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Acupuncture treatment modulates the corticostriatal reward circuitry in major depressive disorder

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A B S T R A C T

Major depressive disorder (MDD) is a common disorder with a high prevalence and significant social and economic impacts. Nevertheless, the treatment of MDD is far from satisfactory. Acupuncture treatment has emerged as a promising method for treating MDD. However, the neural mechanism by which acupuncture reduces depressive symptoms is not fully understood. Studies have shown that the corticostriatal reward circuitry is associated with the pathophysiology of MDD; thus, we investigated the corticostriatal resting-state functional connectivity (rsFC) before and after real and sham acupuncture treatments combined with the antidepressant fluoxetine. Forty-six female major depressive patients were assigned to either verum acupuncture plus fluoxetine ($n = 22$) or sham acupuncture plus fluoxetine ($n = 24$) treatment for 8 weeks, and resting state functional magnetic resonance imaging (fMRI) data were collected before the first and after the last treatment sessions. The results showed that compared with sham acupuncture, the verum acupuncture group showed: (1) significantly increased rsFC between inferior ventral striatum and medial prefrontal cortex, ventral rostral putamen and amygdala/parahippocampus, as well as dorsal caudate and middle temporal gyrus; (2) significantly decreased rsFC between right ventral rostral putamen and right dorsolateral prefrontal cortex, and right dorsal caudate and bilateral cerebellar tonsil. The increased rsFC between the inferior ventral striatum and medial prefrontal cortex, ventral rostral putamen and amygdala/parahippocampus were significantly positively associated with decreased clinical scores (Montgomery–Åsberg Depression Rating Scale and Self-Rating Depression Scale scores) at the end of the eight-week treatment. Our findings suggest that acupuncture may achieve treatment effects by modulating the corticostriatal reward/motivation circuitry in MDD patients.

1. Introduction

Major depressive disorder (MDD) has a high lifetime prevalence rate, and is the fourth leading cause of disability worldwide (Sackeim, 2001). Previous studies show that depression is more frequently observed in females than males (Abate, 2013; Soares and Zitek, 2008), with a female/male risk ratio roughly 2:1 (Kessler, 2003). This increased prevalence is speculated to be associated with female-specific reproductive events such as perimenstrual changes, pregnancy, the postpartum period and menopause (Cyranowski et al., 2000; Soares and Zitek, 2008). Studies suggest that the fluctuations in sex hormones during female reproductive events could influence neurochemical pathways involved in the modulation of mood and behavior linked to depression (Bloch et al.,

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2000; Schmidt et al., 1998; Soares and Zitek, 2008). Thus, it is reasonable to believe that the underlying pathophysiology between male and female MDD patients is not identical (Domes et al., 2008; Eisenberger et al., 2009; Moieni et al., 2015; Pitychoutis and Papadopoulou-Daifoti, 2010).

Although MDD affects a large proportion of the population by significantly impairing occupational, social and academic functioning (Johnson et al., 1992; Lehtinen and Joukamaa, 1994), the antidepressant medications for MDD are not fully satisfactory due to undesirable side effects and a delay in the onset of therapeutic action (Arroll et al., 2005; Chan et al., 2015). Acupuncture, however, has become a promising and effective alternative treatment for depression (Jorm et al., 2002; Kessler et al., 2001; Quah-Smith et al., 2013; Quah-Smith et al., 2012).

In addition, accumulating evidence has indicated that acupuncture combined with antidepressant medication is more effective than antidepressants alone, and is safe, well-tolerated, and has an early onset of action (Chan et al., 2015; Wang et al., 2016; Zhang et al., 2009), which embodies the potential of combining acupuncture and pharmacological treatments for depression.

A core characteristic of patients with depression is the loss of interest in pleasurable activities and limitations in multiple dimensions of well-being (Bogdan et al., 2013; Hasler and Northoff, 2011; Hwang et al., 2016; Naranjo et al., 2001; Russo and Nestler, 2013). The reward system (Bluhm et al., 2009; Naranjo et al., 2001; Pizzagalli et al., 2009) is involved in pleasure and motivation, which have been proven to play important roles in the pathophysiology of MDD (Bluhm et al., 2009; Soares and Zitek, 2008). Reward processing is complex and consists of sensory, attention and valuation components (Schultz, 2015). A number of brain structures are involved in reward processing, including the orbitofrontal cortex, medial prefrontal cortex, dorsolateral prefrontal cortex, motor cortex, parietal association cortex, visual cortex, striatum, and amygdala (Carl et al., 2016; Schultz, 2015).

The striatum is a central region of the reward circuit (Alexander et al., 1986; Braunlich and Seger, 2013; Di Martino et al., 2008; Felger et al., 2015), which receives excitatory afferents from cortical areas modulating ventral striatal activity during encoding of reward prediction and the mediation of motivational state (Choi et al., 2012; Di Martino et al., 2008). Previous studies have identified the dorsal and ventral divisions of the striatum (Alexander et al., 1990; Choi et al., 2012; Draganski et al., 2008; Leh et al., 2007). The dorsal striatal regions (including the dorsal caudate nucleus and dorsal putamen) receive inputs from the dorsolateral prefrontal cortex, which support motor and executive function, and the ventral striatal regions (including the nucleus accumbens, ventral putamen and ventromedial caudate) project to the orbitofrontal cortex, which is involved in affective division (Furman et al., 2011; Selemon and Goldman-Rakic, 1985; Voorn et al., 2004).

Reward circuit activity may be used as an effective predictor of treatment response in adolescent depression (Forbes et al., 2010; Phillips et al., 2015) with respect to neurotransmitter abnormalities in the striatum in depression (Ebert et al., 1996; Martin et al., 2001). Interpersonal psychotherapy and venlafaxine hydrochloride can increase blood flow in the striatum (Martin et al., 2001). Deep brain stimulation to the ventral striatum, especially the nucleus accumbens, has also been applied to treat adults with severe depression (Schlaepfer et al., 2008).

Previous studies suggest that the autonomic nervous system (ANS), particularly the vagus nerve, may be an important mediator of acupuncture needle stimulation (Janig, 2006; Kavoussi and Ross, 2007). Lim and colleagues (Lim et al., 2016) found that acupuncture may achieve treatment effects through vagal nerve modulation of inflammatory responses in internal organs. A recent study also showed that direct stimulation of the peripheral branch of the vagus nerve can relieve symptoms in MDD patients (Rong et al., 2016). Taken together, these studies suggest that the vagus nerve may play an important role in acupuncture treatment of depression.

In addition, a number of neuroimaging studies indicate that acupuncture could modulate activity in multiple cortical and subcortical brain areas (Chae et al., 2013; Dougherty et al., 2008; Huang et al., 2012; Hui et al., 2000, 2005; Kong et al., 2007; Kong et al., 2002; Meng et al., 2014; Shan et al., 2014) involved in cognition, somatosensory processing, pain, and affective/emotional processing (Sun et al., 2011; Zhang et al., 2012). Animal studies have shown that acupuncture stimulation facilitates the normalization of striatum activity and improves motor function in mouse models of Parkinson's Disease (Kim et al., 2011). In a previous study, we found functional magnetic resonance imaging signal changes in the orbitofrontal cortex, which is a region involved in reward and endogenous opioid modulation during acupuncture analgesia (Dougherty et al., 2008).

In recent decades, rsFC has drawn the attention of investigators. The rsFC measures the temporal dependency of neuronal activation patterns between anatomically separated brain regions during rest (Biswal et al., 1995). This approach helps to better elucidate the function of one brain region in terms of network and explore how brain regions sub-serve the common cognitive procedures (Bullmore and Sporns, 2009). For instance, Felger and colleagues (Felger et al., 2015) found that the corticostriatal reward circuitry rsFC decreased with increased symptoms of depression, and the rsFC between the ventral striatal and ventral medial prefrontal cortex was related to increased anhedonia, while the dorsal striatal rsFC was related to reduced motor function.

Recently, rsFC has been used to investigate the underlying mechanism of acupuncture in healthy subjects (Bai et al., 2009; Dhond et al., 2008; Hui et al., 2009; Liu et al., 2009; Qin et al., 2008; Zhong et al., 2012) and patient populations, such as patients with MDD (Deng et al., 2016; Yi et al., 2012), knee osteoarthritis (Chen et al., 2015; Egorova et al., 2015), migraines (Li et al., 2016) and Alzheimer's disease (Wang et al., 2014). For instance, investigators found that peripheral nerve stimulation and acupuncture can significantly modulate the rsFC of the default mode network (Deng et al., 2016; Fang et al., 2016), amygdala (Liu et al., 2016), and anterior cingulate cortex (Yi et al., 2012) in MDD patients. Taken together, these results suggest that rsFC can be a useful tool to investigate the mechanism of acupuncture treatment of MDD.

In this study, we investigated the corticostriatal rsFC changes before and after verum and sham acupuncture treatment plus fluoxetine in females with depression. We only recruited female patients to increase the homogeneity of this study. Considering the different corticostriatal projections, we divided the striatum into ventral and dorsal striatal regions based on previous studies (Di Martino et al., 2011; Di Martino et al., 2008; Felger et al., 2015; Furman et al., 2011; Gabbay et al., 2013; Harrison et al., 2009; Kelly et al., 2009; Kwak et al., 2010). We hypothesized that compared with sham acupuncture plus fluoxetine, verum acupuncture plus fluoxetine treatment could effectively modulate the corticostriatal rsFC, and changes in rsFC before and after acupuncture treatment may be associated with corresponding changes in depressive symptoms.

2. Materials and methods

In our previous study, we reported how acupuncture plus fluoxetine treatment modulates the rsFC of the amygdala related network (Wang et al., 2016). In this manuscript, we focus on how acupuncture modulates the rsFC of the extended corticostriatal network using a seed-to-whole-brain method, which has never been reported before.

2.1. Participants

The study protocol was approved by the Institutional Review Board of the 2nd Affiliated Hospital of Guangzhou University of Chinese Medicine. The study was enrolled online on the Chinese Clinical Trial Registry (ChiCTR) (www.chictr.org.cn, ChiCTR-TRC-14005228). Each subject provided written informed consent before participation in the study. Patients with MDD were recruited for this study through community postings, and all eligible participants were required to meet the specific inclusion/exclusion criteria.

2.2. Inclusion criteria

1) Women meeting the criteria of depression in ICD-10; 2) aged 30–60 years old and able to provide voluntary informed consent; 3) standard scores of the Self-Rating Depression Scale (SDS) $\geq$ 53 or total scores of Montgomery-Åsberg Depression Rating Scale (MADRS) $\geq$ 14 (Ball et al., 2016; Daniel et al., 1999; Treasure and Treasure, 1987; van Noorden et al., 2012); 4) exhibit normal cognitive functioning, and with no aphasia and intellectual disabilities; 5) have primary school education or higher; and 6) right-handed.

In this study, the liver function of all the participants was tested using alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and kidney function was tested using blood urea nitrogen (BUN) and creatinine tests (Cr). All participants' test results were within normal ranges, and there were no significant differences between the two groups in the liver and kidney function tests. All patients received a physician screening and completed self-reports to determine comorbidities. The structural clinical interview was not applied.

2.3. Exclusion criteria

1) Pregnant or breastfeeding women; 2) patients with severe damage of liver, kidney function, or with neurological deficits, rheumatologic disorders, cardiac disease, diabetes, malignant tumors and any other significant systemic disorders that might affect the results; 3) presence of any somatic diseases (such as cerebral infarction, cerebral hemorrhage, Parkinson's or cerebral tumor) and any other significant systemic disorders that might affect the results; 4) presence of severe psychoses (schizophrenia, mania, paranoid psychosis and depression with suicidal intent) or dementia; 5) use of antipsychotics or antidepressants within a month before the study; 6) consumption of alcohol or illicit substances; 7) women with metallic implants; and 8) refused to sign informed content.

2.4. Intervention

All participants were given fluoxetine (20 mg) by mouth once per day, and then they were randomly assigned to verum or sham acupuncture groups.

2.5. Verum and sham acupuncture administration

Verum acupuncture: Abdominal acupuncture was the school of acupuncture chosen for this study (Zhiyun, 2001), as several studies have shown that abdominal acupuncture treatment is effective for treatment of depression (Cheng and Tang, 2007; Wang et al., 2010; Wu et al., 2012).

Abdominal acupuncture uses only acupoints in the abdomen. It only produces mild sensations, thus making it more acceptable to patients. The rationale of abdominal acupuncture is that CV 8 (umbilicus) plays a crucial role in propelling and regulating the flow of Qi (Zhiyun, 2001); thus, the acupoints around the CV 8 in the abdomen may regulate the flow of Qi more efficiently.

Based on a previous study from our group (Wang et al., 2008), the acupoints applied in this study were: Zhongwan (RN12), Xiawan (RN10), Qihai (RN6), Guanyuan (RN4), Shangqu (KL17), Huaroumen (ST24), and Qipang (extra-point) (Fig. 1). These acupoints are close to important meridians and can easily communicate with five zang and six fu organs through channels like the Conceptional Vessel, Governor Vessel, Thoroughfare Meridian and Belt Meridian. This prescription could harmonize zang-fu five viscera, tonify qi, and replenish blood to relieve depression.

An acupuncturist with at least 3 years of experience administered all acupuncture treatments. Before abdominal acupuncture administration, subjects were instructed to lie in a supine position and place a mask over their eyes. Next, the subject's abdomen was exposed and the skin was disinfected at the acupuncture points. Then, an acupuncture specialist inserted fine needles (0.22 mm $\times$ 40 mm) through short plastic tubes or sheaths. The needles were inserted intramuscularly to a depth of 15–20 mm and were left in situ for 20 min. The patient's abdomen was covered with a basket underneath a sheet during the treatment period.

To accumulate the effect of acupuncture quickly and enhance the motivation and compliance of patients at the beginning of the study, patients received abdominal acupuncture once a day for the first three days and subsequently once every three days for the reminder of the 8-week trial.

Sham acupuncture operation: The acupoints were the same as in the treatment group. Before abdominal acupuncture administration, subjects were instructed to lie in a supine position and put a mask over the eyes. Then, the subject's abdomen was exposed and the skin was disinfected at the acupoints. Next, short plastic needle sheaths not containing any needles were tapped against the skin at the patient's acupoints, but no needles were inserted into the skin through the sheaths. The patient's abdomen was covered with a basket underneath a sheet during the 'treatment' period. The time

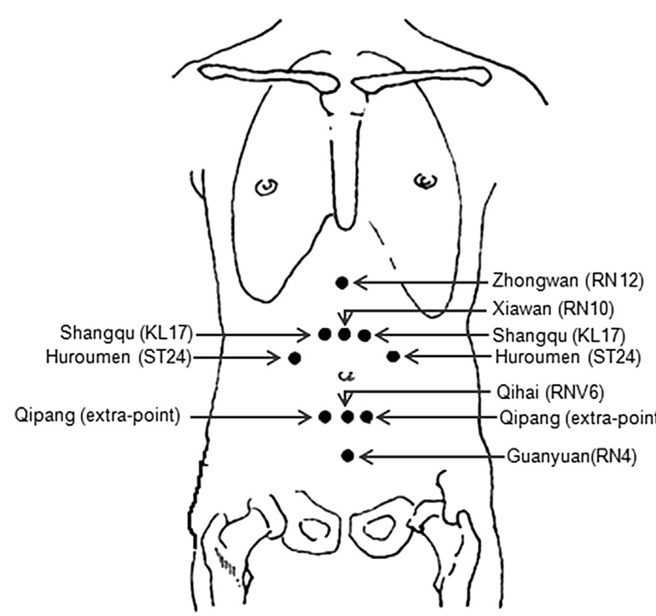

Fig. 1. Locations of acupoints applied in this study.

and frequency of the sham abdominal acupuncture treatments were the same as in the acupuncture group.

2.6. Clinical outcomes

The evaluations used to assess clinical outcomes of this study were MADRS and SDS, evaluated before the first treatment and after the last treatment.

2.7. MRI data acquisition

The fMRI brain imaging acquisition was conducted on a 1.5 Tesla Siemens Avanto scanner. High-resolution brain structural images were acquired with a T1-weighted three-dimensional multi-echo magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (repetition time: 1900 ms, echo time: 2.3 ms, data matrix: 256×256, field of view: 256 mm $\times$ 256 mm, slice thickness 1 mm, flip angle: 15°, and 176 sagittal slices covering the whole brain). T2*-weighted functional images encompassing the whole brain were acquired with the gradient-echo EPI sequence (echo time: 30 ms, repetition time: 2000 ms, data matrix: 64×64, field of view: 240 mm, flip angle: 90°, slice thickness: 4 mm, interslice gap: 0.88 mm, 31 slices paralleled by anterior commissure-posterior commissure line, and 180 time points). Two 6-min resting state fMRI scans were applied while the subjects were required to keep their eyes closed.

2.8. Statistical analysis

2.8.1. Clinical data analysis

Statistical analysis was performed using SPSS 19.0 Software (SPSS Inc., Chicago, IL, USA). Two sample t-tests were applied to compare the baseline characteristics of the subjects between groups. Analysis of covariance ANCOVA was applied to compare primary and secondary outcomes. Age was included in the model to adjust the effects.

2.8.2. Resting-state fMRI data analysis

Functional BOLD data were preprocessed using SPM8 (Statistical Parametric Mapping. Welcome Department of Cognitive Neurology, London, UK; implemented by MATLAB R3012b, Math Works, Inc., Natick, MA, USA). During the preprocessing, images were realigned, segmented and co-registered to each subject's high-resolution T1 scan, which was used to normalize to the standard Montreal Neurological Institute (MNI) template. Images were also smoothed using an 8 mm full-width at half-maximum (FWHM) Gaussian kernel, filtered with a frequency window of 0.008–0.09 Hz. In addition to these steps, we employed segmentation of gray matter, white matter, and cerebrospinal fluid (CSF) areas for the removal of temporal confounding factors (white matter and CSF) (Whitfield-Gabrieli and Nieto-Castanon, 2012). Finally, data were then submitted to motion correction using the artifact detection toolbox (http://www.nitrc.org/projects/artifact_detect/). Time points in subjects' scans were marked as outliers if the global signal exceeded three standard deviations from the mean or if scan to scan motion exceeded 0.5 mm deviation (Redcay et al., 2013).

Resting-state functional connectivity analysis was conducted using the CONN toolbox v15.g (Whitfield-Gabrieli and Nieto-Castanon, 2012) (http://www.nitrc.org/projects/conn). We used a priori ventral striatum seeds centered on ventral and dorsal striatal regions (Fig. 1a), (Supplementary Table S1) (Felger et al., 2015). The ventral striatal areas are inferior ventral striatum (iVS) (including nucleus accumbens) and ventral rostral putamen (vrP), and the dorsal striatal subdivisions are dorsal caudal putamen (dcP) and dorsal caudate (dC). The ventral and dorsal regions were assessed separately. Functional connectivity measures were computed between each of these seeds and every other voxel in the brain. First-level correlation maps were produced by extracting the residual BOLD time course from each ventral striatal seed and by computing Pearson's correlation coefficients between that time course and the time courses of all other voxels in the brain. Correlation coefficients were transformed into Fisher's z scores, which increases normality and allows for improved second-level General Linear Model analyses.

The treatment effect (post-treatment minus pre-treatment) on striatum seed-to-voxel rsFC between group analyses (verum vs sham) was performed using two sample t-tests. A threshold of a voxel-wise $p < 0.005$ (uncorrected) and cluster-level $p < 0.05$ (FDR correction) were applied for data analyses.

We also conducted an exploratory regression analysis to investigate the association between corticostriatal rsFC modulated by acupuncture treatment effect and the clinical outcome changes (Cullen et al., 2014; Esterman et al., 2010). To do this, we extracted the peak z value from the significant cluster resulting from group analysis from each participant's corticostriatal rsFC z score map. Within the verum and sham acupuncture group, regression analyses were computed on theses z scores with changes of clinical outcomes, with ages included as covariates.

3. Results

3.1. Patient characteristics

Forty-six subjects (22 in acupuncture group, 24 in sham group) were recruited into the study, and only thirty-six subjects (18 in acupuncture group, 18 in sham group) were scanned twice (week 0 and week 8). Four subjects from the verum acupuncture group dropped out (3 due to only scan once and 1 due to a scheduling

Table 1
Demographic and clinical characteristics of participants in this study.

Characteristic	Conditions	Acupuncture Mean (SD)	Sham Mean (SD)	Statistic	*p*-value
N		18	18		
Age (years)		44.5 (10.47)	43.78 (9.10)	$t_{(34)} = 0.22$	0.83
BMI		21.45 (2.51)	20.82 (2.36)	$t_{(34)} = 0.77$	0.45
MADRS	pre-treatment	22.94 (7.36)	22.83 (9.17)	$F_{(1,33)} = 0.001$	0.97
	post-treatment	5.44 (5.37)	14.06 (4.39)	$F_{(1,33)} = 26.86$	<0.01
	post-pre	−17.5 (7.89)	−8.78 (7.94)	$F_{(1,33)} = 10.86$	<0.01
SDS	pre-treatment	47.833 (6.46)	47.44 (9.23)	$F_{(1,33)} = 0.01$	0.94
	post-treatment	26.83 (6.46)	34.94 (5.40)	$F_{(1,33)} = 16.29$	<0.01
	post-pre	−21.00 (9.11)	−12.50 (8.65)	$F_{(1,33)} = 8.21$	<0.01

Abbreviations: BMI, Body Mass Index; MADRS, Montgomery-Asberg Depression Rating Scale; SDS, Self-rating Depression Scale; ‘post-pre’ means treatment effect between pre- and post-treatment.

Table 2
Regions showed significantly increased connectivity of corticostriatum to other brain regions after acupuncture treatment and sham treatment, controlling for age as a covariate (voxel-wise, $p < 0.005$, uncorrected; cluster–wise, $p < 0.05$, FDR corrected).

Conditions	Seeds	Brain regions	Brodmann area	mm^3	Cluster centroid (MNI)			z-value
					x	y	z	
Verum acupuncture > sham acupuncture	iVS							
	Right	Left rMPFC	BA10	246	−6	60	24	3.54
		Right occipital gyrus	BA18	1028	42	−94	−4	4.19
		Left inferior occipital gyrus	BA19	314	−40	−74	−4	4.1
	Left	No regions survive the threshold						
	vrP							
	Left	Right amygdala/parahippocampus		398	22	−10	−10	4.72
	Right	No regions survive the threshold						
	dcP							
	Right	Right lingual/fusiform gyrus	BA18	621	20	−72	−4	4.27
		Left lingual/fusiform gyrus	BA19	364	−34	−72	0	4.14
		Right cuneus gyrus	BA17	214	18	−88	8	3.6
	Left	No regions survive the threshold						
	dC							
	Left	Bilateral cuneus gyrus	BA18	2003	−16	−82	22	4.82
	Right	Left middle temporal gyrus	BA39	344	−26	−52	34	4.63
Verum acupuncture < sham acupuncture	vrP							
	Right	Right DLPFC	BA9	276	36	42	38	3.81
	dC							
	Left	Right cerebellar tonsil		235	16	−38	−40	4.09
		Left cerebellar tonsil		270	−20	−44	−44	4.07

Abbreviations: iVS, inferior ventral striatal; vrP, ventral rostral putamen; dcP, dorsal caudal putamen; dC, dorsal caudate; rMPFC, rostral medial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex.

conflict), six subjects from the sham acupuncture group dropped out (2 uncomfortable with treatment, 1 due to a scheduling conflict, and 3 due to only scan once). All analyses were based on these 36 subjects who completed the study.

There were no significant differences between the two groups with respect to age, scale of MADRS, and SDS at baseline (Table 1). After treatment, ANCOVA analysis (dependent variable is the change (post- minus pre-treatment) of MADRS/SDS score, the independent is the type of treatments (verum or sham), and covariate variables are age of participants) showed a significant difference between the verum and sham acupuncture groups on both MADRS and SDS scores and verum acupuncture showed significantly greater clinical improvement (Table 1).

Given the important role of the reward network in anhedonia, we also compared the anhedonia changes between the two treatment groups using the item “Inability to feel” from MADRS. ANCOVA analysis showed that there was no significant anhedonia difference between the verum acupuncture plus fluoxetine group and sham group at baseline ($F_{(1, 33)} = 0.001$, $p = 0.972$), but there was a significant difference after treatment between the two groups ($F_{(1, 33)} = 7.353$, $p = 0.011$). The verum acupuncture plus fluoxetine treatment produced greater treatment effects (post-treatment minus pre-treatment) ($F_{(1, 33)} = 4.551$, $p = 0.040$) in the anhedonia subscale (Table 1).

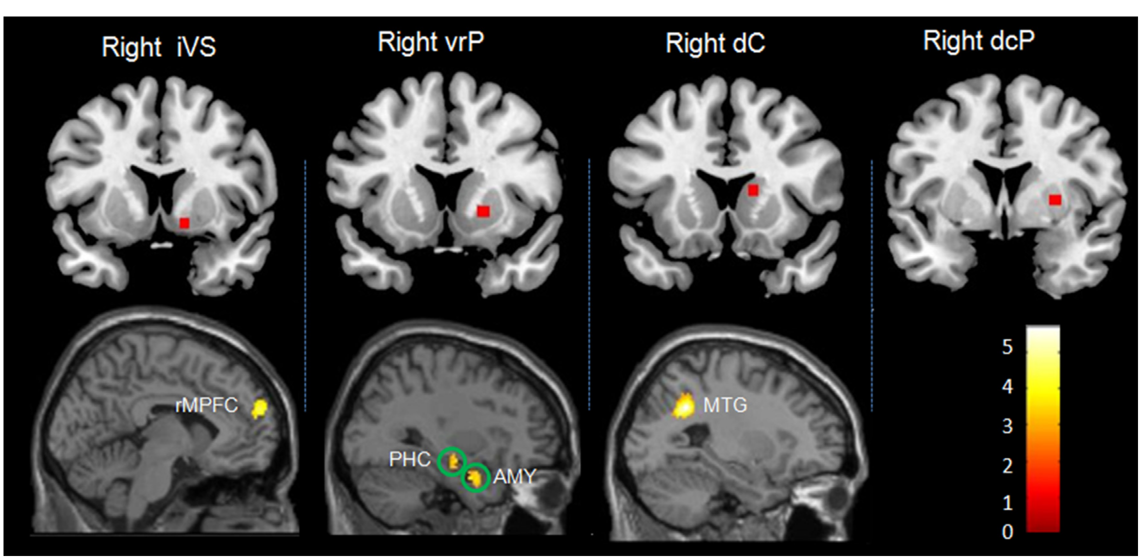

Fig. 2. Top row indicates locations of striatum seeds. Bottom row indicates the corresponding significant rsFC changes (post minus pre) evoked by verum acupuncture as compared with sham treatment. iVS, inferior ventral striatum; vrP, ventral rostral putamen; Dc, dorsal caudate; dcP, dorsal caudal putamen; rMPFC, rostral medial prefrontal cortex; PHC, parahippocampus; AMY, amygdala; MTG, middle temporal gyrus. Images were presented in neurological orientation.

3.2. Resting state functional connectivity results

After 8 weeks of treatment, compared with sham acupuncture plus fluoxetine, the verum acupuncture plus fluoxetine group showed significantly increased rsFC in both the ventral and dorsal striatal areas with cortical cortices. In particular, there were greater rsFC increases in the rsFC of right iVS-left rostral medial prefrontal cortex (rMPFC), left vrP – right amygdala (AMY)/parahippocampus (PHC) and right dC – left middle temporal gyrus (MTG) (Table 2, Fig. 2). Verum acupuncture plus fluoxetine induced greater decreased rsFC between right vrP-right dorsolateral prefrontal cortex (DLPFC) and left dC-bilateral cerebellar tonsil compared with sham acupuncture treatment. We also found increased rsFC between striatum seeds and occipital regions in verum acupuncture plus fluoxetine group compared to the sham group, i.e. rsFC increased between right iVS-bilateral lingual gyrus, right iVS-right fusiform gyrus, and right iVS-left cuneus gyrus; right dcP – bilateral fusiform gyrus, right dcP- right cuneus gyrus and left dC – bilateral cuneus (Table 2).

To further explore the association between the rsFC changes and the corresponding clinical outcome changes, we extracted the increased rsFC z scores (peak with 3 mm radius) of left rMPFC, right AMY/PHC and MTG. We only focused on the rsFC changes from rMPFC, AMY/PHC and MTG because previous studies suggested these regions may play important roles in the neuropathology of MDD (Drevets, 2001; Ma et al., 2012). Then we applied a multiple regression analysis to investigate the association between the rsFC changes and the corresponding improvement of clinical outcomes, including age as a covariate across all participants. The results showed that the standardized reduction of depressive symptoms of MADRS negatively correlated (FDR corrected) with rsFC of iVS-rMPFC ($p = 0.009$), vrP-AMY/PHC ($p = 0.048$), and dC-MTG ($p = 0.009$). In addition, the standardized reduction of depressive symptoms of SDS was significantly negatively correlated with rsFC of vrP-AMY/PHC ($p = 0.048$) and dC-MTG ($p = 0.016$).

4. Discussion

In this study, we investigated the corticostriatal rsFC changes before and after 8 weeks of acupuncture plus fluoxetine treatment as compared with sham acupuncture plus fluoxetine in females with depression. The results showed a significant remission of depression symptoms in the verum acupuncture plus fluoxetine group compared with the sham group. In addition, we also found verum acupuncture plus fluoxetine can significantly increase the rsFC of the corticostriatal reward circuits and decrease the rsFC of the striatal-cerebellar regions. The rsFC changes in the cortico-striatum are also significantly associated with the symptom severity changes as indicated by MADRS and SDS scores, implying that acupuncture plus fluoxetine may achieve treatment effects by modulating the rsFC of corticostriatal reward circuits.

Consistent with previous studies (Chan et al., 2015; Duan et al., 2008; Liu et al., 2008; Roschke et al., 2000; Zhang et al., 2009), we found that the acupuncture stimulation plus fluoxetine could significantly relieve symptoms of depression, including anhedonia, compared with sham acupuncture plus fluoxetine treatment. In addition, we found that the symptoms in the sham acupuncture plus fluoxetine group showed a significant decrease after treatment (MADRS: $p < 0.001$; SDS: $p < 0.001$). We speculate that this may be attributed to the treatment effect of fluoxetine (Lam et al., 2016). The additional effect of verum acupuncture demonstrated that acupuncture can be combined with pharmacological treatments to achieve greater therapeutic effects in MDD patients.

Our results showed that the ventral corticostriatum (iVS and vrP) was more affected by verum acupuncture plus fluoxetine treatment than by sham acupuncture plus fluoxetine treatment. Specifically, we found that the rsFC was significantly increased between the right iVS-left rMPFC and the left vrP-right AMY/PHC. This result is consistent with previous studies showing the ventral striatum plays an important role in acupuncture treatment (Lee et al., 2015; Li et al., 2016; Pariente et al., 2005). The rMPFC is an important region dedicated to representing the hedonic properties of reward, focusing on learning appropriate action-reward contingencies, and selecting those actions that potentially lead to reward (Ridderinkhof et al., 2004). Studies found that the MPFC showed significant rsFC with subdivisions of striatal areas, especially with the ventral striatum (Felger et al., 2015; Meng et al., 2014). A previous study in MDD patients (Furman et al., 2011) showed attenuated rsFC between VS-MPFC in MDD compared with healthy controls. A previous study from our group also found verum acupuncture can significantly increase the rsFC between the MPFC and ventral striatum in knee osteoarthritis patients (Chen et al., 2014).

Previous studies found that the rate of reduction of anxiety symptoms was associated with the reactivity of the ventral striatum and MPFC (Forbes et al., 2010; Fu et al., 2013; Phillips et al., 2015). Felger and colleagues (Felger et al., 2015) observed a negative correlation between decreased rsFC of left iVS-vmPFC and increased anhedonia subscale of the Inventory of Depressive Symptomatology-Self-Report in MDD. Consistent with the above studies, we also found the increased rsFC of iVS-mPFC was negatively correlated with standardized symptom reduction as measured by MADRS and SDS scores.

At a less conservative subthreshold (voxel wise $p < 0.01$, cluster wise $p < 0.05$, FDR correction), we found that verum acupuncture increased the rsFC of right vrP- rMPFC ($p = 0.02$; peak Z value: 3.66; peak: 12, 72, 14 and voxel number: 503). The rsFC between vrP-MPFC is also found in healthy controls (Di Martino et al., 2008). Felger and colleagues also found (2015) decreased right vrP-MPFC rsFC was negatively correlated with increased anhedonia. We also observed verum acupuncture plus fluoxetine treatment enhanced the rsFC between left vrP-AMY/PHC, which is negatively associated with the rate of symptom reduction. The vrP-AMY/PHC circuit is important to explain the increased memory sensitivity for negative stimuli in depressed subjects compared with healthy controls (Hamilton and Gotlib, 2008). The verum acupuncture plus fluoxetine treatment decreased the right vrP-right DLPFC more than sham acupuncture plus fluoxetine treatment. The DLPFC is one important region involved in emotion regulation (Erk et al., 2010; Goldin et al., 2008; Hwang et al., 2015; Staudinger et al., 2011), and the DLPFC could modulate the putamen activity during reappraisal of reward anticipation (Staudinger et al., 2011).

In our study, the verum acupuncture plus fluoxetine treatment significantly increased rsFC changes between right dC-left MTG and right dC-bilateral cuneus compared with the sham acupuncture plus fluoxetine treatment. Recent studies found that brains of patients with MDD showed reduced activity in the temporal lobe and caudate during reward/decision-making processing as compared to healthy controls (Segarra et al., 2016; Yang et al., 2016). Resting-state fMRI studies also found that depressive disorders were accompanied by increased amplitude of low-frequency fluctuations in the temporal gyrus (Liu et al., 2011) and lower effective connectivity from the temporal lobe to caudate (Gao et al., 2016). As the temporal lobe is involved in motor-sensory control and perception (Kilintari et al., 2014; Xu et al., 2015), we speculate that the dorsal caudate's influence on the temporal cortex and visual areas may have an impact on the somatization effects of MDD, including sleep disturbance and pain conditions such as tension headaches and musculo-tendinous pain. More studies are needed to investigate the association between the striatum and temporal lobe.

Another finding of our present study is that we found increased rsFC changes between subdivisions of striatal regions with occipital regions and decreased rsFC changes with the cerebellum (Table 2). Despite its roles in motor coordination and motor behavior (Flourens, 1842), the cerebellum is also involved in cognition and emotional processing through interaction with other brain areas (D'Angelo and Casali, 2013; Xi-Jian et al., 2013), such as the prefrontal cortex, temporal lobe, amygdala and striatum. Many previous studies have demonstrated the abnormal activity of the cerebellum and occipital areas (Guo et al., 2011; Liu et al., 2010; Peng et al., 2011; Wang et al., 2012) in MDD. Thus, it is important to consider whether the posterior brain is home to the longer-term consolidated effects of acupuncture (Huang et al., 2012; Hui et al., 2005; Li et al., 2008; Yoo et al., 2004; Zhang et al., 2015). In this case, acupuncture treatment could benefit the depressed patient by increasing his or her resilience to a recurrent depressive episode.

There are several limitations in our study. First, we only recruited females with depression to increase the homogeneity of the study, and thus our external validity may only be applied to interpret the acupuncture mechanism on female patients. Secondly, the exploratory association analyses may induce variance inflation between the rsFC changes and the corresponding clinical outcome changes (Esterman et al., 2010), and thus other approaches are needed to explore the relationship between the acupuncture treatment effect and clinical outcome changes. Finally, we only focus on the effect of acupuncture treatment plus fluoxetine in this study; there is no placebo fluoxetine, which prevents us from exploring the effect and mechanism of fluoxetine as well as the interaction between fluoxetine and acupuncture.

In conclusion, we found that verum acupuncture modulates the rsFC of the ventral and dorsal portions of the striatum differently; the ventral portion of the striatum showed increased rsFC with the medial prefrontal cortex following acupuncture treatment, but the dorsal portion showed increased rsFC at the temporal cortex and visual areas. The observed rsFC change of the corticostriatum was associated with clinical improvement in MDD patients, and the modulation process is believed to be underlying acupuncture treatment of MDD.

Contributors

Experimental design: XYW, BL, GNN, KCS.
Data collection: JL, JC, XL, BL, GNN, KCS.
Data analysis: ZJW, JK.
Manuscript preparation: ZJW, JK, XYW, JL, KJ, RWH, ML, BL.

Conflict of interest statement

All authors declare no conflict interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2016.09.014.

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