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Parsing Brain Activity Associated with Acupuncture Treatment in Parkinson's Diseases

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Abstract: Acupuncture, a common treatment modality within complementary and alternative medicine, has been widely used for Parkinson's disease (PD). Using functional magnetic resonance imaging (fMRI), we explored the neural mechanisms underlying the effect of specific and genuine acupuncture treatment on the motor function in patients with PD. Three fMRI scans were performed in random order in a block design, one for verum acupuncture (VA) treatment, another one for a covert placebo (CP), and the third one for an overt placebo (OP) at the motor function implicated acupoint GB34 on the left foot of 10 patients with PD. We calculated the contrast that subtracts the blood-oxygen-level dependent (BOLD) response for the acupuncture effect (VA vs. CP) and the placebo effect (CP vs. OP). We found a significant improvement in the motor function of the affected hand after acupuncture treatment. The putamen and the primary motor cortex were activated when patients with PD received the acupuncture treatment (VA vs. CP) and these activations correlated with individual enhanced motor function. Expectation towards acupuncture modality (CP vs. OP) elicited activation over the anterior cingulate gyrus, the superior frontal gyrus, and the superior temporal gyrus. These findings suggest that acupuncture treatment might facilitate improvement in the motor functioning of patients with PD via the basal ganglia-thalamocortical circuit. © 2009 Movement Disorder Society

Key words: acupuncture; Parkinson's disease; fMRI; placebo; putamen

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized clinically by tremor, rigidity, and bradykinesia and pathologically by the neuronal loss in the nigrostriatal dopaminergic system.[1] Acupuncture has been widely used to treat a range of neurological disorders, including PD.[2] Although evidence of the effectiveness of acupuncture for treating PD remains unconvincing, a recent systematic review has suggested that beneficial effects are associated with this modality.[3] Our previous studies demonstrated that acupuncture not only prevented 6-hydroxydopamine-induced neuronal death in the nigrostriatal dopaminergic system but also inhibited microglial activation in a PD animal model.[4,5] We also found that electro-acupuncture at acupoint GB34 changed protein expression profiles in the substantia nigra in favor of dopaminergic neuronal survival in PD mice model.[6] However, few studies have examined the neural substrate of acupuncture action in patients with PD.

Functional brain imaging techniques have opened a window into the brain and made it possible to unravel the neural mechanisms underlying acupuncture in humans.[7–9] Functional magnetic resonance imaging (fMRI) investigations have revealed that acupuncture stimulation at the motor function implicated acupoint GB34 modulated the cortical activities of the somatomotor area in humans.[10–12] Our previous study examined the neu-

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ral substrates correlated with verum acupuncture compared to those correlated with non-penetrating placebo needles to exclude the impact of interfering factors, such as pain or emotion, during acupuncture.[13] Although several studies have revealed the potential mechanisms associated with acupuncture among healthy subjects, generalization of these findings to the clinical effects of acupuncture in patients with PD is problematic.

The placebo effect has played a prominent role in understanding such medical conditions as pain, depression, and PD[14] and has been considered as representing a potential confounder in assessing the efficacy of any therapeutic intervention, including acupuncture.[15] The placebo needle is designed to address this problem. As the shaft of the needle disappears into the handle, similar to a stage dagger, the newly developed placebo sham needle gives the impression of skin penetration without piercing the skin.[16,17] It was reported that the placebo needle produced acupuncture analgesia through multiple brain regions including the rostral anterior cingulate cortex (rACC) and lateral prefrontal cortex (PFC).[18] Pariente et al. also revealed that expectancy and belief modulated the actions of the dorsolateral PFC, rACC, and midbrain by comparing verum acupuncture (VA), covert placebo (Streitberger needle), and overt placebo (subjects were instructed to feel stimulated by a placebo) conditions.[19] To elucidate the neural mechanisms associated with the acupuncture effect in PD, we must differentiate specific effects from non-specific effect of acupuncture.

In the present study, we differentiated between covert placebo (CP) and overt placebo (OP) conditions, using a Park Sham needle, in terms of subjects' awareness, or lack thereof, of whether the treatment was actually inert. In the CP condition, patients were not aware that they were receiving a placebo treatment; in the OP condition, they were aware. Next, we used fMRI technology to explore the neural mechanisms underlying a specific and genuine acupuncture effect (VA vs. CP) and a placebo effect (CP vs. OP) among patients with PD.

PATIENTS AND METHODS

Patients

We studied 10 patients who were mildly affected by Parkinson's disease (six men, four women; age range: 45–66 years; disease duration 3.0 ± 2.0 years; Modified Hoehn and Yahr stage 1.6 ± 0.2; total Unified Parkinson's Disease Rating Scale scores: 33.0 ± 15.5) and had not been treated with anti-Parkinsonian medication for at least 12 hours.[20,21] All participants were diagnosed by a neurologist with idiopathic PD made (Chang DI) before participation in this study. Patients with medical histories of other neurological illnesses were excluded. All patients provided informed consent and this investigation was approved by the Institutional Review Board of Kyung Hee University, Oriental Medical Hospital, Seoul, Republic of Korea.

Acupuncture

Acupuncture was performed by an experienced Korean medical doctor. Each patient received verum acupuncture (VA), covert placebo (CP), or overt placebo (OP) in a random order at acupoint GB34 located in the depression anterior and distal to the head of the fibula (Fig. 1). The VA needle (sterile, disposable, stainless steel, 40 mm long and 0.25 mm diameter) was inserted perpendicularly to the skin surface to a depth of 10 mm. The needle was manually rotated clockwise and counterclockwise once per second (1 Hz) for 60 seconds (the ON phase). The needle was then withdrawn for 120 seconds (the OFF phase). The CP needle procedure was performed using a blunt, telescopic, non-penetrating Park Sham needle.[16] As the blunt tip was pushed against the skin, the shaft moved into the handle, giving the impression that it had penetrated the skin. The manipulations were exactly same as in the VA treatment. The patients were told that they would be treated with either real or sham acupuncture in the VA and CP sessions. The OP needle was physically identical to the CP needle. However, patients were told that the needle produced no therapeutic effect without piercing the acupoint.

Behavioral Task

We used a simple finger-tapping task to evaluate the motor function of patients with PD. Since these tasks could produce motion artifacts that influenced the results, and movement itself could induce striatal release of dopamine, we assessed changes in motor functions before and after three consecutive scans. Patients were instructed to tap their right index fingers against their right thumbs as fast as possible for 60 seconds. An independent assessor evaluated the motor improvement by watching a video record of the finger-tapping task without knowing the particular treatment given.

After each session, patients were also asked, "Did you think the acupuncture stimulation you just received was real or sham?" To provide more detailed information on

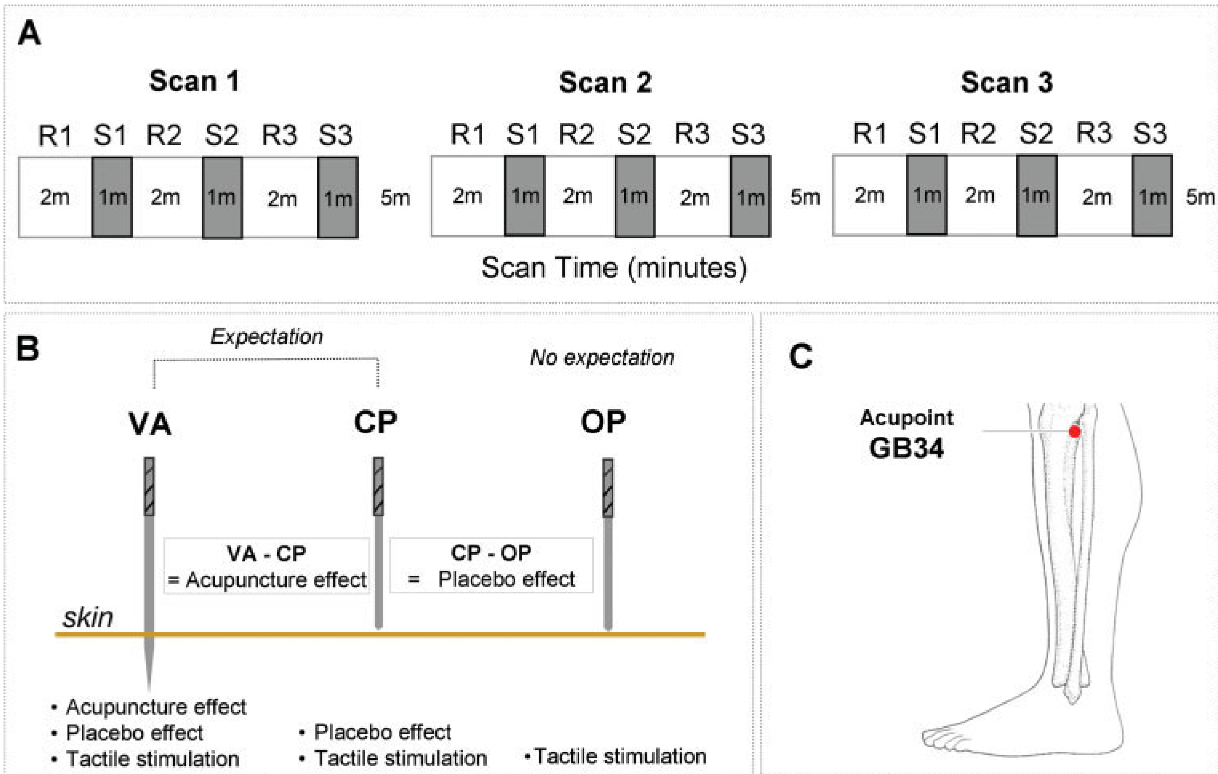

FIG. 1. Total scan time for each scan session was 9 min in the upper panel (**A**). Scanning commenced with a rest period (R1) and was followed by three identical active blocks of needle stimulation (S1, S2, and S3) separated by a rest period (R2 and R3). Three fMRI scans were performed on each participant using the above block design; one scan involved VA only, another separate scan involved CP only, and the other scan involved OP only. These sessions were randomly ordered. The diagram of acupuncture and location of acupoint GB34 are presented in the lower panel. The VA needle (sterile, disposable, stainless steel, 40 mm long, and 0.25 mm diameter) was inserted perpendicularly to the skin surface to a depth of 1.0 cm. The CP needle was performed using a new, blunt, telescopic, non-penetrating Park Sham needle. The OP needle was physically identical to the CP needle. However, patients were told that the needle would not have any therapeutic effect without piercing the acupoint (**B**). Acupoint GB34 located in the depression anterior and distal to the head of the fibula (**C**). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the credibility of sham acupuncture, we also estimated a blinding index following the logic of Bang et al.[22]

fMRI Session

Patients were instructed to lie still and keep their eyes closed during the scan. The order of the three fMRI scans was randomized and counterbalanced across patients in a block design over three 9 min periods; one scan involved VA only, a separate scan involved CP only, and the remaining scan involved OP only. The total scan time for each session was 9 min (Fig. 1). Scanning commenced with a rest period (2 min) and was followed by three identical active blocks of needle stimulation (1 min) separated by a rest period (2 min).

Image Data Acquisition

Brain imaging was conducted on a 3T MR scanner (ISOL Tech, Republic of Korea). BOLD functional imaging was performed with a gradient echo planar imaging (EPI) T2*-weighted sequence (TR 3 seconds, TE 25 milliseconds, flip angle 90 degree, acquisition matrix 64 × 64, FOV 220 mm, slice thick 4 mm without gap, voxel size 3.43 × 3.43 × 4 mm). Image collection was preceded by four dummy scans to allow for equilibration of the MRI signal. The anatomical image data set was obtained using a 3D gradient-echo T1-weighted sequence (TR 2800 milliseconds, TE 16 milliseconds, flip angle 60 degrees, FOV 192 × 220, slice thickness 5 mm) after the functional scans.

Data Management and Statistical Analysis

Pre-processing and statistical analysis were performed with Statistical Parametric Mapping software (SPM5, http://fil.ion.ac.uk). Each image volume was motion-corrected and registered to the image space of the first scan session. Six motion regressors (three rotation and three translation) characterizing subject

TABLE 1. *Credibility of sham acupuncture for patient blinding*

Intervention	Patient's answer (No.) Real	Sham	Don't know	Total	Blinding indices
VA	9	1	0	10	0.80 (95% CI, 0.43 to 0.17)
CP	7	1	2	10	−0.60 (95% CI, −1.01 to −0.19)
Total	16	2	2	20	$\chi^2 = 2.250$, $P > 0.325$

movements during the scanning were included in the model for each subject as nuisance covariates. Preprocessing included motion correction, normalization to MNI stereotactic space based on Talairach coordinates, and spatial smoothing with an 8 mm full-width-at-half maximum (FWHM) isotropic Gaussian kernel to decrease the spatial noise. To identify the specific area activated by a genuine acupuncture effect or a placebo effect, we constructed the matrix of activation/deactivation functional maps comparing VA with CP and comparing CP with OP. We constructed a design matrix for each subject that separately included regressors representing the blocks of acupuncture application for VA, CP, and OP conditions. Contrast maps were generated between VA and CP regressors for the acupuncture specific effect and between CP and OP for the placebo effect for each subject. The resulting individual contrast maps were used in random-effect group analyses such as one-sample *t*-tests and multiple regression analyses. Resulting *t* statistics were normalized to *Z* scores and clusters of significant activation were defined using the joint expected probability distribution of height ($Z > 2.81$, $P < 0.005$ uncorrected). A spatial threshold of 10 continuous active voxels was applied to avoid spike activations in each contrast.

Finally, we conducted regression analyses to explore whether individual differences in the observed verum acupuncture-related activity (VA–CP) covaried with individual differences as assessed by the changes in the motor function before and after scans. More specifically, first level contrast images reflecting the acupuncture specific effect (i.e., the difference between the VA and CP conditions) were entered into a regression analysis at the second level with a regressor, the increased rate characterizing the finger tapping tasks.

RESULTS

Behavioral Tests

In the examination of the simple finger-tapping task, we observed a significant improvement of the motor function of the affected hand before and after the scans (paired *t*-test, 60.7 ± 16.3 vs. 69.0 ± 19.5 frequency, $P < 0.05$). There was no significant difference of the enhanced motor function regardless of the order of VA and CP condition, suggesting that it was not confounded by order effects. The post-scan interview revealed that responses were similar for both VA and CP conditions (Chi-squared tests, $\chi^2 = 2.250$, 2 df, $P > 0.325$). In addition, Bang et al.'s blinding index estimates the percentage of correct guessing beyond the chance level in each treatment condition.[22] The blinding index was 0.80 (95% CI, 0.43 to 1.17) in the VA session and −0.60 (95% CI, −1.01 to −0.19) in the CP session (Table 1).

Functional Brain Mapping of Genuine Acupuncture Effect (VA vs. CP)

We arranged contrasts between VA and CP conditions. The main contrast of VA versus CP (VA–CP), using a random effect analysis, showed a significant effect in the right primary motor cortex (MI, BA4), the left middle frontal gyrus (BA9), the putamen, and the precuneus (see Fig. 2, Table 2 for complete list of regions activated).

Functional Brain Mapping of Placebo Effect (CP vs. OP)

Contrasts were set up between CP and OP. The main contrast of CP versus OP (CP–OP), using a random effect analysis, showed a significant effect in the right anterior cingulate gyrus (BA24 and BA32), the left supramarginal gyrus (BA40), the left superior temporal gyrus (BA22 and BA38), the left superior frontal gyrus (BA6), the right middle frontal gyrus (BA9), and the right thalamus (see Fig. 2, Table 2 for complete list of regions activated).

Functional Brain Mapping of the Mixed Effect (VA vs. OP)

Contrasts were set up between VA and OP. The main contrast of VA versus OP (VA–OP), using a random effect analysis, showed a significant activation in the right primary motor cortex (BA4), the precuneus

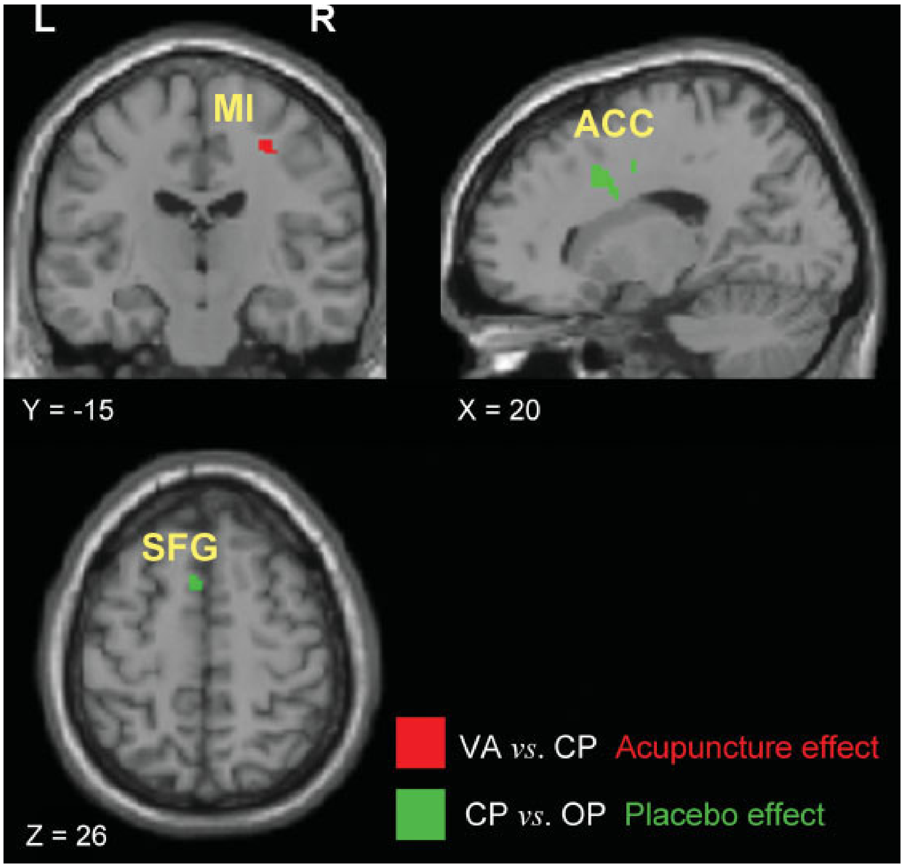

FIG. 2. Differential neural activations in acupuncture versus placebo conditions among patients with PD. The patients with PD showed activations in the right MI (x = 26, y = −15, z = 49; Z = 3.03) when they received verum acupuncture compared to covert placebo acupuncture. The patients with PD showed activations in the right ACC (x = 20, y = 13, z = 34; Z = 3.21) and the left SFG (x = −4, y = 12, z = 49; Z = 3.02). Stronger activation was detected in the M1 when treated with verum acupuncture (marked with red color) whereas stronger activation was found in the ACC and SFG when covert placebo acupuncture was used (marked with green color).

(BA7), the bilateral anterior cingulate gyrus (BA24 and BA32), the right superior temporal gyrus (BA41), the right inferior temporal gyrus (BA20), the right superior frontal gyrus (BA8), and the right insula (see Table 2 for complete list of regions activated).

Correlation Between the Signal Intensity and the Change in Motor Function

To explore further the role of the putamen and the MI, the major regions of the basal ganglia-thalamocortical circuit stimulated by verum acupuncture compared to covert acupuncture, we determined whether individual differences in changes in motor function (finger tapping frequency after treatment–finger tapping frequency before treatment) co-varied with brain activity in the genuine acupuncture-specific condition (VA–CP). The increase in the motor function showed significant co-variation with activity in the left (x = −24, y = 0, z = 4; Z = 3.19, r = 0.848, $P < 0.01$) and the right (x = 28, y = 14, z = 7; Z = 3.48, r = 0.917, $P < 0.01$) putamen and the right MI (x = 24, y = −13, z = 50; Z = 3.37, r = 0.960, $P < 0.001$; Fig. 3). The enhanced motor function was correlated with the basal ganglia-thalamocortical circuits, such as the putamen and the MI, but not with any other placebo-related brain areas.

DISCUSSION

Our findings show that acupuncture at acupoint GB34 led to increased activation of the putamen and the primary motor cortex in patients with PD. In addition, the expectation of acupuncture produced a significant activation in the right cingulate gyrus, the supramarginal gyrus, the superior temporal gyrus, the superior frontal gyrus, the middle frontal gyrus, and the thalamus. The brain activity in the putamen and

TABLE 2. *Activated brain regions: Contrast of VA versus CP, CP versus OP, and VA versus OP conditions in patients with PD*

Activated regions	BA	Coordinates in Talairach's space X	Y	Z	Z score	P Value (uncorrected)
VA versus CP						
(L) Middle frontal gyrus	9	−34	32	21	3.15	0.001
(R) Precuneus	7	28	−62	33	3.08	0.001
(R) Primary motor cortex	4	26	−15	49	3.03	0.001
(L) Putamen		−28	−25	−2	2.81	0.002
CP versus OP						
(R) Anterior cingulate gyrus	24	20	0	39	3.21	0.001
(R) Anterior cingulate gyrus	32	20	13	34	3.21	0.001
(L) Supramarginal gyrus	40	−51	−51	30	3.61	0.000
(L) Superior temporal gyrus	22	−50	−53	19	3.07	0.001
(L) Superior temporal gyrus	38	−46	1	−14	3.55	0.000
(L) Superior frontal gyrus	6	−4	12	49	3.02	0.001
(R) Middle frontal gyrus	9	28	38	26	2.90	0.002
(R) Thalamus		4	−9	19	3.23	0.001
VA versus OP						
(R) Primary motor cortex	4	36	−12	39	2.93	0.002
(R) Precuneus	7	26	−61	27	3.26	0.001
(R) Anterior cingulate gyrus	24	14	−6	35	3.68	0.000
(L) Anterior cingulate gyrus	32	−14	6	40	3.43	0.000
(R) Superior temporal gyrus	38	40	−35	4	3.31	0.000
(R) Inferior temporal gyrus	20	44	−62	−5	2.84	0.002
(R) Superior frontal gyrus	8	18	18	41	3.11	0.001
(R) Insula		36	−30	18	3.52	0.000

Mean stereotactic coordinates (mm) of peak voxel are listed according to the atlas of Talairach and Tournoux.
All Z value thresholds are >2.81.
BA, Brodmann area.

the MI demonstrated a significant correlation with the degree of the enhanced motor function associated with acupuncture treatment in the patients with PD. Our study represents the first use of fMRI results to demonstrate the neural mechanisms associated with acupuncture treatment of patients with PD.

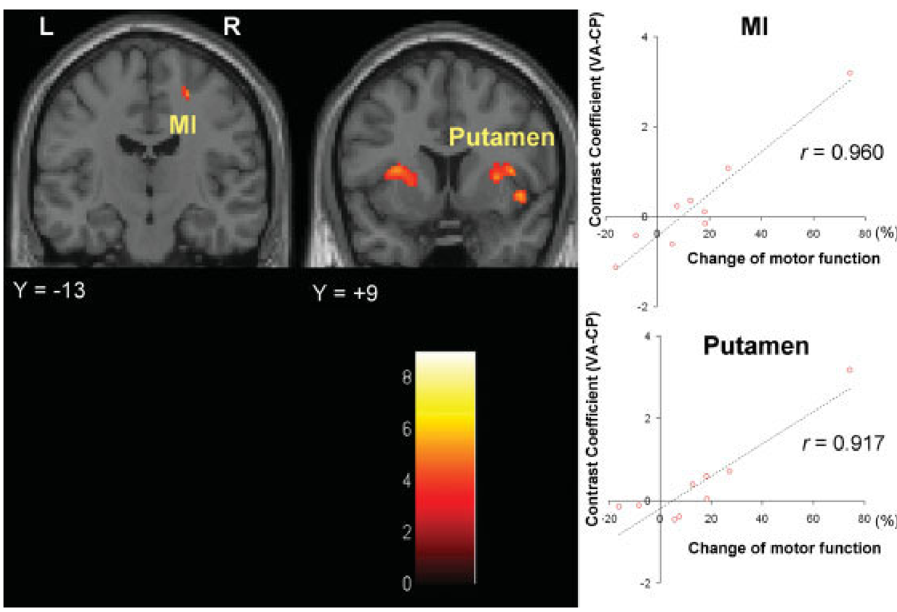

FIG. 3. Correlation between motor function recovery and brain response to verum acupuncture compared to covert placebo. Activation of the right MI (x = 24, y = −13, z = 50; r = 0.960) and the right putamen (x =28, y = 14, z = 7; r = 0.917) were positively correlated with the increase in finger-tapping task before and after acupuncture treatment. The horizontal axis measures the change of motor function [(finger tapping frequency after treatment-finger tapping frequency before treatment)/finger tapping frequency before treatment × 100). The vertical axis computes the contrast coefficient (VA–CP) from the general linear model in the individual peak voxels of the MI and the putamen.

According to the basal ganglia-thalamocortical circuit model, hypokinesia in PD is considered to result from dopamine depletion in the motor circuit, including the primary motor cortex.[23] Evidence from neuroimaging studies has indicated abnormal basal ganglia functioning in patients with PD.[24] It has been demonstrated using fMRI scans that stimulation induced by acupuncture at the motor function implicated acupoint GB34 modulated the cortical activities of the somatomotor area in healthy volunteers.[10–12] In the current study, we demonstrated that VA stimulation at the motor function-implicated acupoint GB34 elicited significantly higher activation than did CP (Park Sham needle) stimulation over the putamen and the primary motor cortex. Our findings indicate that acupuncture stimulation might be beneficial in improving the symptoms of patients with PD by modulating the basal ganglia-thalamocortical circuit. In the case of acupoint GB34, it has been one of the most often used acupoints to generally improve symptoms in motor impairment patients. There are clinical case studies describing an improvement in body posture, tremor, or rigidness[25] but whether this applies to specific hand/leg areas or whether it improves only the voluntary or autonomic motor responses is still unknown. In the present study, when the left GB34 acupoint was stimulated, the verum acupuncture-specific brain activation was coordinated at the contralateral hand motor area (BA4, $x = 26$, $y = -15$, $z = 49$). However, further studies are needed to explain these lateralizations of brain response to acupuncture.

The placebo (from Latin for "I shall please") effect has been prominent in PD and is related to the release of dopamine in the striatum.[26] The expectation driven by prefrontal cortical and limbic areas might trigger a downstream biochemical response specific to the condition (e.g., in the case of PD, dopamine release in the striatum; in placebo analgesia, endogenous opioid release).[27] To find the neural mechanism underlying the possible placebo effect in treatment of PD with acupuncture, we manipulated the cognitive set regarding the intervention and then compared the CP with the OP condition using the same placebo sham needle. Thus, we found that the CP needle elicited significantly higher activation than the OP in the ACC and the superior frontal gyrus, but not in the mesolimbic and nigrostriatal dopaminergic pathways mediating expectation or reward. These findings were not consistent with the other reports that dopamine activation of the nucleus accumbens has been detected with positron emission tomography during placebo analgesia in health volunteers or receipt of a placebo in PD patient.[26,28] The neuroanatomical localization of our findings indicates that placebo acupuncture (CP) did not activate the same brain network that had been activated by other placebo and active dopaminergic drugs, suggesting that expectation itself could not facilitate the reward-related dopamine system in the patients with PD in our study. Instead, expectation of the intervention modulated the multiple brain pathways in ways similar to the mechanism associated with placebo acupuncture analgesia through the ACC, the PFC, and the supramarginal gyrus.[18] In the context of these findings, it is conceivable that the increased BOLD signal in the ganglia-thalamocortical circuit, including the putamen and the MI, observed in the comparison of the VA and the CP were attributable to a genuine acupuncture effect and not to a non-specific effect of acupuncture.

In this study, we observed that acupuncture treatment was associated with enhanced motor function among the patients with PD as measured by a simple finger-tapping task. Considering the possibility of motion artifact, we compared the motor function before and after all sessions. The enhanced motor function assessed through the finger tapping task might be not only due to the effect of verum acupuncture, because there is the possibility that CP or OP also contributed to the improvement. However, with regression analysis, we demonstrated that the enhanced motor function showed a significant correlation with the activity in the putamen and the MI. These results are consistent with previous clinical studies of acupuncture showing that acupuncture at GB34 improved the motor function of patients with PD.[29] Generalization of these findings must await further study among a larger sample size using randomized clinical trials.

One might wonder whether the brain activations to VA represent both acupuncture-specific and placebo-related responses. In the current study, we found that VA stimulation elicited significantly higher activation than OP stimulation over both the acupuncture-specific brain areas, such as the MI, the precuneus, and the placebo-related brain areas such as the ACC, the superior frontal gyrus, and the superior temporal gyrus. These findings are in agreement with the previous report that both specific and non-specific factors of acupuncture treatment play a role in pain control.[19]

Even though previous studies have repeatedly confirmed the valid use of placebo needles, there is still the possibility that participants could be aware of the different stimulation procedure. The post-scan interview revealed that participants couldn't discriminate the difference between the needling stimulations used in both VA and CP conditions, suggesting that blinding of the two conditions was successful in the present study. The blinding index was 0.80 (95% CI, 0.43 to 1.17) and −0.60 (95% CI, −1.01 to −0.19) in the VA and CP session, respectively, implying that 60% of CP patients guessed they had real acupuncture, whereas 80% of VA patients did. According to the logic of Bang et al., it is conceivable that these results indicate high "response bias" instead of declaring it a failure in blinding.[22] This response bias—CP stimulation appeared as convincing as VA stimulation—could be explained by the high expectation of patients to benefit from the acupuncture treatment during the experiment. All patients except one were convinced that they were stimulated with real acupuncture, regardless of VA and CP conditions. These findings were consistent with other reports that a majority of study participants tends to believe that they were assigned an active or a more effective intervention.[30] However, we could not completely exclude the possibility of the patient's awareness of the treatment procedure, which might affect their expectancy.

In summary, we have demonstrated that the putamen and the primary motor cortex were activated when patients with PD received acupuncture treatment at acupoint GB34 and that these activations were correlated with enhanced motor function. In addition, expectations towards acupuncture treatment elicited activation over the ACC and the superior frontal gyrus but not the reward-related dopaminergic pathways. The current investigation of the specific brain activation patterns associated with genuine acupuncture provides more information about the neurobiological mechanisms underlying the operation of this modality among those with Parkinson's diseases.

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