16). However, the differences in efficacy and cerebral responses between acupuncture and sham acupuncture were not addressed in our previous study. Hence, the present study aimed to (i) assess the efficacy of acupuncture treatment for FD by comparing the differences in therapeutic effects between acupuncture and sham acupuncture and (ii) investigate the influence of acupuncture and sham acupuncture on cerebral glycometabolism and analyze the possible correlations between clinical variables and brain responses in order to explore the potential central mechanism of acupuncture treatment.

METHODS

Participants

FD patients were recruited from the outpatient department in the 1st Teaching Hospital of the Chengdu University of Traditional Chinese Medicine from December 2008 to May 2010. Patients were enrolled if they met the following criteria: (i) were right-handed and aged 20 to 30 years; (ii) matched the Rome III diagnosis criteria for FD; (iii) matched the Rome III diagnosis criteria for postprandial distress syndrome; (iv) were acupuncture-naïve; and (v) signed an informed-consent form. Participants were screened out if they (i) were pregnant, might become pregnant, or were lactating; (ii) suffered from or had a history of serious neurological, cardiovascular, respiratory, or renal illnesses; (iii) had a history of head trauma with loss of consciousness; (iv) suffered from mental disorders including major depressive disorder such as anxiety disorder, bipolar disorder, schizophrenia, or claustrophobic syndrome; (v) were using aspirin, nonsteroidal anti-inflammatory drugs, steroids, phenothiazines, selective serotonin reuptake inhibitors, medications affecting gastrointestinal motility, or certain other drugs; (vi) were currently participating in other clinical trials; or (vii) had any contraindications to acupuncture (e.g., anticoagulation therapy).

After a 2-week baseline period, the enrolled patients were randomly assigned to either the acupuncture group or the sham acupuncture group using a computer-generated randomization sequence. The sequence was concealed from the care providers through the use of sealed, opaque, sequentially numbered envelopes. Patients were blinded to group assignment.

This study was performed according to the principles of the Declaration of Helsinki (Edinburgh version, 2000). The study protocol was approved by the Ethics Committee of the 1st Teaching Hospital of the Chengdu University of Traditional Chinese Medicine.

Acupuncture interventions

Each group's treatment consisted of 20 sessions of acupuncture treatment, with a duration of 30 min, each administered over a period of 4 weeks (five sessions per week). The acupuncture treatment was performed on four classic acupuncture points for gastric disorders: ST34 (*Liangqiu*), ST36 (*Zusanli*), ST40 (*Fenglong*), and ST42 (*Chongyang*). The sham acupuncture treatment was performed on four non–acupuncture points (points 1–4), which were selected in accordance with the findings of previous studies (17–19) (**Figure 1**).

All acupuncture points and non–acupuncture points were punctured unilaterally and alternated between left side and right side. After the skin was cleaned with tincture iodine and alcohol, sterile acupuncture needles (0.25 mm in diameter, 25 or 40 mm long, Hwatuo, Suzhou, China) were inserted for 15–25 mm and gently twisted, lifted, and thrusted in even amplitude, force and speed four to six times until a *deqi* response (soreness, numbness, distension, and heaviness) was obtained. Then, auxiliary needles were inserted in the proximal limbs or trunk laterally to the acupuncture points and non–acupuncture points to a depth of 2 mm without stimulation. Each acupuncture needle and its auxiliary needle were connected to the electrical leads of the HAN Acupoint Nerve Stimulator (HANS, Model LH 200A TENS, Nanjing, China) for 30 min, with a stimulation frequency of 2/100 Hz and a stimulation intensity varying from 0.1 to 1.0 mA.

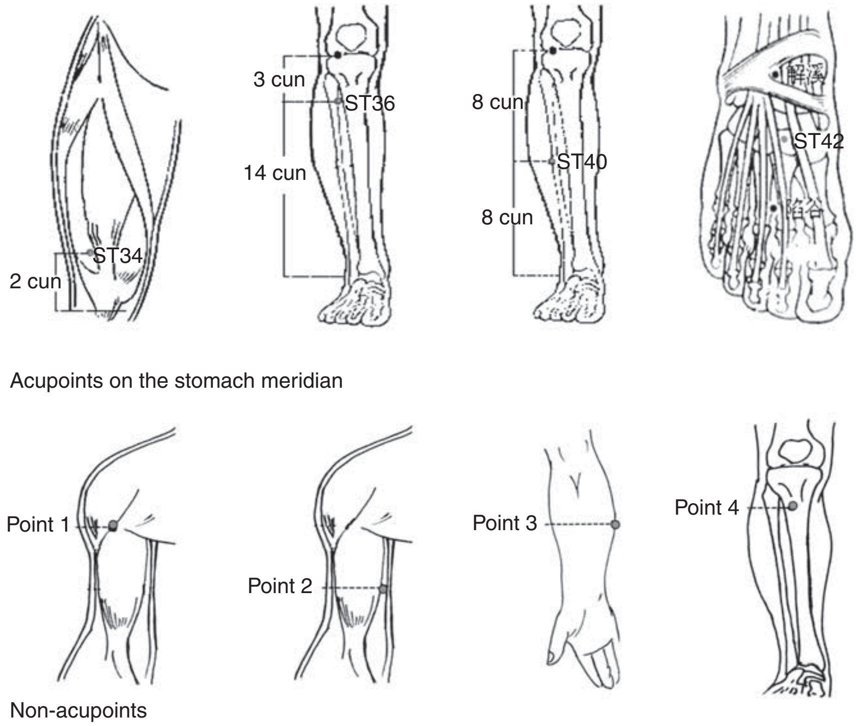

Figure 1. Locations of acupuncture points and non–acupuncture points. The acupuncture points were located as follows: (i) ST34 (*Liangqiu*), 2 *cun* above the laterosuperior border of the patella; (ii) ST36 (*Zusanli*), four fingers' breadth below the lower margin of the patella and one finger's breadth laterally from the anterior crest of the tibia; (iii) ST40 (*Fenglong*), 8 *cun* superior and anterior to the external malleolus, one finger's breadth from the anterior crest of the tibia; and (iv) ST42 (*Chongyang*), in the depression between the second and the third metatarsal bones and the cuneiform. The non–acupuncture points were located as follows: (i) point 1, on the anterior border of the deltoid muscle, at the junction of the deltoid and biceps muscles; (ii) point 2, at the midpoint between the tip of the elbow and the apex of axillae; (iii) point 3, at the midpoint between the epicondylusmedialis of the humerus and ulnar side of the transverse creases of the wrist; and (iv) point 4, on the lateral side of the tibia, 1–2 cm lateral to the ST36 (*Zusanli*).

Outcome measurement

In the absence of well-validated, Rome III–based patient-reported outcome measures for FD (20), we used the Symptom Index of Dyspepsia (SID) and the Nepean Dyspepsia Index (NDI) for QOL to assess clinical efficacy. The SID is a commonly used Rome III–based scale (21) that focuses on the chief symptoms of FD. Symptoms are graded on a 4-point Likert scale: asymptomatic (0 point), mild (1 point), moderate (2 points), or severe (3 points) (22). In this study, all patients were free of the symptoms of epigastric pain syndrome, so the scores on the two symptoms of postprandial distress syndrome (postprandial distension and early satiety) are summed to evaluate the severity of dyspepsia. A higher SID score mean more severe symptoms. NDI for QOL is a dyspepsia-specific index (23) that includes 25 items and covers four domains: interference, know/control, eat/drink, and sleep/disturb. The NDI score ranges from 0 to 100. Its minimal clinically important difference is 10 points. A higher NDI score indicates better QOL and milder symptoms. The Chinese version of the NDI was found by a previous study to be reliable and valid for measuring health-related QOL and disease severity in Chinese FD patients (24).

PET computed tomography scan

In all, 10 patients in each group were randomly selected for ^{18}F-FDG (fluorine-18 fluorodeoxyglucose) PET computed tomography (CT) scans at the end of baseline and at the end of treatment. After an overnight fast of at least 12 h, patients went through the following sequential procedure on an empty stomach: (i) measurements of blood pressure and blood glucose, (ii) a 20-min rest in a dark room, (iii) a tracer injection (^{18}F-FDG, synthesized with Mini Tracer accelerator 0.11 mci/kg dosage) at the back of the right hand, (iv) a 40-min rest, and then (v) a PET-CT scan (Biograph Duo BGO scanner, Siemens, Germany). Patients were instructed to remain relaxed throughout the study with their eyes blindfolded and ears plugged.

PET-CT images covered the whole brain and were parallel to the AC–PC line. Image acquisition began after a 40-min uptake period (bed: 1; collection mode: 3D; slice thickness: 2 mm; slice interval: 1.5 mm; matrix size: 256×256; total counts: 3×10^9). Upon completion of data acquisition, the images were reconstructed using ordered subset expectation maximization with 6 iterations and 16 subsets.

Statistical analysis

Sample size. Because there was no reference to indicate the effect size that could be expected from the use of acupuncture to treat postprandial distress syndrome (the relevant subtype of FD), we did not estimate the sample size based on a power calculation. Instead, we enrolled 72 participants with a 20% withdrawal rate to provide 30 patients in each group in order to meet the requirement of minimum sample size.

Clinical variables. The clinical variables were analyzed with SPSS 16.0 (SPSS, Chicago, IL) by two blinded evaluators. The data analysis was based on an intention-to-treat population. We omitted the cases with missing data, which reflected only the baseline measurement. Analysis of variance and the Kruskal–Wallis test were used for numerical variables. A χ^2 test was used for categorical variables. A two-sided test was applied for all available data. A P value <0.05 was considered statistically significant.

PET-CT data. The PET-CT data were processed with the statistical parametric mapping technique (SPM5; http://www.fil.ion.ucl.ac.uk/spm) and MATLAB (The Math Works, Sherborn, MA). The data preprocessing entailed the following steps. (i) Individual PET images were subjected to coregistration onto their corresponding CT images to improve the accuracy of the spatial normalization. (ii) The PET images from each subject were spatially normalized to the standard SPM-PET template and resliced to 2-mm isotropic resolution. The first step of the normalization was to determine the optimal 12-parameter affine transformation. The affine registration was followed by estimation of nonlinear deformations, whereby the deformations are defined by a linear combination of three-dimensional discrete cosine transform basis functions. (iii) The resultant transformation was applied to the coregistered PET images so that all subjects matched the same spatial template. (iv) The normalized data set was spatially smoothed with a 6-mm full width at half maximum Gaussian kernel.

To detect the cerebral activity changes in FD patients after treatment, we compared the differences in the cerebral glycometabolism pattern between FD patients at baseline and after treatment. Statistical parametric maps were constructed by computing a paired t-test, which was defined as FD patients after treatment minus FD patients at baseline. To explore the possible correlation between cerebral responses and clinical efficacy, we employed correlation analysis to investigate the correlations of cerebral glycometabolism changes with the decrease in SID score (end of treatment minus baseline) and increase in NDI score (end of treatment minus baseline). The selection of regions of interest was based mainly on our previous study (15) and involved the within-group subtraction analysis. In our previous study (15), we found that the glycometabolism increase in the ACC, middle cingulate cortex, insula, thalamus, cerebellum, hypothalamus, prefrontal cortex, brainstem, hippocampus, and parahippocampal gyrus was significantly related to or tended to be associated with the symptom severity of FD patients. In the present study, the within-group analysis showed that the activity of these regions changed to a different degree after treatment. Hence, we chose these 10 regions for correlation analysis. For each patient, we chose the MNI coordinates of the maximally abnormal voxel within an anatomical area as the center to draw a sphere 8 mm in diameter (25). Within this sphere, the voxels located in the white matter and ventricles were removed to ensure the integrity of its structure and function. In this way, we could gain regions of interest for correlation analysis. After voxels not belonging to the same anatomical region within the cluster were discarded, the activities of the survived voxels were extracted and averaged. Pearson coefficients were calculated between the mean activity of the cluster and the increase in NDI score, the mean activity of the cluster, and the decrease in SID score.

Based on individual cerebral activity changes before and after real/sham acupuncture treatment, we performed a two-sample t-test to further detect between-group differences using the following contrast: real acupuncture group (each FD patient: after treatment minus at baseline) minus sham acupuncture group (each FD patient: after treatment minus at baseline).

For visualization, all results were transformed into the Talairach stereotactic space and overlaid on MRIcro (http://www.sph.s.c.edu/comd/rorden/mricro.html) for presentation.

RESULTS

From December 2008 to May 2010, 72 FD patients were randomly assigned. In all, 64 patients (34 in the acupuncture group and 30 in the sham acupuncture group) comprised the pre-protocol population. Twenty patients (10 in each group) finished the PET-CT scans.

The baseline characteristics

Demographics, including age, sex, weight and height, and disease status as indicated by, for example, duration of symptoms, NDI score, and SID score, did not differ between the two groups ($P>0.05$) (**Table 1**).

The therapeutic effects

In the acupuncture group, the SID score for postprandial distension significantly decreased, from 1.912±0.571 to 0.880±0.640 ($P<0.05$); the SID score for early satiety significantly decreased, from 1.352±0.810 to 0.530±0.661 ($P<0.05$); and the NDI score significantly increased, from 77.812±10.121 to 90.028±8.910 ($P<0.05$) after treatment (**Table 2**).

In the sham acupuncture group, the SID score for postprandial distension significantly decreased, from 1.930±0.641 to 1.400±0.721 ($P<0.05$), and the NDI score significantly increased, from 78.212±9.223 to 86.040±9.210 ($P<0.05$) after treatment. The decrease in SID score for early satiety was not significant ($P>0.05$) (**Table 2**).

The decrease in SID scores (end of treatment minus baseline) in the acupuncture group was significantly greater than that in the sham acupuncture group ($P<0.05$). The increase in NDI score (end of treatment minus baseline) between the two groups was not significant ($P>0.05$). Only the increase in NDI score in the acupuncture group was clinically significant because it was greater than the minimal clinically important difference (**Table 3**).

Cerebral glycometabolism changes

In the acupuncture group, a decrease in cerebral glycometabolism was observed after treatment in the bilateral brainstem,

Table 1. Baseline characteristics

Characteristic	Acupuncture group	Sham acupuncture group	Statistical value	*P* value
No. of patients (*n*)	34	30		
No. of women, *n* (%)	21 (61.765%)	18 (60.000%)	0.021	0.885
Age (years), mean (95% CI)	23.971 (22.903; 25.038)	23.833 (22.665; 25.002)	489.000	0.776
Height (cm), mean (95% CI)	164.441 (161.405; 167.477)	162.967 (160.758; 165.176)	489.500	0.782
Weight (kg), mean (95% CI)	54.000 (50.936; 57.064)	53.067 (50.140; 55.994)	477.000	0.656
Course of disease (M), mean (95% CI)	39.029 (27.937; 50.122)	40.967 (28.349; 53.585)	493.000	0.819
NDI score, mean (95% CI)	77.812 (74.282; 81.343)	78.212 (74.770; 81.654)	503.000	0.925
SID score: postprandial distension, mean (95% CI)	1.910 (1.710; 2.110)	1.930 (1.690; 2.170)	502.500	0.906
SID score: early satiety, mean (95% CI)	1.350 (1.070; 1.640)	1.100 (0.780; 1.420)	416.500	0.179

CI, confidence interval; NDI, Nepean Dyspepsia Index; SID, Symptom Index of Dyspepsia.

Table 2. Clinical outcome measurements in each group before and after treatment

Items	Acupuncture group	Sham acupuncture group
NDI scores		
Baseline, mean (95% CI)	77.812 (74.282; 81.343)	78.212 (74.770; 81.654)
End of treatment, mean (95% CI)	90.028 (86.920; 93.136)	86.040 (82.600; 89.480)
Statistical value	203.000	254.500
P value	0.000	0.004
SID score: postprandial distension		
Baseline, mean (95% CI)	1.910 (1.710; 2.110)	1.930 (1.690; 2.170)
End of treatment, mean (95% CI)	0.880 (0.660; 1.110)	1.400 (1.130; 1.670)
Statistical value	149.500	261.000
P value	0.000	0.002
SID score: early satiety		
Baseline, mean (95% CI)	1.350 (1.070; 1.640)	1.100 (0.780; 1.420)
End of treatment, mean (95% CI)	0.530 (0.300; 0.760)	0.930 (0.620; 1.240)
Statistical value	258.000	396.500
P value	0.000	0.388

CI, confidence interval; NDI, Nepean Dyspepsia Index; SID, Symptom Index of Dyspepsia.

cerebellum, ACC (BA32, BA24), middle cingulate cortex (BA32), posterior cingulate cortex (BA23), insula, thalamus, putamen, caudate, hippocampus, hypothalamus, inferior frontal gyrus (BA47), superior medial frontal gyrus (BA32, BA10), orbital gyrus (BA11), precentral gyrus (BA6), lingual gyrus (BA18), parahippocampal gyrus (BA37), temporal pole (BA38), middle temporal gyrus (BA21) and inferior temporal gyrus (BA20), left middle occipital gyrus (BA39), and right rectal gyrus (BA11). An increase in cerebral glycometabolism was detected in the bilateral precuneus (BA7), right postcentral gyrus (BA3), and left parietal inferior lobe (BA7) ($P<0.05$, family-wise error corrected with a minimal cluster size of 50 voxels) (**Table 4**) (**Figure 2**).

In the sham acupuncture group, a signal decrease was observed after treatment in the bilateral brainstem, thalamus, posterior cingulate cortex (BA23), left cerebellum, right middle cingulate cortex (BA23), lingual gyrus (BA27), middle temporal gyrus (BA21), middle occipital gyrus (BA18), and precuneus (BA30). A signal increase was detected in the bilateral caudate, left superior medial frontal gyrus (BA8), rectal gyrus (BA11), and precentral gyrus (BA6) ($P<0.05$, family-wise error corrected with a minimal cluster size of 50 voxels) (**Table 4**) (**Figure 2**).

Compared with that of the sham acupuncture group, the glycometabolism in the bilateral ACC, putamen, thalamus, middle frontal gyrus and middle temporal gyrus, left hippocampus and inferior temporal gyrus, right superior medial frontal gyrus, medial frontal gyrus, precentral gyrus, cerebellum, and lingual gyrus of acupuncture group was significantly reduced ($P<0.001$, uncorrected with a minimal cluster size of 20 voxels) (**Table 5**).

Correlation coefficients of brain responses and clinical variables

In the acupuncture group, (i) the increase in NDI score was significantly related to the glycometabolism decrease in the insula ($r=-0.847$), thalamus ($r=-0.867$), brainstem ($r=-0.846$), ACC ($r=-0.841$), and hypothalamus ($r=-0.759$) ($P<0.05$, corrected) (**Figure 3a**); (ii) the decrease in SID score was significantly related to the glycometabolism decrease in the insula ($r=0.774$), thalamus ($r=0.826$), ACC ($r=0.783$), and hypothalamus ($r=0.793$) ($P<0.05$, corrected) (**Figure 3c**); and the decrease in SID score tended to be associated with the glycometabolism decrease in the brainstem ($r=0.720$) ($P<0.1$, corrected). The phenomenon that the correlations of the deactivation in the same area with

Table 3. Comparison of the therapeutic effects between acupuncture group and sham acupuncture group

Items	Acupuncture group	Sham acupuncture group	Statistical value	*P* value
No. of patients	34	30		
NDI score				
End of treatment, mean (95% CI)	90.028 (86.920; 93.136)	86.040 (82.600; 89.480)	368.000	0.056
End of treatment—baseline, mean (95% CI)	12.216 (8.533; 15.898)	7.828(4.912; 10.743)	376.500	0.072
SID score: postprandial distension				
End of treatment, mean (95% CI)	0.880 (0.660; 1.110)	1.400 (1.130; 1.670)	321.000	0.003
End of treatment—baseline, mean (95% CI)	−1.029 (−1.333; −0.726)	−0.533 (−0.768; −0.299)	343.000	0.014
SID score: early satiety, mean (95% CI)				
End of treatment, mean (95% CI)	0.530 (0.300; 0.760)	0.930 (0.620; 1.240)	365.000	0.030
End of treatment—baseline, mean (95% CI)	−0.824 (−1.102; −0.546)	−0.167 (−0.428; 0.094)	277.500	0.001

CI, confidence interval; NDI, Nepean Dyspepsia Index; SID, Symptom Index of Dyspepsia.

SID or with NDI were not even might be attributable to the different numerical ranges in the SID and NDI scores.

In the sham acupuncture group, the increase in NDI score tended to be associated with the glycometabolism decrease in the brainstem ($r = -0.720$) and thalamus ($r = -0.724$) ($P<0.1$, corrected) (**Figure 3a**).

DISCUSSION

This is the first neuroimaging study that focuses on the potential central mechanism of real and sham acupuncture treatments for FD. It demonstrates the similarities and differences in clinical efficacy and brain responses between real and sham acupuncture treatments.

Similarities and differences in clinical efficacy between real and sham acupuncture treatments

In this study, clinical improvements were found in both groups after treatment. Both treatments remarkably alleviated postprandial distension and improved the QOL ($P<0.05$) (**Table 2**); in addition, the improvement in QOL between the two groups did not differ ($P>0.05$) (**Table 3**). These similarities might result from a placebo effect. In fact, placebo response rates are found to be high in functional gastrointestinal disorder (26). A recent systematic review (27) demonstrated that in all trials of acupuncture treatments for gastrointestinal diseases, the significant improvements of QOL were independent of real or sham acupuncture. The efficacy of acupuncture in improving QOL in irritable bowel syndrome and inflammatory bowel disease may be explained by nonspecific effects, whereas specific acupuncture effects may be shown by clinical scores.

However, based on the results, we found that acupuncture treatment was significantly superior to sham acupuncture treatment, especially in alleviating symptoms. First, sham treatment was effective only for postprandial distension, whereas acupuncture treatment alleviated both postprandial distension and early satiety (**Table 2**). Second, the alleviations in postprandial distension and early satiety in acupuncture group were greater than those in the sham acupuncture group ($P<0.05$) (**Table 3**). Furthermore, only the improvement in QOL caused by acupuncture treatment was clinically valuable (**Table 2**). Therefore, the differences in clinical efficacy between the two groups indicated that the efficacy of acupuncture treatment was not nonspecific and that acupuncture treatment was more effective than sham acupuncture treatment for FD patients.

Our results were partly in line with those of a study by Park *et al.* (28), who found that both acupuncture at classic points (real acupuncture) and acupuncture at nondefined points (sham acupuncture) decreased dyspepsia symptoms and improved the QOL of FD patients and that there were no significant differences between the real acupuncture group and sham acupuncture group. Some methodology issues, including the method of acupuncture stimulation (manual acupuncture vs. electro-acupuncture), the length of time the needle was kept inserted, duration of treatment, and location of non–acupuncture point, probably contribute to the differences in results. Furthermore, the differences in treatment frequency might be a factor causing the efficacy difference (29). In our study, the electro-acupuncture treatment was performed five times per week on each patient for 4 weeks, consistent with the standard practice in China, whereas in the study by Park*et al.*, the manual acupuncture treatment was performed on patients three times per week for 2 weeks. Hence, the stimulating quantity in our study was greater than that in the study by Park *et al.* However, the influence of treatment frequency on clinical efficacy needs further investigation.

Similarities and differences in cerebral responses to real and sham acupuncture treatments

The potential common mechanism of real acupuncture and sham acupuncture treatments for FD. In the present study, both acupuncture treatment and sham acupuncture treatment elicited cerebral glycometabolism changes to different degrees. The common areas responding to acupuncture and sham acupuncture

Table 4. **The cerebral glycometabolism changes in FD patients after real or sham acupuncture treatment (end of treatment minus baseline)**

Region	Side	Acupuncture group						Sham acupuncture group					
		Talairach			*t* value	BA	Sign	Talairach			*t* value	BA	Sign
		X	*Y*	*Z*				*X*	*Y*	*Z*			
Inferior frontal gyrus	L	−34	25	2	−9.33	BA47	↓						
	R	38	25	2	−6.32	BA47	↓						
Superior medial frontal gyrus	L	−20	34	19	−10.5	BA32	↓	−4	39	33	18.01	BA8	↑
	R	20	10	47	−6.12	BA32	↓						
	L	−28	63	8	−13.6	BA10	↓						
	R	30	51	1	−11.3	BA10	↓						
Rectal gyrus	L							−12	38	−18	9.17	BA11	↑
	R	3	34	19	−6.91	BA11	↓						
Orbital gyrus	L	−11	60	−7	−10.08	BA11	↓						
	R	16	54	−4	−7.81	BA11	↓						
Precentral gyrus	L	−35	−16	64	−8.27	BA6	↓	−51	11	43	−8.04	BA6	↑
	R	27	−22	72	−10.76	BA6	↓						
Caudate	L	−16	−7	24	−10.7	—	↓	−9	3	20	7.13	—	↑
	R	17	19	2	−9.85	—	↓	18	10	19	8.25	—	↑
Brainstem	L	−4	−25	−19	−25.48	—	↓	−2	−16	−14	−9.40	—	↓
	R	4	−21	−15	−17.1	—	↓	5	−25	−17	−7.36	—	↓
Cerebellum	L	−21	−55	−41	−14.38	—	↓	−4	−72	−43	−8.04	—	↓
	R	8	−54	−6	−8.04	—	↓	30	−69	−25	−19.33	—	↓
ACC	L	−7	41	22	−15.97	BA32	↓						
	R	4	49	26	−8.04	BA32	↓						
	R	7	25	19	−18.16	BA24	↓						
MCC	L	−9	15	39	−9.52	BA32	↓						
	R	10	15	46	−9.40	BA32	↓	5	−12	33	−6.68	BA23	↓
PCC	L	−5	−50	23	−11.88	BA23	↓	−3	−39	25	−14.16	BA23	↓
	R	7	−43	29	−17.33	BA23	↓	6	−38	27	−8.95	BA23	↓
Lingual gryrus	L	−7	−60	1	−10.05	BA18	↓						
	R	8	−60	3	−8.77	BA18	↓	15	−42	3	−9.17	BA27	↓
Insula	L	−35	18	1	−17.05	—	↓						
	R	36	−25	24	−22.09	—	↓						
Putamen	L	−29	−11	5	−13.7	—	↓						
	R	18	6	9	−16.4	—	↓						
Thalamus	L	−20	−17	−10	−19.8	—	↓	−10	−6	1	−7.36	—	↓
	R	21	−17	9	−17.1	—	↓	17	−30	12	−7.11	—	↓
Hypothalamus	L	−8	−6	−3	−7.66	—	↓						
	R	11	−6	−9	−6.17	—	↓						
Hippocampus	L	−33	−29	−9	−12.13	—	↓						
	R	35	−18	−16	−7.36	—	↓						
Parahippocampal	L	−33	−32	−5	−11.21	BA37	↓						
	R	24	−33	−9	−6.09	BA37	↓						

Table 4. Continued

Region	Side	Acupuncture group						Sham acupuncture group					
		Talairach			*t* value	BA	Sign	Talairach			*t* value	BA	Sign
		X	*Y*	*Z*				*X*	*Y*	*Z*			
Temporal pole	L	−44	15	−30	−7.59	BA38	↓						
	R	47	21	−23	10.53	BA38	↓						
Middle temporal gryrus	L	−56	−2	−25	−7.59	BA21	↓						
	R	58	−4	−24	−8.04	BA21	↓	59	1	−20	−13.22	BA21	↓
Inferior temporal gryrus	L	−40	−15	−20	−9.63	BA20	↓						
	R	51	−10	−35	−8.27	BA20	↓						
Middle occipital gryrus	L	−35	−65	26	−24.58	BA39	↓						
	R							32	−94	12	−9.89	BA18	↓
Postcentral gyrus	R	48	−21	39	16.65	BA3	↑						
Precuneus	L	−11	−64	34	16.88	BA7	↑						
	R	9	−69	45	15.97	BA7	↑	5	−45	18	−8.04	BA 30	↓
Parietal inferior lobe	L	−29	−54	45	18.01	BA7	↑						

ACC, anterior cingulate cortex; BA, Brodmann area; FD, functional dyspepsia; L, left; MCC, middle cingulate cortex; PCC, posterior cingulate cortex; R, right.
Up or down arrow (↑/↓) indicates whether the structure showed a signal increase or decrease, respectively.
P<0.05, family-wise error corrected with a minimal cluster size of 50 voxels.

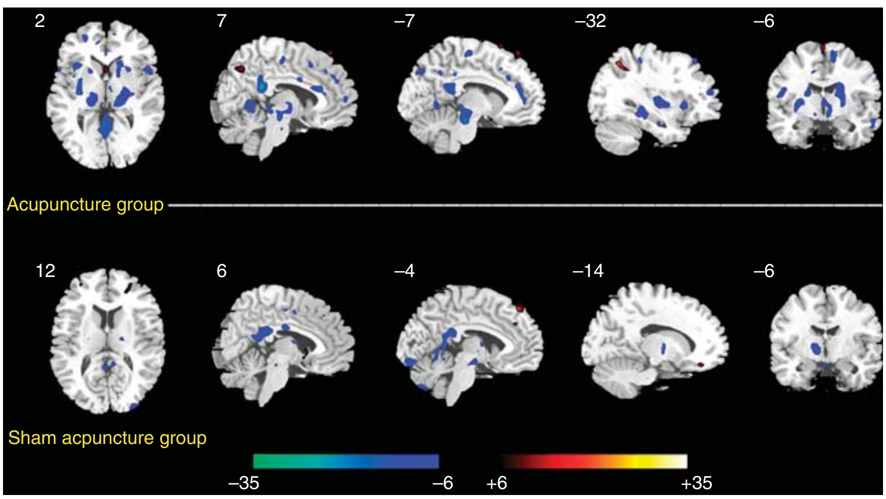

Figure 2. Cerebral glycometabolism changes in functional dyspepsia (FD) patients after treatment. Acupuncture and sham acupuncture elicited cerebral glycometabolism changes to different degrees, but acupuncture evoked more pronounced changes in cerebral activity, especially in the homeostatic afferent processing network. *P*<0.05, family-wise error corrected with a minimal cluster size of 50 voxels.

included the brainstem, thalamus, some regions in the prefrontal cortex, somatosensory cortex, and visual-related cortex. Among these areas, the glycometabolism decrease in the brainstem and thalamus were significantly related to the increase in NDI score in the acupuncture group (*P*<0.05, corrected) and tended to be associated with an increase in NDI score in the sham acupuncture group (*P*<0.1, corrected). The results suggested that the improvement of QOL might be associated with the deactivations of the brainstem and thalamus in both groups.

The brainstem is the pathway for all fiber tracts passing up and down from the peripheral nerves and spinal cord to the highest parts of the brain, and it serves as a lower center in functions such

Table 5. Comparison of the cerebral glycometabolism changes in FD patients between the acupuncture group and the sham acupuncture group (acupuncture group minus sham acupuncture group)

Region	Side	Talairach			*t* value	BA	Sign
		X	*Y*	*Z*			
Superior medial frontal gyrus	R	11	53	18	−4.46	BA11	↓
Medial frontal gyrus	R	4	−7	56	−3.77	BA6	↓
Middle frontal gyrus	L	−30	15	56	−4.85	BA8	↓
	R	31	43	−9	−5.18	BA11	↓
Precentral gyrus	R	40	−25	55	−5.46	BA4	↓
Cerebellum	R	4	−47	2	−3.82	—	↓
ACC	L	−8	25	30	−4.07	BA32	↓
	R	10	32	15	−4.11	BA24	↓
Lingual gyrus	R	4	−93	−2	−3.82	BA17	↓
Thalamus	L	17	−25	3	−3.69	—	↓
	R	19	−19	2	−4.01	—	↓
Putamen	L	−28	−9	4	−3.28	—	↓
	R	28	13	3	3.51	—	↓
Hippocampus	L	−33	−34	−6	−3.71	—	↓
Inferior temporal gyrus	R	59	−53	−7	−3.90	BA37	↓
Middle temporal gyrus	L	−50	−72	29	−3.77	BA39	↓
	R	57	−51	−8	−4.21	BA37	↓

ACC, anterior cingulate cortex; BA, Brodmann area; FD, functional dyspepsia; L, left; R, right.
Up or down arrow (↑/↓) indicates whether the structure showed a signal increase or decrease, respectively.
$P<0.001$, uncorrected with a minimal cluster size of 20 voxels.

as visceral regulation, pain sensitivity control, and consciousness. A large volume of information about the physiological status of the gut is directly transmitted to the brainstem to modulate gastric function. The thalamus acts as the “gateway to the cortex.” Its functions include relaying sensation, spatial sense, and motor signals to the cerebral cortex, along with regulation of consciousness, sleep, and alertness. Our previous study showed that cerebral glycometabolism in the brainstem and thalamus of FD patients was higher than that in healthy subjects (15) and that short-term manual acupuncture treatment decreased cerebral glycometabolism in the brainstem and thalamus of FD patients (16). In the present study, acupuncture or sham acupuncture was performed by inserting a thin needle into the skin and the underlying muscle layer and was stimulated by electricity. This procedure stimulated the somatic afferent nerves of the skin and muscles. The somatic sensory information from the body is projected to the various nuclei at the brainstem and thalamus. We predict that deactivations in the brainstem and thalamus might be the common mechanism of acupuncture and sham acupuncture, manual acupuncture, and electro-acupuncture and might not be related to acupuncture point/therapy specificity. For example, a study in healthy adults (30) demonstrated that acupuncture stimulation at either real or sham acupuncture points led to functional magnetic resonance imaging signal reduction within the thalamus.

In the current study, the similarities in both clinical improvements and cerebral responses between acupuncture and sham acupuncture were possibly due to placebo effect. Recent papers have described the effect of placebo on neural processing, and certain findings are similar to those of our study. For example, some researchers (31,32) found that both analgesia and placebo effect are accompanied by a reduction in the activation of the brainstem and thalamus. However, the differences in both clinical variables and neuroimaging data between the two groups indicated that the placebo effect did not fully explain the effect of acupuncture.

The possible mechanism of acupuncture treatment for FD. In this study, acupuncture treatment elicited more extensive and remarkable cerebral glycometabolism decrease as compared with sham acupuncture. The deactivations in the insula, ACC, prefrontal cortex, putamen, hypothalamus, hippocampus, parahippocampal gyrus, temporal pole, and other areas were found only in the acupuncture group and not in the sham acupuncture group (**Table 4**) (**Figure 2**). Furthermore, the between-group analysis indicated that the glycometabolism decreases in the thalamus, ACC, hippocampus, middle frontal gyrus, middle temporal gyrus, and cerebellum elicited by acupuncture were more significant than those elicited by sham acupuncture (**Table 5**) (**Figure 3b**).

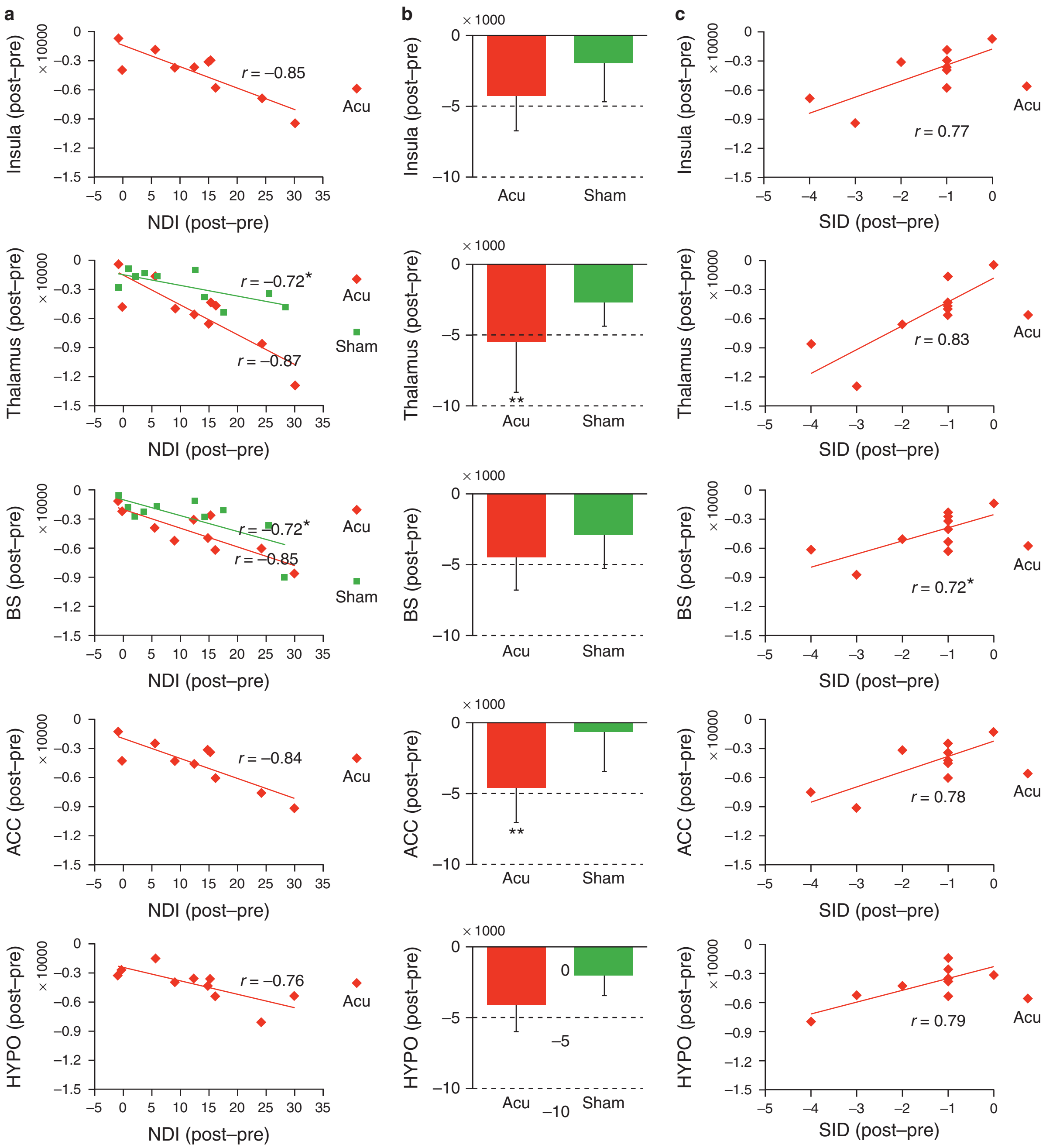

Figure 3. The correlation coefficients of brain responses and clinical variables. (**a**) In the acupuncture group, the increase in Nepean Dyspepsia Index (NDI) score was significantly related to the glycometabolism decrease in the insula, thalamus, brainstem, anterior cingulate cortex (ACC), and hypothalamus ($P<0.05$, corrected); in the sham acupuncture group, the increase in NDI score tended to be associated with the glycometabolism decrease in the brainstem and thalamus ($P<0.1$, corrected). (**b**) Compared with the sham acupuncture group, the glycometabolism in the thalamus and ACC in the acupuncture group significantly decreased ($P<0.05$). (**c**) In the acupuncture group, the decrease in Symptom Index of Dyspepsia (SID) score was significantly related to the glycometabolism decrease in the insula, thalamus, ACC, and hypothalamus ($P<0.05$, corrected); the decrease in SID score tended to be associated with the glycometabolism decrease in the brainstem ($P<0.1$, corrected). BS, brainstem; Hypo, hypothalamus; *r*, correlation coefficient; **P*<0.1, corrected; ***P*<0.05.

The majority of these deactivated regions in the acupuncture group belong to the homeostatic afferent processing network as well as the corticolimbic network.

The homeostatic afferent processing network is a brain network that is consistently activated in response to homeostatic afferent fiber activation. Nonpainful and painful visceral and somatic stimuli, as well as emotional stimuli, can activate this network (33). Our previous study (15) indicated that, as compared with healthy subjects, FD patients showed higher glycometabolism in the key regions of the homeostatic afferent processing network, including the ACC, insula, brainstem, and thalamus/hypothalamus, and that the abnormal hyperactivities of these regions were significantly related to the severity of FD symptoms. The results suggested that successful treatment should modulate the functions of this network.

Interestingly, the current study indicated that acupuncture treatment markedly decreased glycometabolism in the insula, thalamus, brainstem, ACC, and hypothalamus and that the glycometabolism decrease in these five regions is nearly all positively related to the decrease in SID score and negatively related to the increase in NDI score. This means that the deactivations in these regions were associated with the alleviation of symptoms and the improvement in QOL. However, in the sham acupuncture group, significant glycometabolism decreases in the insula, ACC, and hypothalamus were not found, and the deactivations in the thalamus and in the brainstem tended to be associated only with improvement in QOL. The results suggested that, compared with sham acupuncture treatment, acupuncture treatment might not only affect the activity of the common pathway of somatic and visceral sensation but also modulate the activity of the insula, ACC, and hypothalamus. The insula, ACC, and hypothalamus, considered the key regions of "gut–brain communication," play important roles in processing and modulating pain, emotion, and visceral sensation as well as in maintaining homeostasis (34,35). Activations in the insula, ACC, and thalamus/hypothalamus can be found in nearly all reported studies of functional gastrointestinal disorders, regardless of study paradigm and analysis method (36). In our study, the modulation of acupuncture on the insula and ACC might be related to regulation of the process of homeostatic emotion. "Homeostatic emotions" refers to motivations and feelings associated with changes in the body's physiological condition and with the autonomic responses and behaviors that restore an optimal balance (37). The insula has long been regarded as limbic sensory cortex for its association with visceral sensation, whereas the ACC is regarded as limbic behavioral motor cortex for its association with autonomic and emotional control (35). Hence, we hypothesized that the efficacy of acupuncture treatment for FD might result partly from regulating the functions of the homeostatic afferent processing network and driving the homeostatic mechanism to restore balance. According to the theory of traditional Chinese medicine, the purpose of acupuncture treatment is to maintain the equilibrium of the human body. This might be translated into the Western medicine concept that acupuncture modulates the imbalance of the homeostatic afferent processing network.

LIMITATIONS

The main limitation of this study is that the PET scan was not performed on all FD patients for the radiation of ^{18}F-FDG, so the correlation analysis of clinical variables and the brain images involved only the 20 patients (10 in each group) who finished the PET scans.

In summary, this study reported the similarities and differences in clinical efficacy and brain responses between real acupuncture treatment and sham acupuncture treatment. Modulation of the activities of the brainstem and the thalamus might be the common mechanism in real/sham acupuncture treatment. The more remarkable modulation on the homeostatic afferent processing network, especially the insula, ACC, and hypothalamus, might be the potential mechanism of acupuncture treatment for FD.

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CONFLICT OF INTEREST

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Acupuncture is being increasingly accepted as an alternative treatment for functional dyspepsia (FD) although the mechanism remains unclear.
- ✓ Neuroimaging studies indicate that the cerebral activity of FD patients differs from that of healthy subjects. Abnormal cerebral activity plays an important role in the pathogenesis of FD.

WHAT IS NEW HERE

- ✓ Modulation on the brainstem and thalamus might be the common mechanism in real/sham acupuncture treatment for functional dyspepsia (FD).
- ✓ The more remarkable modulation on the homeostatic afferent processing network, including the insula, ACC, and hypothalamus, was the potential mechanism of acupuncture treatment for FD.
- ✓ The results provide support for the use of acupuncture in treating FD in clinical practice.

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