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Acupuncture Stimulation on GB34 Activates Neural Responses Associated with Parkinson's Disease

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SUMMARY

Background: Parkinson's disease (PD) is a degenerative brain disorder that is caused by neural defects in the substantia nigra. Numerous studies have reported that acupuncture treatment on GB34 (Yanglingquan) leads to significant improvements in patients with PD and in PD animal models. Studies using functional magnetic resonance imaging (fMRI) have shown that patients with PD, compared to healthy participants, have lower neural responses in extensive brain regions including the putamen, thalamus, and the supplementary motor area. **Objective:** This study investigated the reported association between acupuncture point GB34 and PD. **Methods:** Using fMRI, neural responses of 12 patients with PD and 12 healthy participants were examined before and after acupuncture stimulation. **Results:** Acupuncture stimulation increased neural responses in regions including the substantia nigra, caudate, thalamus, and putamen, which are impaired caused by PD. **Conclusions:** Areas associated with PD were activated by the acupuncture stimulation on GB34. This shows that acupuncture treatment on GB34 may be effective in improving the symptoms of PD. Although more randomized controlled trials on the topic will be needed, this study shows that acupuncture may be helpful in the treatment of symptoms involving PD.

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Introduction

Acupuncture, used in Eastern Medicine, is increasingly gaining focus as a form of complementary treatment [1–3]. According to survey, it was found that 61% [4] of patients with PD in Singapore and 76% [5] of patients with PD in Korea reported using complementary treatment, with acupuncture being the most frequent method used. In Washington State, a recent survey revealed that 32% of the hospices offer acupuncture as complementary treatment to patients with PD [6]. Accordingly, many studies have been performed to prove the efficacy of this treatment [7–10]. Several studies have reported that acupuncture treatment leads to significant improvements in patients with PD [1,11,12] and significant neuroprotective effects in PD animal models [10,13–15]. Acupuncture prevents 6-hydroxydopamine-induced neuronal death in the nigrostriatal dopaminergic system in the rat PD model [10,13] and inhibits the microglial activation and inflammatory events in the MPTP-induced PD mouse model [15]. Proteomic analysis of the neuroprotective mechanisms of acupuncture treatment suggests that acupoint GB34-specific acupuncture changes protein expression profiles in the substantia nigra in favor of dopamine neuronal survival [14]. In addition, research using neuroimaging demonstrated that acupuncture stimulations can activate neural responses [1,16].

Previous functional neuroimaging experiments have studied event-related neural responses induced by acupuncture stimulations [17,18]. However, recent studies suggest that neural responses in event-related performances also rely on the integrity of the resting-state network [19,20]. With fMRI, the functional changes in neural responses after removal of the acupuncture needle can be evaluated. The results of these studies demonstrate that the resting-state network could be altered after acupuncture stimulation and removal of the needle [19,21,22].

In fMRI studies on healthy participants, the medial prefrontal cortex, posterior cingulate cortex, precuneus, lateral parietal, and medial temporal cortices were reported to exhibit a default mode network [23]. However, patients with PD were shown to have different default mode networks compared to the healthy participants [24]. In these studies, patients with PD not only showed less deactivation of the posterior cingulate cortex and the precuneus, but even demonstrated a reversed pattern of activation and deactivation [24].

Recently, a new method called regional homogeneity (ReHo) has been used to investigate functional modulations during the resting state in patients with Alzheimer's disease [25], schizophrenia [26], and PD [27]. ReHo reflects the temporal homogeneity of the regional BOLD signal. As the BOLD signal of fMRI may reflect neural activity [28], abnormal ReHo is possibly relevant to the changes of the temporal aspects of neural activity in the regional brain, and then, ReHo may detect the brain regions with abnormal activity. In the patients with PD, ReHo was lower in certain brain regions including the putamen, thalamus, and supplementary motor area, and higher in other areas including the cerebellum, primary sensorimotor cortex, and premotor area [27]. In the current study, ReHo was used to investigate whether acupuncture modulates the resting-state network associated with PD.

In this fMRI study on acupuncture, the following hypothesis arose from a review of the scientific literature: acupuncture stimulation modulates the resting-state networks not only in healthy participants but also in patients with PD. Neural responses between healthy participants and patients with PD were expected to differ. Moreover, it was predicted that acupuncture would modulate the areas associated with PD, which could help clarify the efficacy of acupuncture.

Methods

Participants Allowed

Twenty-four volunteers participated in this study following written informed consent procedures according to the institutional guidelines of the Human Research Committee. Twelve participants were idiopathic patients with PD (mean age: 53.5 years [range: 38–72], six men), whereas 12 volunteers were healthy participants, matched for age (mean age: 55.9, [range: 35–71]) and gender (six men). Participants with PD were diagnosed with clinically definite idiopathic PD by a neurologist, and participants with medical histories of other neurological illnesses were excluded. All were studied in the "off" condition; 12 h after all anti-parkinsonian drugs had been withheld. Disability was assessed immediately after the patients were scanned. All had Hoehn and Yahr stage [29] 1, 2, or 2.5. The mean Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) motor score was 7.8 (SD = 3.9 points). All patients with PD were right-handed as verified by Edinburg Handedness Inventory [30]; their mean score was 99.58% (SD = 1.44%). The average duration of the disease was 2.7 years. All patients with PD were responsive to either levodopa or dopamine agonists. The healthy participants were without any neurological or psychiatric history and were all right-handed as verified by Edinburgh Handedness Inventory [30]; their mean score was 100% (SD = 0%). Initial dyskinesia was left-sided in six patients, right-sided in three, and left- and right-sided in three (Table 1).

Table 1 Demographic characteristics of patients with Parkinson's disease (PD) compared to healthy participants

	HP (n = 12)	PD[a] (n = 12)
Sex (male:female)	6:6	6:6
Age (years)	55.9 ± 9.8	53.5 ± 10.9
Disease duration (years)	–	2.67 ± 2.3
Medication duration (years)	–	2.67 ± 2.3
Side of initial dyskinesia (L:R:LR)	–	6:2:3
Hoen and Yahr stage	–	1.5 ± 0.6
UPDRS motor score	–	7.8 ± 3.9
K-MMSE	–	27.8 ± 0.4
BDI II	–	15.36 ± 7.9
EHI (right:left)	12:0	12:0

HP, healthy participants; UPDRS, Unified Parkinson's Disease Rating Scale; K-MMSE, Korean Mini-Mental State Examination; BDI II, Beck Depression Inventory II; EHI, Edinburgh Handedness Inventory. aPatients with PD.

Acupuncture

An experienced Eastern medical doctor conducted acupuncture on patients with PD and healthy participants at right GB34 (Yanglingquan). For acupuncture stimulation (ACUP), the needle (0.25 × 40 mm, Dong Bang Acupuncture Inc. Sungnam, Korea) was manually inserted into the right GB34 to a depth of approximately 1.0 cm. The needle remained in the skin for 1 min and was then rotated bidirectionally for 1 min. After that, needle remained in the skin without rotation for 1 min and then the pattern of 1 min rotation and 1-min rest was repeated. For sham acupuncture stimulation (SHAM), the blunt type needle was used to poke the skin at the right GB34. In contrast to ACUP, the blunt type needle was not inserted into the skin, but only came in contact with the skin. All other aspects followed the same paradigm as for ACUP, and the blunt type needle was also rotated bidirectionally at 1Hz.

MRI Data Acquisition

A Philips 3.0 T MRI system equipped for echo planar imaging (EPI) was used for data acquisition. The fMRI paradigm started with a "REST" condition of 4 min. After both SHAM and ACUP, another "REST" condition of 4 min followed. The structural images were acquired between SHAM and ACUP for 10 min. Although the participants were told that the order was randomized, the actual order was SHAM first and ACUP second.

One hundred and twenty contiguous EPI functional volumes for "REST" and 150 for "ACUP" or "SHAM" (time repetition [TR] = 2000 ms, time echo [TE] = 35 ms, flip angle = 90°, slice thickness = 4.5, number of slices = 30, matrix = 96 × 128, field of view [FOV] = 230 × 182 × 135 mm, acquisition voxel size = 2.4 × 2.4 × 4.5 mm) were collected. During the scanning, participants remained in the supine position with their heads immobilized by cushioned supports and wore ear plugs throughout the experiment to attenuate MRI gradient noise. In addition, they were instructed to rest with their eyes closed and not to move. For spatial normalization and localization, a high-resolution T1-weighted anatomical image was acquired using a magnetization-prepared gradient echo sequence (time repetition [TR] = 9.9 ms, time echo [TE] = 4.6 ms, flip angle = 90°, slice thickness = 1 mm, number of slices = 196, matrix = 236 × 240, field of view [FOV] = 235 × 235 × 196 mm, acquisition voxel size = 1 × 1 × 1 mm).

MRI Data Analysis

The fMRI data were analyzed using SPM5 (Welcome Department of Cognitive Neurology, London, UK). The functional EPI-BOLD images were realigned, and the subject-mean functional MR images were co-registered with the corresponding structure MR images. These images were spatially normalized and transformed into a common space, as defined by the SPM Montreal Neurological Institute (MNI) T1 template.

The Kendal coefficient of concordance (KCC) was used to measure the similarity of the time series within a functional

Table 2 Resting state among healthy participants and patients with Parkinson's Disease (PD) before stimulations and after acupuncture stimulations

		Resting state before stimulation						Resting state after acupuncture stimulation					
		Statistical values		Coordinates anatomical location				Statistical values		Coordinates anatomical location			
Brain region	Hemisphere	Cluster size	*t*-value	x	y	z	Brodmann area	Cluster size	*t*-value	x	y	z	Brodmann area
Healthy participants													
Frontal lobe													
Cingulate gyrus	L	12	12.79	−4	15	35	32	–	–	–	–	–	–
Parietal lobe													
Angular gyrus	R	87	13.5	34	−62	37	39	–	–	–	–	–	–
Inferior parietal lobule	R	–	11.53	43	−43	44	40	–	–	–	–	–	–
	L	–	–	–	–	–	–	118	15.17	−38	−50	42	39/40
Temporal lobe													
Superior temporal gyrus	R	–	11.51	49	−57	16	22	–	–	–	–	–	–
	L	55	18.84	−51	−31	11	13/22/39/41	–	–	–	–	–	–
Middle temporal gyrus	R	15	13.74	54	−47	3	22	20	14.42	54	−30	0	21
	L	–	–	–	–	–	–	148	17.11	−43	−53	9	39
Supramarginal gyrus	R	61	13.31	48	−50	33	40	–	–	–	–	–	–
	L	136	13.41	−51	−52	26	40	–	–	–	–	–	–
Sublobar													
Insula	R	17	12.85	51	−23	19	13	–	–	–	–	–	–
Limbic lobe													
Posterior cingulate	R	13	11.35	4	−53	10	29	–	–	–	–	–	–
	L	–	18.85	−10	−62	14	30	–	–	–	–	–	–
Occipital lobe													
Cuneus	R	–	–	–	–	–	–	795	18.63	1	−75	32	19
Precuneus	L	546	24.48	−4	−69	27	7/31	–	10.67	−27	−57	50	7/31
Cerebellum	R	–	–	–	–	–	–	–	18.07	2	−50	5	–
Patients with PD													
Parietal lobe													
Inferior parietal lobule	L	448	23.64	−35	−53	39	40	56	15.19	−35	−50	39	40
Temporal lobe													
Middle temporal gyrus	R	–	14.77	40	−63	23	39	–	–	–	–	–	–
	L	–	17.44	−43	−63	25	39	–	–	–	–	–	–
Supramarginal gyrus	R	111	15.95	49	−52	25	40	–	–	–	–	–	–
Sublobar													
Insula	R	11	11.6	51	−35	21	13	–	–	–	–	–	–
Thalamus	L	–	–	–	–	–	–	57	15.48	−7	−11	11	–
Limbic lobe													
Posterior cingulate	R	–	–	–	–	–	–	–	14.86	4	−56	7	30
	L	–	15.71	−1	−53	13	29	–	–	–	–	–	–
Occipital lobe													
Precuneus	R	–	12.56	29	−67	34	7	368	18.29	10	−66	23	31
	L	385	16.04	−2	−72	30	7/31	–	11.86	−27	−67	35	7
Cerebellum	R	–	–	–	–	–	–	–	18.03	4	−41	0	–
	L	12	11.95	−31	−57	−34	–	–	–	–	–	–	–

The table describes the location of the peak voxel and the corresponding brain regions and Brodmann areas comprised by the cluster. Results are reported if corrected $P < 0.05$. The cluster level is at least 10 voxels per cluster, and the voxel size is 2.4 × 2.4 × 4.5 mm.

cluster based on the regional homogeneity hypothesis [31,32]. The 27 nearest neighboring voxels were defined as a cluster, and a KCC value (range 0–1) was given to the voxel at the center of this cluster. A custom software routine, Resting-State fMRI Data Analysis Toolkit (REST, http://forum.restfmri.net/rest), was used for ReHo analysis in a voxel-wise fashion. For all participants, the ReHo map was spatially smoothed with 9 mm of full width at half maximum (FWHM). In the analyses, the corrected threshold was $P < 0.05$ for the one-sample *t*-test and corrected cluster level was $P < 0.05$ for the two-sample *t*-test and the paired *t*-test [33]. Rex [34] and (SPSS Inc., Chicago, IL, USA) were used for neural signal change analysis.

Results

Psychophysical Responses

The intensities of sensations measured by an average score (with standard error bars) were reported on a scale from 0 denoting no sensation to 10 denoting an unbearable sensation among patients with PD and healthy participants during ACUP and SHAM. The sensations were compared between stimulation groups using a two-sample *t*-test, significant at $P < 0.05$ (SigmaPlot 9.0, Systat Software Inc., San Jose, CA, USA). The average stimulus intensities (mean ± SE) were approximately similar during ACUP of patients with PD (2 ± 2.4), SHAM of patients with PD (1.3 ± 2.0), ACUP of healthy participants (1.4 ± 2.1), and SHAM of healthy participants (0.9 ± 1.9). There was no significant statistical difference.

Resting-State Results Among Healthy Participants and Patients with PD Before and After ACUP

Before acupuncture stimulations, neural responses for healthy participants and patients with PD commonly demonstrated that the posterior cingulate gyrus (BA 29/30), precuneus (BA 7/31), medial prefrontal cortex, and inferior parietal lobule (BA 40), which are reported as a default mode network in the previous study, exhibited significantly higher neural responses than other brain areas. Through these results, we could confirm our data.

After ACUP, the resting state of healthy participants and patients with PD had changed (see Table 2 for complete list of regions activated).

In healthy participants, the right cuneus (BA 19), right cerebellum, left inferior parietal lobule (BA 39/40), left precuneus (BA 7/31), and left and right middle temporal gyrus (BA 21) exhibited significantly higher neural responses than other brain areas.

In patients with PD, the right cerebellum, right posterior cingulate (BA 30), left thalamus, left inferior parietal lobule (BA 40), and left and right precuneus (BA 7/31) exhibited significantly higher neural responses than other brain areas.

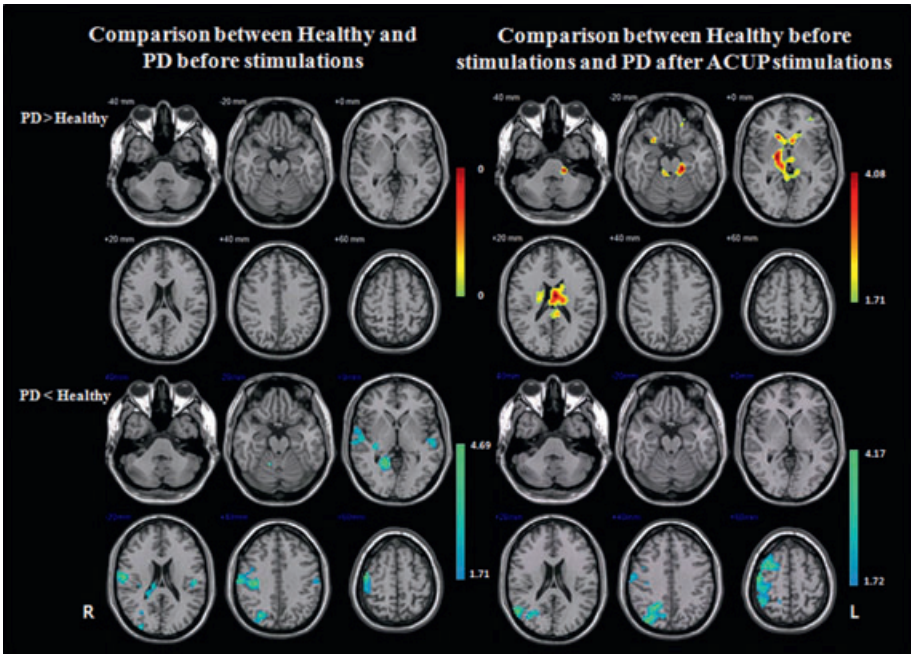

Figure 1 A comparison of the Kendall's coefficient of concordance (KCC) maps between patients with PD and healthy participants during the resting state. "PD > Healthy" indicates more activated neural responses of patients with PD compared to healthy participants, and "Healthy > PD" indicates more activated neural responses of healthy participants compared to patients with PD. "Before stimulations" means comparison of healthy participants and patients with PD before receiving any stimulation, and "Healthy before stimulations and PD after ACUP stimulations" means comparison of healthy participants before any stimulations and patients with PD after removal of the acupuncture needle. The bar is the *t*-value. Note that R, right hemisphere; whereas L, left hemisphere.

Table 3 Higher and lower neural responses among healthy participants before stimulations compared to Parkinson's Disease (PD) before and after acupuncture stimulations

		PD, compared to healthy participants before stimulations					PD after acupuncture stimulations, compared to healthy participants before stimulations				
			Coordinates anatomical location					Coordinates anatomical location			
Brain region	Hemisphere	*t*-value	x	y	z	Brodmann area	*t*-value	x	y	z	Brodmann area
		PD > Healthy participants					**PD > Healthy participants**				
Frontal lobe											
Superior frontal gyrus	L	–	–	–	–	–	3.59	−17	52	−2	10
Middle frontal gyrus	L	–	–	–	–	–	2.08	−31	43	5	10/11
Inferior frontal gyrus	R	–	–	–	–	–	2.41	24	14	−13	47
Cingulate gyrus	R	–	–	–	–	–	2.73	1	−41	27	31
	L	–	–	–	–	–	3.67	−4	−9	22	24
Sublobar											
Thalamus	R	–	–	–	–	–	3.59	16	−11	6	–
	L	–	–	–	–	–	3.72	−4	−16	8	–
Caudate	R	–	–	–	–	–	3.35	13	15	9	–
	L	–	–	–	–	–	4.08	−7	0	12	–
Putamen	L	–	–	–	–	–	2.39	−21	−6	14	–
Limbic lobe											
Parahippocampal gyrus	L	–	–	–	–	–	2.64	−12	−35	−5	30
Occipital lobe											
Posterior cingulate	L	–	–	–	–	–	2.55	−7	−37	20	23
Cerebellum	R	–	–	–	–	–	2.94	10	−24	2	–
	L	–	–	–	–	–	3.14	−15	−25	−15	–
		PD < Healthy participants					**PD < Healthy participants**				
Frontal lobe											
Superior frontal gyrus	R	–	–	–	–	–	3.95	20	0	67	6
Middle frontal gyrus	R	–	–	–	–	–	3.11	40	−4	53	6
Precentral gyrus	R	3.97	48	−12	53	4/6	3.69	51	−6	48	4
Parietal lobe											
Superior parietal lobule	R	–	–	–	–	–	2.81	37	−55	54	5/7
Postcentral gyrus	R	4.7	37	−25	35	2/3	2.71	37	−35	56	2/40
Temporal lobe											
Superior temporal gyrus	R	4.06	55	−13	−1	22/41	–	–	–	–	–
Middle temporal gyrus	R	–	–	–	–	–	3.15	40	−62	13	19
Sublobar											
Insula	R	2.4	43	−20	11	3	–	–	–	–	–
Thalamus	R	3	29	−27	2	–	–	–	–	–	–
Caudate	R	2.18	18	−40	17	–	–	–	–	–	–
Occipital lobe											
Lingual gyrus	R	3.42	16	−52	−1	19	–	–	–	–	–
Superior occipital gyrus	R	–	–	–	–	–	4.18	34	−81	30	19
Posterior cingulate	R	2.22	21	−51	13	23/30	2.97	26	−64	9	30
Precuneus	R	–	–	–	–	–	3.54	18	−58	34	7/31

The table describes the location of the peak voxel and the corresponding brain regions and Brodmann areas comprised by the cluster. Results are reported if corrected cluster level $P < 0.05$. The voxel size is 2.4 × 2.4 × 4.5 mm.

Resting State of Patients with PD Compared to Healthy Participants Before Stimulations

Compared to the healthy participants, patients with PD did not show significantly higher neural responses within our threshold.

Compared to patients with PD, the healthy participants showed significantly higher neural responses in the right precentral gyrus (BA 4/6), right postcentral gyrus (BA 2/3), right thalamus, and right caudate (Figure 1, Table 3).

Higher and Lower Neural Responses Among Patients with PD after ACUP, Compared to Healthy Participants Before ACUP

Compared to the healthy participants, patients with PD showed significantly higher neural responses in the left superior frontal gyrus (BA 10), left middle frontal gyrus (BA 10/11), right inferior frontal gyrus (BA 47), left and right thalamus, left and right caudate, left putamen, and left and right cerebellum.

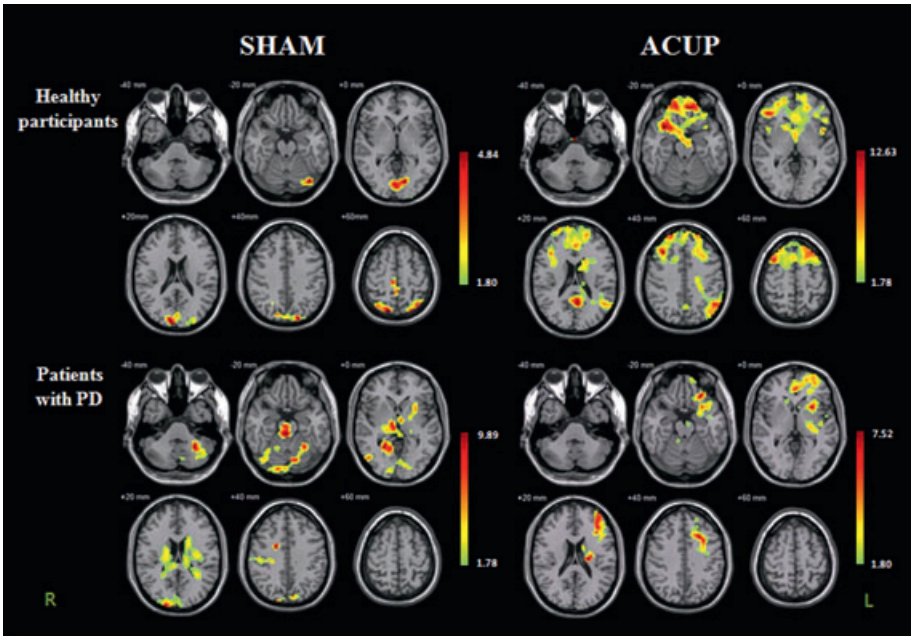

Figure 2 Increased neural responses after removal of the acupuncture needle and sham needle among healthy participants and patients with PD. The bar is the *t*-value. Note that R, right hemisphere; whereas L, left hemisphere.

Patients with PD showed significantly lower neural responses in the right superior frontal gyrus (BA 6), right middle frontal gyrus (BA 6), right precentral gyrus (BA 4), superior parietal lobule (BA 5/7), and right postcentral gyrus (BA 2/40) (Figure 1, Table 3).

Resting-state Modulations Induced by ACUP and SHAM

In comparing the neural responses before and after ACUP, significantly increased foci of healthy participants were found in the left caudate body, left putamen, and left thalamus.

In comparing the neural responses before and after SHAM, however, significantly increased foci of healthy participants were located in the right paracentral lobule (BA 6), left superior parietal lobule (BA 7), right postcenral gyrus (BA 3), and left and right cerebellum (Figure 2, Table 4).

When the same comparison before and after ACUP was made for patients with PD, significantly increased foci were in the right caudate body, left caudate tail, left putamen, left thalamus, and left substantia nigra.

In comparing the neural responses before and after Sham, however, significantly increased foci of patients with PD were in the left and right caudate, left putamen, left lateral globus pallidus, left and right thalamus, right substantia nigra, right cuneus (BA 18), and left and right cerebellum (Figure 2, Table 4).

Compared to the healthy participants, patients with PD showed a significantly higher signal increase in the thalamus after ACUP than before ($p < 0.05$) (Figure 3).

Discussion

Although a relatively recent arrival in many countries, acupuncture is used more frequently as a treatment in addition to conventional medicine for patients with PD [1]. Therefore, it is important to better understand its neural mechanisms. The acupoint GB34 was chosen because it has been reported to lead to significant improvements in patients with PD [1,11,12] and significant neuroprotective effects in PD animal models [10,13–15]. The aim of this study was to demonstrate changes to the resting state modulated by acupuncture stimulations on GB34 and to show that the areas associated with PD could be modulated by acupuncture stimulations.

The analysis of the psychophysical responses to ACUP and SHAM showed that the average stimulus intensities were similar during ACUP of patients with PD and SHAM of patients with PD, as well as during ACUP of healthy participants and SHAM of healthy participants, indicating that in each group, no differences were felt between ACUP and SHAM. These results are in line with previous studies [19,35], in which the general finding was that the psychophysical responses to ACUP and SHAM were similar, although significant neural differences were found [19].

Before stimulations, healthy participants and patients with PD exhibited significantly higher neural responses in the posterior cingulate gyrus, precuneus, medial prefrontal cortex, and inferior parietal lobule than in other brain areas during the resting state (Table 2). These results are consistent with previous research indicating that a set of brain regions, including the posterior cingulate, precuneus, and medial prefrontal cortex, demonstrate higher cerebral blood flow than average for the brain in the resting state [23,36]. After ACUP, the resting state of healthy participants and patients with PD had changed. Especially, significantly higher brain activations of the thalamic regions were shown in patients with PD, but not in healthy participants (Table 2). It is consistently shown in patients with PD compared to healthy participants after ACUP (Table 3).

Table 4 Increased neural responses of healthy participants and patients with Parkinson's Disease (PD), after sham acupuncture stimulation (SHAM) and acupuncture stimulation (ACUP)

		Healthy participants										Patients with PD									
		Sham					Acupuncture					Sham					Acupuncture				
Brain region	Hemisphere	*t*-value	x	y	z	Brodmann area	*t*-value	x	y	z	Brodmann area	*t*-value	x	y	z	Brodmann area	*t*-value	x	y	z	Brodmann area
Frontal lobe																					
Superior frontal gyrus	R	–	–	–	–	–	7.86	21	48	42	6/8/10/11		–	–	–	–	–	–	–	–	–
	L	–	–	–	–	–	6.85	−24	15	62	6/8/9		–	–	–	–	4.99	−29	60	7	10
Middle frontal gyrus	R	–	–	–	–	–	9.97	32	4	59	6/46		–	–	–	–	–	–	–	–	–
	L	–	–	–	–	–	12.63	−29	11	48	6		–	–	–	–	5.56	−23	28	−12	6/9/10/11
Medial frontal gyrus	L	–	–	–	–	–	6.03	−16	8	53	6/10		–	–	–	–	6.3	−17	49	3	-
Inferior frontal gyrus	R	–	–	–	–	–	6.62	33	14	−10	13/46/47		–	–	–	–	–	–	–	–	–
	L	–	–	–	–	–	4.31	−26	25	−7	47		–	–	–	–	4.01	−26	11	−12	47
Paracentral lobule	R	3.17	4	−32	58	6	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Parietal lobe																					
Superior parietal lobule	L	3.09	−32	−66	54	7	5.79	−49	−61	33	39		–	–	–	–	–	–	–	–	–
Angular gyrus	L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Postcentral gyrus	R	3.67	12	−36	69	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Precuneus	R	4.84	4	−52	59	7/19	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	L	4.52	−21	−84	39	7/19	6.56	−4	−60	26	31		–	–	–	–	–	–	–	–	–
Temporal lobe																					
Inferior temporal gyrus	R	–	–	–	–	–	–	–	–	–	–	4.08	43	−69	−2	–	–	–	–	–	–
Sublobar																					
Caudate body	R	–	–	–	–	–	–	–	–	–	–	3.79	18	−10	25	–	3.6	13	17	12	–
	L	–	–	–	–	–	5.78	−18	5	18	–	3.68	−15	−1	23	–	–	–	–	–	–
Caudate tail	L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3.56	−34	−30	4	–
Putamen	L	–	–	–	–	–	4.81	−23	6	15	–	3.45	−26	13	−6	–	5.69	−29	10	2	–
Lateral globus pallidus	L	–	–	–	–	–	–	–	–	–	–	3.83	−20	−7	−2	–	–	–	–	–	–
Thalamus	R	–	–	–	–	–	–	–	–	–	–	5.36	7	−22	5	–	–	–	–	–	–
	L	–	–	–	–	–	4.13	−4	−2	9	–	4.45	−7	−10	−2	–	3.99	−21	−20	16	–
Insula	R	–	–	–	–	–	7.9	44	7	−5	13	–	–	–	–	–	–	–	–	–	–
	L	–	–	–	–	–	–	–	–	–	–	3.82	−29	−17	21	13	10.34	−32	20	14	13
Extranuclear	L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3.37	−37	14	−11	13
Limbic lobe																					
Anterior cingulate	L	–	–	–	–	–	5.12	−12	45	−8	32	–	–	–	–	–	4.28	−1	37	8	24
Posterior cingulate	R	–	–	–	–	–	5.43	1	−51	13	30	4.23	15	−67	6	23/30	–	–	–	–	–
Cingulate gyrus	L	–	–	–	–	–	3.46	−21	−22	40	31	–	–	–	–	–	5.62	−24	12	40	32
Parahippocampal gyrus	R	–	–	–	–	–	–	–	–	–	–	5.23	21	−52	0	19	–	–	–	–	–
	L	–	–	–	–	–	–	–	–	–	–	3.75	−21	−39	6	30	3.71	−20	−17	−9	35
Midbrain																					
Substantia nigra	R	–	–	–	–	–	–	–	–	–	–	4.77	5	−15	−14	–	–	–	–	–	–
	L	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3.92	−12	−20	−6	–
Red nucleus	R	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3.29	2	−26	−12	–

(continued)

Table 4 (Continued)

		Healthy participants									Patients with PD								
		Sham					Acupuncture				Sham				Acupuncture				
Brain region	Hemisphere	*t*-value	x	y	z	Brodmann area	*t*-value	x	y	z	Brodmann area	*t*-value	x	y	z	Brodmann area	*t*-value	x	y	z	Brodmann area
	L	–	–	–	–	–	–	–	–	–	–	6.99	−1	−23	−11	–	–	–	–	–	–
Occipital lobe																					
Cuneus	R	3.27	10	−88	15	18	–	–	–	–	–	9.89	18	−96	12	18	–	–	–	–	–
	L	3.05	−1	−81	10	17	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Fusiform gyrus	R	–	–	–	–	–	–	–	–	–	–	4.14	43	−68	−10	19	–	–	–	–	–
	L	–	–	–	–	–	–	–	–	–	–	3.98	−21	−85	−12	19	–	–	–	–	–
Lingual gyrus	R	3.06	2	−89	−1	18	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	L	3.42	−12	−74	−3	18	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Cerebellum	R	3.88	2	−80	9	–	–	–	–	–	–	5.5	10	−55	2	–	3.02	2	−40	−13	–
	L	3.46	−34	−72	−19	–	–	–	–	–	–	5.68	−15	−68	−19	–	–	–	–	–	–

The table describes the location of the peak voxel and the corresponding brain regions and Brodmann areas comprised by the cluster. Results are reported if cluster level corrected was $P < 0.05$ and *t*-value >3. The voxel size is 2.4 × 2.4 × 4.5 mm.

Previous research has shown that the resting state of patients with PD was different compared to that of healthy participants [24,27]. In these studies, the neural responses of patients with PD were lower in extensive brain regions including the putamen, thalamus, and supplementary motor area and were higher in other areas including the cerebellum, primary sensorimotor cortex, and premotor area [27]. Our study identified somewhat different areas of initially lower neural responses in patients with PD. Before stimulations, patients with PD showed significantly lower neural responses compared to the healthy participants in the precentral gyrus, postcentral gyrus, thalamus, and caudate. It is interesting that a reduced neural response was observed in the right and not the left precentral gyrus in patients with PD (Figure 1, Table 3). For this reason, it may be worth noting that initial dyskinesia was left-sided in six patients, right-sided in three, and left- and right-sided in three. The dominance of initial left-sided bradykinesia could help explain these data.

Compared to the healthy participants before stimulations, patients with PD showed significantly higher neural responses after ACUP in certain areas (Figure 1, Table 3). Among these, the thalamus [37], putamen [38], and caudate [24,39] are the areas that were reported to be associated with PD in previous studies. Moreover, the thalamus and caudate of patients with PD had lower neural responses compared to healthy participants before ACUP (Table 3). These results suggest that acupuncture stimulation may increase brain activations of regions associated with PD.

Our first hypothesis was that ACUP could modulate the resting-state network not only in healthy participants [19,22,40] but also in patients with PD. When comparing the neural responses before and after ACUP, significantly increased foci of each healthy participants and patients with PD were found (Figure 2, Table 4). Moreover, different neural responses between healthy participants and patients with PD were observed (Figure 2). When the resting-state changes caused by ACUP and SHAM were compared among healthy participants, no commonly changed areas were found except the left precuneus (Table 4). In comparing these changes in patients with PD, significantly increased foci were common in the right caudate body, left putamen, left thalamus, left insula, left parahippocampal gyrus, and right cerebellum. Additionally, the basal ganglia areas exhibited resting-state changes in response to both ACUP and SHAM in patients with PD. In contrast, healthy participants only showed changes in these areas after ACUP stimulations. The pressure of sham stimulations on the acupoint may have evoked such responses only in patients with PD. This is consistent with previous reports which stated that the neural responses between patients and healthy participants differed [41–44]. These differences between patients with PD and healthy participants were thought to come from cognitive impairment. In Parkinson's disease, cognitive impairment [45,46], which is related with the sensory nerve system [47], visuospatial and visuoperceptual problems [48], influence of vestibular loss [49], was reported. Cognitive impairment of patients with PD may also affect the brain activations on ACUP and SHAM, so the neural responses were different compared to healthy participants. In our study, the basal ganglia areas exhibited the resting-state changes in response to SHAM only in the patients with PD. In contrast, the healthy participants did not show the changes in these areas after

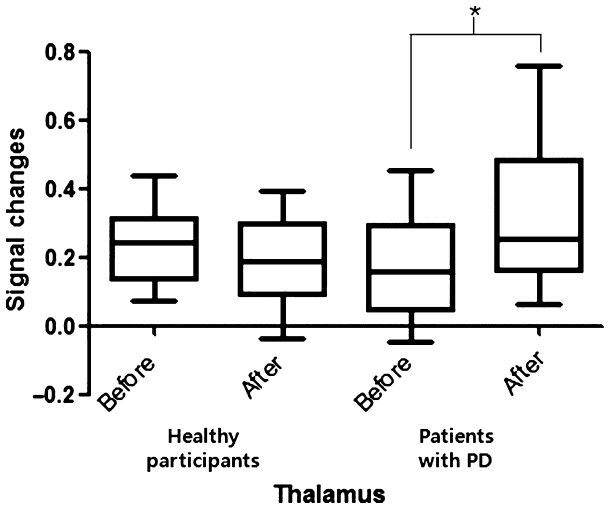

Figure 3 Neural signal changes after removal of the acupuncture needle among healthy participants and patients with PD in the thalamus. $*P < 0.05$.

SHAM. These different observations may depend on the cognitive impairment in PD. The patients with PD must have had neuronal dysfunction by the nigral dopamine depletion, which might cause abnormal activations of the basal ganglia compared to the healthy participants. For this reason, studies on acupuncture efficacy should thus investigate its effects on patients with diseases as well as healthy participants.

In previous fMRI studies of patients with PD, the brain activation in patients with PD also differed from that of healthy participants during performance of a motor task [42,50–52]; patients with PD exhibited a markedly different pattern of activation characterized by a significant over-activation in the ipsilateral cerebellar hemisphere [50] and a significant under-activation in the supplementary motor area [50–52] and right dorsolateral prefrontal cortex [42,51,52]. The differences found in patients with PD performing motor tasks can be explained by a functional deficit of the striato-cortical-motor loops [42,50,53]. To compensate for the dopamine deficit in the striato-cortical-motor loops, other areas are activated in the brain that are likely to participate in the same putative attempt by the dopamine-denervated brain to recruit parallel motor circuits. After examining the literature, we hypothesized that brain activations induced by acupuncture stimulations would be shown in the malfunctional areas to make effect. Moreover, these brain activations would differ from those of healthy participants. In a previous study, the neural responses of patients with PD compared to those of healthy participants were lower in extensive brain regions, including the putamen, thalamus, and supplementary motor area [27]. Our results demonstrated that the initial neural responses were lower in extensive brain regions of patients with PD including the postcentral gyrus, superior temporal gyrus, precentral gyrus, lingual gyrus, thalamus, insula, posterior cingulate, and caudate (Table 3). After receiving ACUP, neural responses in patients with PD increased in the caudate, putamen, cingulate gyrus, thalamus, substantia nigra, anterior cingulate, prefrontal gyrus, insula, parahippocampal gyrus, and cerebellum (Table 4). In addition, the caudate, insula, putamen, and thalamus, which demonstrated lower neural responses when compared to the healthy participants before ACUP (Table 3), showed statistically significant signal increases after receiving ACUP (Table 4).

In a simple finger-tapping task, acupuncture at GB34 showed a significant improvement in the motor function of the affected hand before and after acupuncture stimulations on GB34, 13% [12]. Considering the previous motor task studies [42–44,50,53] and the previous acupuncture studies on PD with GB34 [12,54], it was expected that the patients with PD would have different neural responses to overcome their functional deficiencies in the striato-cortical-motor loops. Several studies have shown that patients with PD use different motor pathways to compensate for the functional deficiencies of the striato-cortical-motor loops [37,42,43,50, 53,55], one of which is the cerebello-thalamic pathway [37,55]. The fact that neural responses increased in the thalamus and cerebellum after ACUP in patients with PD therefore supports the hypothesis that acupuncture modulates the resting state of areas associated with PD. Interestingly, the neural responses of areas shown to be associated with PD in previous studies such as the substantia nigra [56], caudate [24,39], thalamus [37], and putamen [38] also increased after ACUP. This suggests that acupuncture stimulations have effect on the brain areas that are impaired caused by PD. These results were consistent with the previous study, which demonstrated that the putamen and primary motor cortex were activated when patients with PD received ACUP on GB34 and that acupuncture treatment might facilitate improvement in the motor functioning of patients with PD via the basal ganglia–thalamocortical circuit [12].

The limitations of this study are that acupuncture stimulations were short term, and we should have observed motor improvement instead of just referring to existing literature. Moreover, the patients' mean disease duration of our participants was 2.67 years, which is a relatively benign state of PD, so the results were slightly differing from previous research and might only apply to relatively patients with early PD. Although future randomized controlled trials of neural response increases in these areas are needed to confirm acupuncture's role in improving symptoms of PD, the results of this study support the hypothesis that acupuncture stimulations on GB34 modulate the resting state of areas associated with PD. We believe that our study holds importance for future clinical and acupuncture studies in patients with neurodegenerative diseases, especially PD.

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Conflict of Interest

The authors declare no conflict of interest.

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