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A study of the effects of 8-week acupuncture treatment on patients with Parkinson's disease

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Abstract

Background: Parkinson's disease (PD) is a degenerative brain disorder, resulting in decreased neural responses in the supplementary motor area, putamen, and thalamus. Previous research showed that acupuncture was able to improve the motor dysfunction. The primary aim of this study is to assess the efficacy of longer acupuncture treatment for preventing brain degeneration in patients with PD.

Methods: Ten outpatients with PD were recruited from Kyung Hee Medical Hospital. Behavioral and neural responses were examined before and after 8 weeks of acupuncture treatment. A semi-individualized treatment approach was used; patients were treated for 15 minutes with 120-Hz electro-acupuncture at the right GB34 and Taechung (LR3), followed by manual acupuncture based on the individual symptoms of the patient.

Results: Immediately after 8 weeks of acupuncture treatment, the Unified Parkinson's Disease Rating Scale (UPDRS) sub-scores and the depression scores for the patients had statistically decreased compared to the scores before acupuncture treatment; moreover, 8 weeks later, these scores remained stable. Compared to the neural responses before the acupuncture stimulation, those after the acupuncture treatment were significantly higher in the thalamus, cingulate gyrus, anterior cingulate, lingual gyrus, parahippocampal gyrus, lateral globus pallidus, mammillary body, middle temporal gyrus, cuneus, and fusiform gyrus. Finally, a positive correlation was found between the UPDRS and the mean magnetic resonance signal change for the thalamus.

Conclusion: This study found beneficial clinical effects of 8-week acupuncture treatment in the brains of patients with PD.

Abbreviations: ADL = activities of daily living score, BDI-II = Beck depression inventory score-II, BOLD = blood-oxygen-level-dependent, fMRI = functional magnetic resonance imaging, GB 34 = yanglingquan, H–E = Hoehn and Yahr, LR3 = Taechung, PD = Parkinson's disease, ReHo = regional homogeneity, UPDRS = Unified Parkinson's disease rating scale.

Keywords: acupuncture, functional magnetic resonance imaging, neurodegeneration, Parkinson's disease, treatment effects

1. Introduction

Acupuncture is increasingly gaining recognition as a form of complementary treatment.[1–3] Previous studies have found that 61%[4] of patients with Parkinson's disease (PD) in Singapore and 76%[5] of patients with PD in Korea have reported using complementary treatments, with acupuncture being the most frequently employed method. A recent survey revealed that 32% of hospices in the state of Washington in the United States offer acupuncture as a complementary treatment for patients with PD.[6] Accordingly, many studies have been performed to investigate the efficacy of this treatment.[7–10] Acupuncture treatments have been reported to lead to significant improvements in the symptoms of patients with PD,[3,11,12] and significant neuroprotective effects have been demonstrated in animal models of PD.[10,13–15]

Evidence for the effectiveness of acupuncture in treating patients with PD is increasing.[16,17] Previous clinical trials have shown a positive effect of long-term acupuncture treatment in patients with PD[17]; however, they have not demonstrated any changes in the brain. PD is caused by neuro-degeneration of the brain, so investigating whether the treatment improves neural activity, in addition to the symptoms, is important. Moreover, the brain areas that are reported as being impaired in patients with PD should be examined for improved function induced by the acupuncture treatment. Several studies using functional magnetic resonance imaging (fMRI) have reported that acupuncture treatment leads to significant improvements in patients with PD; however, those studies involved short-term acupuncture treatments of 1 session or 1 day.[16]

In recent years, acupuncture researchers have used fMRI to study the so-called post-effect of acupuncture.[18] This means that they were not just studying the simultaneous neural responses attributable to stimulation but also detecting longer term neural changes after the acupuncture treatment. Some clinical reports have indicated that acupuncture efficacy is sustained for a period

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of time after removal of the needle.[18] Therefore, studies on the post-effect of acupuncture stimulations are important for acquiring a better understanding of the neural changes occurring after acupuncture stimulations.

Previous fMRI experiments have studied event-related neural responses induced by acupuncture stimulations.[19,20] However, recent studies suggest that neural responses to event-related tasks also rely on the integrity of the resting-state networks.[21,22] fMRI allows evaluation of changes in neural responses following removal of an acupuncture needle, and studies have demonstrated that the resting-state network may be altered after acupuncture stimulation and removal of the needle.[21,23,24]

A method called regional homogeneity (ReHo) has been used to investigate functional modulations during the resting-state in patients with PD.[25] ReHo reflects the temporal homogeneity of the regional blood-oxygen-level-dependent (BOLD) signal. As the BOLD signal detected in fMRI may reflect neural activity,[26] abnormal ReHo may possibly reflect changes in the temporal aspects of neural activity in regions of the brain. Therefore, ReHo has been used to detect brain regions with abnormal activity.[25] Previous research found that in patients with PD, ReHo was lower in certain brain regions: the putamen, thalamus, and supplementary motor area.[25] In this study, based on our previous fMRI acupuncture stimulation findings on patients with PD and healthy controls,[27,28] ReHo was used to investigate whether acupuncture modulated the resting-state network associated with PD and whether it could significantly change the neural responses of regions showing impaired responses in patients with PD. Therefore, we examined the effects of longer (8-week) acupuncture treatment on the brain response, as well as the symptoms, of patients with PD.

2. Methods

2.1. Study design

This study evaluated the effectiveness of acupuncture in the treatment of patients with PD and included the collection of neuroimaging evidence for changes in brain activity. Data on observational and self-reported outcome measures were collected at baseline, after 2 months (post-intervention) and after 4 months (follow-up) (see Supplementary Fig. 1, http://links.lww.com/MD/C674). Full ethical approval was granted by the Institutional Review Board of Kyung Hee Medical Hospital, Seoul, Korea (KMC IRB 0861-06); the trial is registered at cris.nih.go.kr (KCT0001122) and was conducted in accordance with the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) (note that on request, all data can be anonymously accessed by contacting 1 of the authors).

2.2. Participants

As can be seen in Supplementary Table 1, http://links.lww.com/MD/C674, 10 volunteers participated in this study following written informed consent procedures according to the institutional guidelines of the Human Research Committee. The 10 participants were idiopathic patients with PD (mean age: 56.9 (SD = 9.49) years, 5 males). 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 PD participants were scanned in the "off" condition; that is, 12 hours after all anti-Parkinson drugs had been withheld. Disability was assessed immediately after the patients had been scanned. All had Hoehn and Yahr (H–E) score[29] 1.15 (SD = 0.7). The mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score was 6.8 (SD = 3.7). All patients with PD were right-handed, as verified by the Edinburg Handedness Inventory[30]; their mean score was 100 (SD = 0)%. The average duration of the disease was 2.55 (SD = 1.8) years. All patients with PD were responsive to either levodopa or dopamine agonists.

2.3. Acupuncture

An experienced Korean medical female doctor conducted acupuncture on patients with PD over an 8-week period following the initial clinical evaluation and the first fMRI scan. The acupuncture treatments were provided 2 times per week. A semi-individualized approach was used. Every subject was treated for 15 minutes with 120-Hz electro-acupuncture at the right GB34 and at the right Taechung (LR3). In addition to these 2 standard acupuncture points, the practitioner performed manual acupuncture treatment based on the individual symptoms of the presenting patient. The acupuncture points LR3, Gokji (LI11), Joksamli (ST36), Pungji (GB20), Sameumkyo (SP6), Hapgok (LI4), and Yanglingquan (GB 34) (For more detailed information about these acupuncture points, we refer the readers to the report: WHO Standard Acupuncture Point Locations in the Western Pacific Region[31]) were included within the individualized approach. All of these non-standard acupuncture points were bilateral. One-way needles (0.25×30 mm, Dong Bang Acupuncture Inc., Korea) were used for acupuncture stimulation.

The acupuncture points for treating the PD patients were chosen according to the report of Lee et al,[32] with modifications made by Korean medical doctors, all of whom had over 5 years of experience. The principle of the procedure and the acupuncture points chosen were based on Korean medical theory, and the Korean medical doctors involved in the study had all received complete training from Kyung Hee University, Seoul, Korea. The guidelines of the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)[33] were followed in our study[34] and are listed in Supplementary Table 2, http://links.lww.com/MD/C674. The depths of the acupuncture points were from 3 to 15 mm, and manual stimulation was performed for about 15 minutes per session. At the end of the session, all the needles were removed from the subjects.

2.4. Data collection and management

The demographic data were collected by a trained nurse when the participants were recruited. Clinical outcome measurements and questionnaire-based assessment of treatment effects were measured by doctors after the treatment course had been completed. During the follow-up period, which was defined as 8 weeks post treatment, a questionnaire-based assessment of treatment effects was conducted.

2.5. MRI data acquisition

A Philips 3.0 T MRI system (Philips Medical Systems, Best, The Netherlands) equipped for echo planar imaging (EPI) was used for data acquisition. The fMRI paradigm used a resting condition of 4 minutes, with 120 contiguous EPI functional volumes being acquired during this condition (repetition time [TR] = 2000 ms,

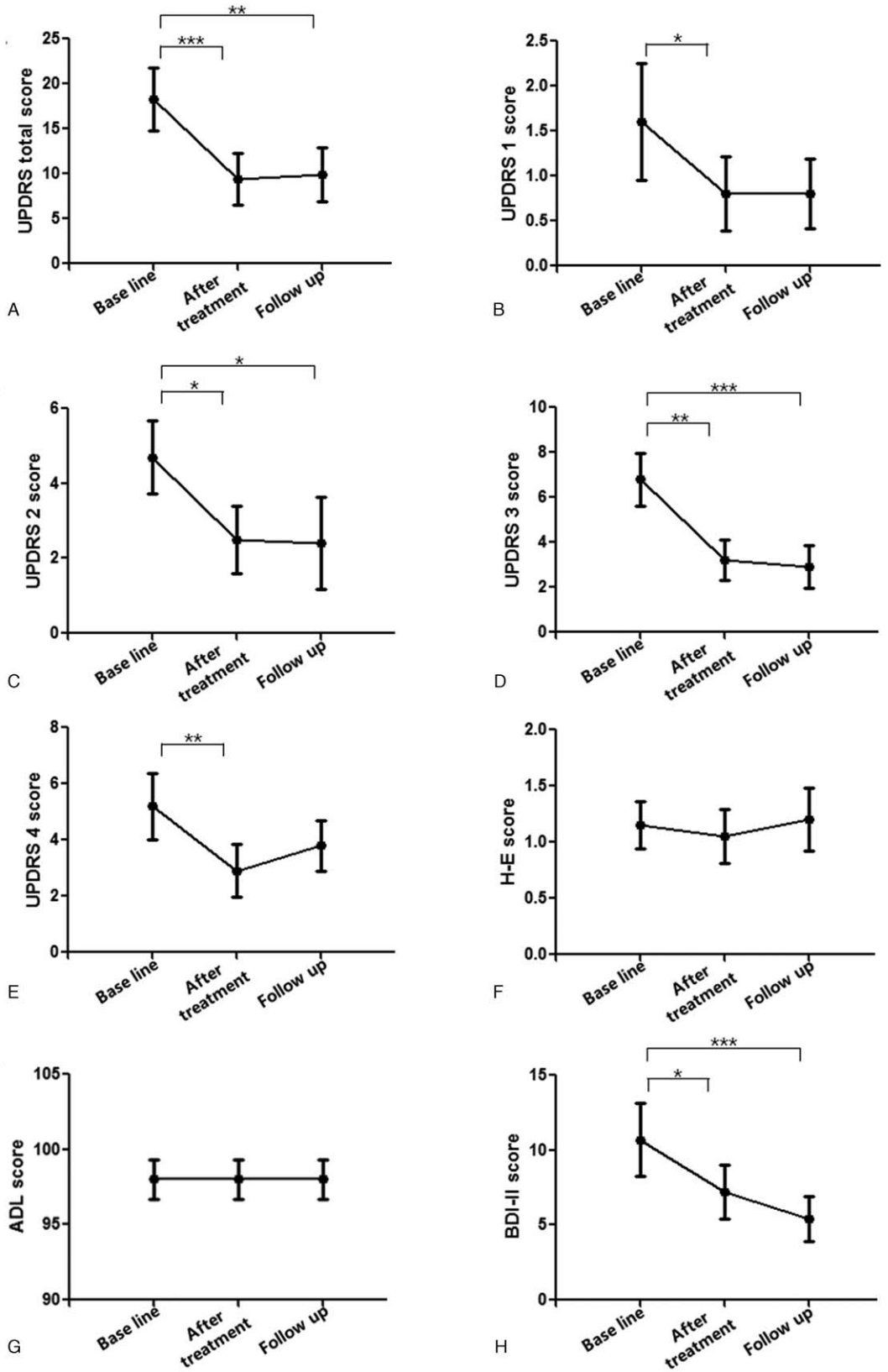

Figure 1. Change in mean score from baseline. The UPDRS total score was statistically lower after 8 weeks of acupuncture treatment and remained stable at the follow-up 8 weeks later (A). The UPDRS 1 score was statistically lower after 8 weeks of acupuncture treatment (B). The UPDRS 2 score was statistically lower after 8 weeks of acupuncture treatment and remained stable at the follow-up 8 weeks later (C). The UPDRS 3 score was statistically lower after 8 weeks of acupuncture treatment and remained stable at the follow-up 8 weeks later (D). The UPDRS 4 score was statistically lower after 8 weeks of acupuncture treatment (E). The H-E score was not statistically different after 8 weeks of acupuncture treatment (F). The ADL score was not statistically different after 8 weeks of acupuncture treatment (G). The BDI-II score was statistically lower after 8 weeks of acupuncture treatment and was still significantly lower at the 8-week follow-up (H). *$P>.05$, **$P>.01$, ***$P>.005$. ADL = activities of daily living, UPDRS = Unified Parkinson's Disease Rating Scale.

echo time [TE] = 35 ms, flip angle = 90°, slice thickness = 4.5, number of slices = 30, matrix = 96 x 128, field of view [FOV] = 230 x 182 x 135 mm^3, acquisition voxel size = 2.4 x 2.4 x 4.5 mm^3). During the scanning, participants remained in the supine position with their heads immobilized by cushioned supports. They wore ear plugs throughout the experiment to attenuate the 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 (TR = 9.9 ms, TE = 4.6 ms, flip angle = 90°, slice thickness = 1 mm, number of slices = 196, matrix = 236 x 240, field of view [FOV] = 235 x 235 x 196 mm^3, acquisition voxel size = 1 x 1 x 1 mm^3).

2.6. MRI data analysis

The fMRI data were analyzed using SPM5 (www.fil.ion.ucl.ac.uk/spm). The functional EPI-BOLD images were realigned, and the subject-mean functional MR images were co-registered with the corresponding structural MR images. These images were spatially normalized and transformed into a common space, as defined by the SPM Montreal Neurological Institute (MNI) T1 template.

On the basis of the ReHo hypothesis, the Kendall coefficient of concordance was used to measure the similarity of the time series within a functional cluster.[35,36] The 27 nearest neighboring voxels were defined as a cluster, and a Kendal coefficient of concordance 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://resting-fmri.sourceforge.net), was used for the ReHo analysis in a voxel-wise fashion. For all participants, the ReHo map was spatially smoothed using a Gaussian kernel with a 9-mm full width at half maximum. Rex[37] was used for neural signal change analysis.

2.7. Statistical analysis

The primary outcomes underwent intention-to-treat analyses based on the initial treatment assignment, and the focus was on assessing of the main effects of the acupuncture treatment on the symptoms of PD. Analyses was performed using IBM SPSS 22 (version 22.0, IBM Corp., New York, NY). The continuous variables and the descriptive values were expressed using means with standard deviations or medians with ranges. For the variables with a normal distribution, statistical comparisons between the groups were made using *t* tests.

3. Results

3.1. Psychophysical response results

As can be seen in Figure 1A, compared to base line, the UPDRS total score was statistically lower immediately after 8 weeks of acupuncture treatment and remained stable at follow-up 8 weeks later. Compared to base line, the UPDRS 1 score was statistically lower after 8 weeks of acupuncture treatment (see Fig. 1B). As can be seen in Figure 1C, compared to base line, the UPDRS 2 score was statistically lower after 8 weeks of acupuncture treatment and remained stable at follow-up 8 weeks later. Compared to base line, the UPDRS 3 score was statistically lower after 8 weeks of acupuncture treatment and was even lower at follow-up 8 weeks later (see Fig. 1D). The UPDRS 4 score was statistically lower after acupuncture treatment for 8 weeks (see Fig. 1E).

Figure 1F shows that the H–E score was not statistically different after 8 weeks of acupuncture treatment. As can be seen in Figure 1G, the Activities of Daily Living (ADL) score was not statistically different after 8 weeks of acupuncture treatment. The Beck Depression Inventory (BDI)-II score was statistically lower after 8 weeks of acupuncture treatment and was found to be even lower at follow-up 8 weeks later (see Fig. 1H).

Table 1

Resting-state results among patients with PD before acupuncture stimulation.

Statistical values		Coordinates anatomical location					
Cluster size	*t* value	*x*	*y*	*z*	Hemisphere	Brain region	Brodmann area
4015	65.3	26	−41	25	Right	Cingulate gyrus	24/31/32
	63.57	18	−34	15	Right	Thalamus	
35	48.16	32	−63	−10	Right	Cerebellum	
175	47.6	29	−70	39	Right	Precuneus	7/19/31
	44.43	32	−68	20	Right	Posterior cingulate	31
	36.03	32	−72	3	Right	Lingual gyrus	19
222	45.14	43	−32	18	Right	Insula	13
	40.91	60	−49	28	Right	Supramarginal gyrus	40
71	43.46	43	−41	−4	Right	Sub-gyral	37
16	36.27	13	−13	−29	Right	Uncus	36
48	31.53	35	20	45	Right	Middle frontal gyrus	8/9
79	31.51	4	30	23	Right	Anterior cingulate	25/32
30	31.11	54	14	17	Right	Inferior frontal gyrus	44
309	52	−21	−80	−1	Left	Lingual gyrus	18
224	32.59	−21	−71	19	Left	Precuneus	7/31
65	40.76	−5	−5	66	Left	Superior frontal gyrus	6/9
64	36.79	−9	15	−24	Left	Rectal gyrus	11
	35.85	−9	−5	−21	Left	Parahippocampal gyrus	34
48	33.9	−39	−45	−41	Left	Cerebellum	
33	30.72	−4	3	40	Left	Cingulate gyrus	24/32
21	27.69	−12	16	−5	Left	Caudate head	

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 *P* corrected FWE <0.0001. The cluster-level is at least 20 voxels per cluster and the voxel size is 2.4 × 2.4 × 2.4 mm^3.

3.2. fMRI results

3.2.1. Resting-state results among patients with PD before acupuncture stimulation. Before acupuncture stimulations, the neural responses for our patients with PD demonstrated that the right thalamus, right cerebellum, right posterior cingulate (Brodmann area (BA) 31), right insula (BA 13), right supramarginal gyrus (BA 40), right uncus (BA 36), right middle frontal gyrus (BA 8/BA 9), right anterior cingulate (BA 25/BA 32), right inferior frontal gyrus (BA 44), left superior frontal gyrus (BA 6/BA 9), left rectal gyrus (BA 11), left parahippocampal gyrus (BA 34), left cerebellum, left caudate head, left and right cingulate gyrus (BA 24/BA 31/BA 32), left and right lingual gyrus (BA 18/BA 19), and left and right precuneus (BA 7/BA 19/BA 31) exhibited significantly higher neural responses than other brain areas (see Table 1, Fig. 2).

3.2.2. Resting-state results among patients with PD after acupuncture treatment. After acupuncture stimulations, the

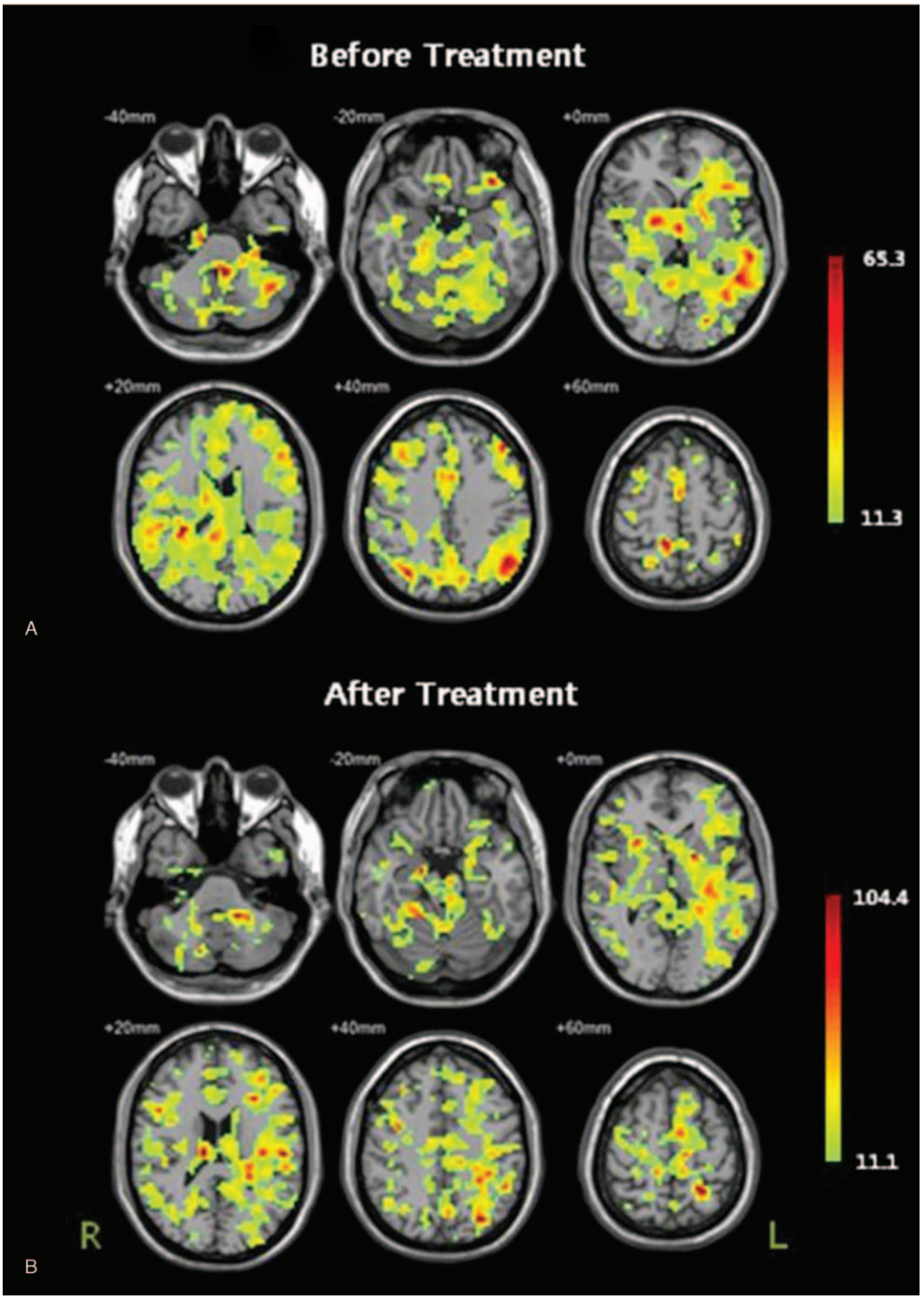

Figure 2. Maps of KCC for patients with PD during the resting-state before (A) and after (B) receiving acupuncture stimulation. The bar is the *t*-value. Note that R = right hemisphere whereas L = left hemisphere. KCC = Kendall's coefficient of concordance, PD = Parkinson's disease.

neural responses for patients with PD demonstrated that the right anterior cingulate (BA 32), right medial frontal gyrus (BA 9), right caudate body, right putamen, right cerebellum, right lingual gyrus (BA 18), right substantia nigra, right superior temporal gyrus (BA 13), right paracentral lobule (BA 5), right hippocampus, right thalamus, left medial frontal gyrus (BA 6), left supramarginal gyrus (BA 40), left and right insula (BA 13), left and right precuneus (BA 31), left and right parahippocampal gyrus (BA 34/BA 35), left and right middle frontal gyrus (BA 6/BA 9), left and right precentral gyrus (BA 4), left and right middle temporal gyrus (BA 39), and left and right cingulate gyrus (BA 31/BA 32) exhibited significantly higher neural responses than other brain areas. Among these, the caudate body, putamen, substantia nigra and thalamus are areas associated with PD. Except for the thalamus, the caudate body, putamen, and substantia nigra were found to be affected after acupuncture treatment (see Table 2, Fig. 3).

3.2.3. Changes in neuronal responses after acupuncture treatment. Compared to the neural responses before stimulation, those after acupuncture treatment was shown to be significantly higher in the right thalamus, cingulate gyrus (BA 24), right anterior cingulate (BA 24), right cerebellum, left lingual gyrus (BA 30), parahippocampal gyrus (BA 30), lateral globus pallidus, mammillary body, middle temporal gyrus (BA 21), cuneus (BA 18), and fusiform gyrus (BA 18). Among the areas associated with PD, the increase in the neural response in the thalamus was demonstrated to be statistically significant (see Table 3). Compared to the neural responses before stimulation, those after acupuncture treatment were significantly lower in the right medial frontal gyrus (BA 8), right superior frontal gyrus (BA 8), left supramarginal gyrus (BA 40), and left superior temporal gyrus (BA 13) (see Table 3). The increase in the UPDRS 3 motor score at the end of the 8-week acupuncture treatment was associated with an increase in brain activity in the thalamus (see Fig. 4).

4. Discussion

In our study, we investigated whether 8-week acupuncture treatment was able to improve the functions of the brain areas that are reported to suffer abnormal activity in patients with PD; we also assessed the symptoms of PD. We obtained important evidence to help interpret previous clinical trials that studied the effects of acupuncture on patients with PD.

In psychophysical responses, the UPDRS total, 1, 2, 3, 4, and Beck depression inventory score-II (BDI-II) scores were statistically lower after acupuncture treatment for 8 weeks, and the UPDRS total, 2, 3, and BDI-II scores remained stable for at least the next 8 weeks (8-week follow-up). Because decreases in these scores mean improvements in the symptoms related to these scores in patients with PD, these data indicate that after acupuncture treatment for 8 weeks, our patients with PD seem to have improved.

Previous fMRI research has shown that the resting-state of patients with PD is different from that of healthy participants.[25,38] In those 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

Table 2

Resting-state results among patients with PD after 8-week acupuncture treatment.

Statistical values		Coordinates anatomical location					
Cluster size	*t* value	*x*	*y*	*z*	Hemisphere	Brain region	Brodmann area
100	64	2	33	21	Right	Anterior cingulate	32
	47.71	4	38	32	Right	Medial frontal gyrus	9
483	58.79	46	1	−1	Right	Insula	13
	50.95	16	1	13	Right	Caudate body	
	49.19	27	10	3	Right	**Putamen**	
64	52.66	13	−68	−40	Right	Cerebellum	
148	34.34	15	−69	25	Right	Precuneus	31
	33.62	15	−73	6	Right	Lingual gyrus	18
64	49.59	22	−8	−23	Right	Parahippocampal gyrus	34/35
	29.02	10	−20	−14	Right	**Substantia nigra**	
31	45.35	40	−28	8	Right	Superior temporal gyrus	13
115	42.26	26	−11	44	Right	Middle frontal gyrus	6/9
	39.82	34	−12	52	Right	Precentral gyrus	4
107	38.71	43	−61	32	Right	Superior temporal gyrus	39
23	37.82	4	21	28	Right	Cingulate gyrus	31/32
24	36.29	9	−41	55	Right	Paracentral lobule	5
100	32.22	27	−35	−4	Right	Hippocampus	
30	29.82	10	−30	4	Right	Thalamus	
3486	104.43	−26	−28	15	Left	Insula	13
	64.37	−21	−36	6	Left	Parahippocampal gyrus	30/37
75	68.45	−24	−20	51	Left	Precentral gyrus	4
	24.74	−21	−5	41	Left	Middle frontal gyrus	6/8
148	52.31	−4	−69	27	Left	Precuneus	31
147	48.75	−4	−1	53	Left	Medial frontal gyrus	6
	46.64	−4	5	48	Left	Cingulate gyrus	24
31	31.16	−49	−47	31	Left	Supramarginal gyrus	40
21	30.39	−42	5	−36	Left	Middle temporal gyrus	21/38

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 *P* corrected FWE <0.0001. The cluster-level is at least 20 voxels per cluster and the voxel size is $2.4 \times 2.4 \times 2.4$ mm^3.

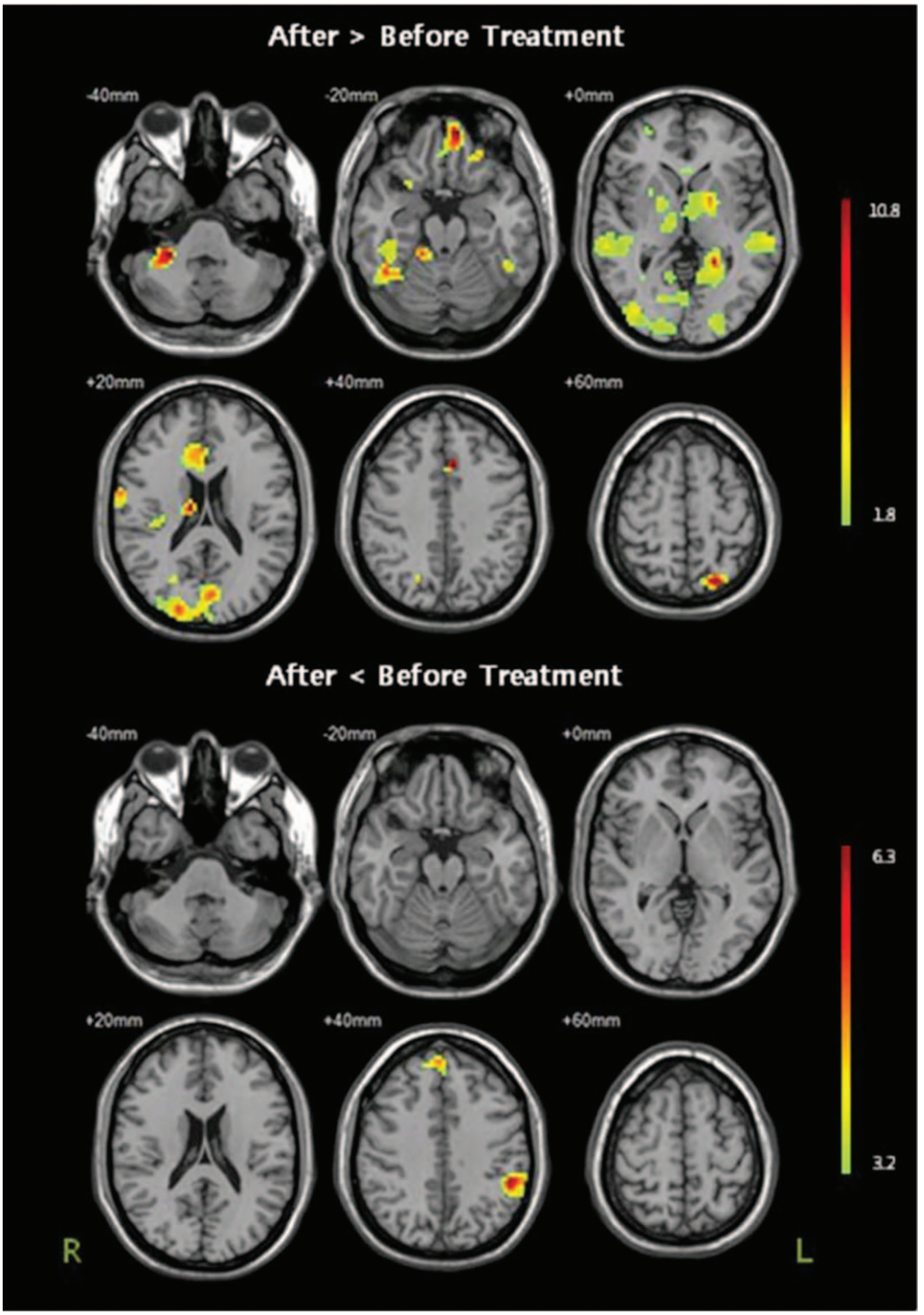

Figure 3. Resting-state comparison between before and after acupuncture stimulation in patients with PD. "After >Before treatment" means that compared to before acupuncture treatment, after acupuncture treatment, the patients showed significantly higher neural responses within our threshold. "After <Before treatment" means that compared to before acupuncture treatment, after acupuncture treatment, the patients showed significantly lower neural responses within our threshold. The bar is the *t* value. Note that R=right hemisphere whereas L=left hemisphere.

cortex, and premotor area.[25] The differences found in patients with PD can be explained by a functional deficit of the striato-cortical-motor loops.[39–41] To compensate for the dopamine deficit in the striato-cortical-motor loops, other areas in the brain that are likely to participate in the same putative attempt by the dopamine-denervated brain to recruit parallel motor circuits are activated. In our data, compared to the neural responses before acupuncture treatment in the putamen[42] and the substantia nigra,[43] which have been reported as impaired brain areas in patients with PD, those after the 8-week acupuncture treatment were demonstrated to be higher (see Table 1 and Table 2).

Table 3

Neural response changes after acupuncture treatment compared to before stimulation.

Statistical values		Coordinates anatomical location					
Cluster size	***t* value**	***x***	***y***	***z***	**Hemisphere**	**Brain region**	**Brodmann area**
After > Before acupuncture treatment							
30	5.71	10	−17	19	Right	Thalamus	29
	5.46	4	16	27	Right	Cingulate gyrus	24
	3.8	2	24	26	Right	Anterior cingulate	24
28	5.42	16	−82	−14	Right	Cerebellum	
52	10.82	−21	−44	−1	Left	Lingual gyrus	30
	3.71	−26	−52	2	Left	Parahippocampal gyrus	30
63	6.66	−18	1	7	Left	Lateral globus pallidus	
	6.11	−4	−10	−5	Left	Mammillary body	
23	4.66	−59	−29	−5	Left	Middle temporal gyrus	21
23	4.65	−2	−82	18	Left	Cuneus	18
32	4.3	−23	−93	−13	Left	Fusiform gyrus	18
After < Before acupuncture treatment							
92	4.78	1	42	43	Right	Medial frontal gyrus	8
	4.49	13	43	36	Right	Superior frontal gyrus	8
149	6.27	−49	−44	34	Left	Supramarginal gyrus	40
	3.84	−51	−40	21	Left	Superior temporal gyrus	13

The table describes the location of the peak voxel and the corresponding brain regions and Brodmann areas comprised by the cluster. "After >Before acupuncture treatment" means that compared to before acupuncture treatment, after acupuncture treatment showed significantly higher neural responses within our threshold. "After < Before acupuncture treatment" means that compared to before acupuncture treatment, after acupuncture treatment showed significantly lower neural responses within our threshold. Results are reported if *P* corrected cluster level <.005. The cluster-level is at least 20 voxels per cluster and the voxel size is 2.4 × 2.4 × 2.4 mm^3.

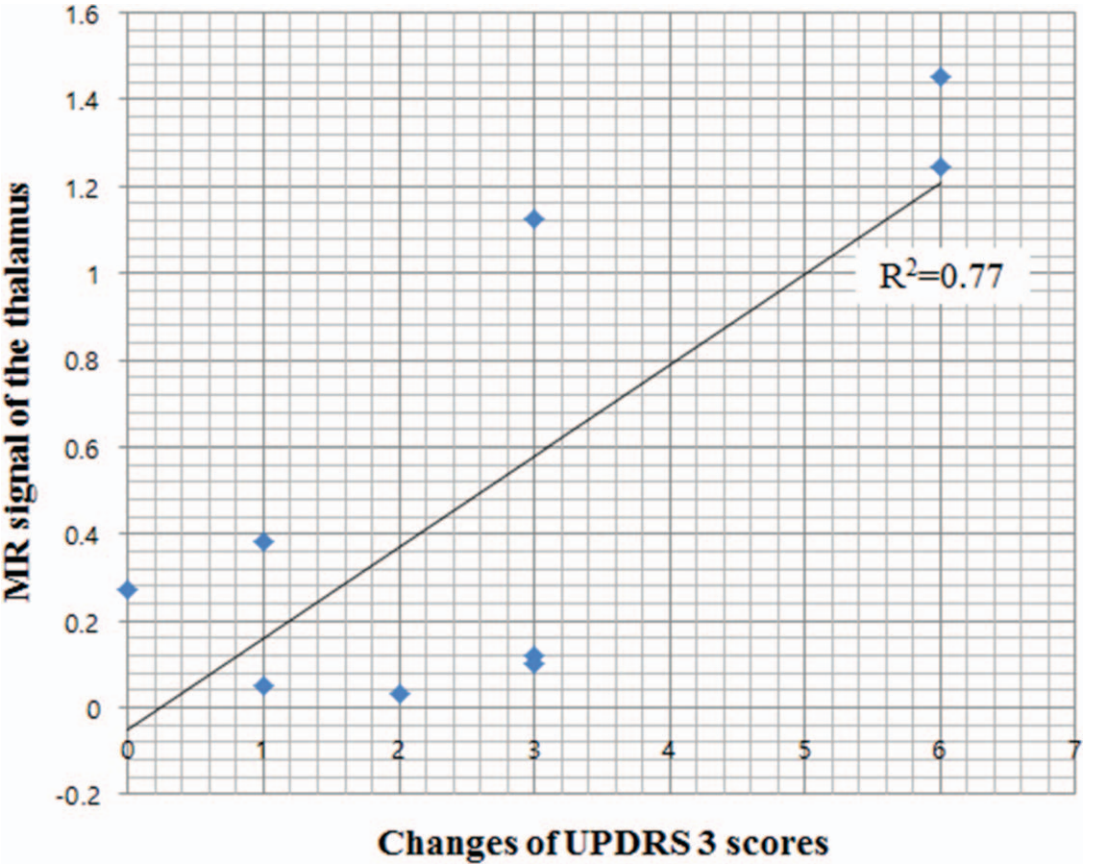

Figure 4. The variance in the UPDRS 3 score is accounted for by the mean MR signal change between before and after acupuncture treatments for 8 weeks. A positive correlation was shown between the UPDRS 3 score and the mean MR signal change for the thalamus. UPDRS = Unified Parkinson's Disease Rating Scale.

The neural activities of the thalamus were determined before and after the 8-week acupuncture treatment (see Table 1 and Table 2), and the neural responses were found to be significantly increased after the acupuncture treatment (see Table 3). Previous fMRI research found the thalamus to be 1 of the impaired areas of the brain in patients with PD.[25] Accompanying the improved UPDRS motor scores were significant changes in the fMRI signals of the thalamus after 8 weeks of acupuncture treatment. Moreover, the changes in the UPDRS 3 (motor) scores and in the fMRI signals showed a high correlation (see Fig. 4). This suggests that the motor improvement in patients with PD may involve changes in the neural activity of the thalamus and that in this research; acupuncture treatment had an effect on the thalamus which is involved in motor symptoms. Several studies have shown that patients with PD use different motor pathways to compensate for the functional deficiencies of the striato-cortical-motor loops,[39,40,44–46] 1 of which is the cerebello-thalamic pathway.[27,44,46] The facts that the neural responses were increased in the thalamus and the motor symptoms were improved after acupuncture treatment in patients with PD and that they were closely correlated clearly supports the conclusion that acupuncture treatment modulates the resting-state of areas associated with PD. This suggests that acupuncture stimulations have an effect on the areas of the brain that are impaired by PD and that acupuncture treatment might facilitate improvement in the motor functioning of patients with PD via the basal ganglia–thalamocortical circuit.[12,27]

In a previous study, in which scans were done just after the acupuncture stimulation, acupuncture stimulation induced changes in the fMRI signals in the thalamus and in the putamen, which have been reported to be impaired in patients with PD.[27] However, in the present study, the maintaining area was the thalamus, not the putamen. Our scanning time was 3 or 4 days after the last acupuncture stimulation, so the scanned areas are thought to have continuously maintained the changes. However, a limitation of our study is that in order to assert that the changes in neural activity are maintained, a longer treatment duration would be needed. In our study, the duration of the acupuncture treatment was 8 weeks. The use of longer treatment durations in future studies might show more changes in areas of the brain that are impaired in patients with PD. Moreover, in future research, the present ReHo findings need to be replicated in patients with PD and healthy controls, in order to confirm our ReHo findings. Another limitation of our study is that previous studies have reported ethnic differences in brain morphology.[47,48] Thus, in the present study, a possible bias in the functional or structural localization might exist because we used the Western instead of the Asian brain template.[49]

To conclude, as to the best of our knowledge, this is the first trial to use fMRI to specifically evaluate the effects of longer (8-week) acupuncture therapy on the brains of patients with PD. Our study shows the importance of study protocols that use more than just 1 treatment session when investigating the possible added effect of acupuncture treatment on the brain functions in patients with PD.

Author contributions

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