Quantitative analysis of cerebrovascular characteristics of Parkinson’s disease treated with acupuncture based on magnetic resonance angiography

Yuan Yang1, Le He2, Suhua Miao1, Rongsong Zhou1, Yuqi Zhang1, Yu Ma1(✉)

1 Tsinghua University Yuquan Hospital, Beijing 100040, China
2 Center for Biomedical Imaging Research, School of Medicine, Tsinghua University, Beijing 100084, China

ARTICLE INFO
Received: 25 March, 2021
Revised: 15 June, 2021
Accepted: 21 June, 2021

© The authors 2021. This article is published with open access at journals.sagepub.com/home/BSA

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

KEYWORDS
acupuncture, Parkinson's disease, magnetic resonance angiography, quantitative cerebrovascular characteristics, cerebral blood flow

ABSTRACT
Background: Acupuncture has become an important alternative clinical treatment for Parkinson’s disease (PD), but its efficacy and the underlying mechanisms remain debatable. Using a newly developed magnetic resonance angiography (MRA) method that has higher sensitivity for smaller and distal vessels and a novel tool that can trace vessels and extract vascular features, the immediate effects of acupuncture on intracranial vessels and blood flow in patients with PD as well as correlations with clinical outcomes were quantitatively evaluated.

Methods: Fifteen PD patients received acupuncture at the Dazhui and Fengchi acupoint positions. MRA was performed before and after 30 min of treatment. The cerebral blood flow (CBF) and the length, volume, diameter, and signal intensity of the intracranial internal carotid artery (ICA) and middle cerebral artery (MCA) were measured. The Unified Parkinson’s Disease Rating Scale part III (UPDRS-III) and Visual Analogue Scale (VAS) were used to evaluate the motor symptoms and the subjective feelings of discomfort.

Results: Acupuncture significantly reduced UPDRS-III and VAS scores. No significant changes were noted in the overall CBF before and after treatment. However, there was a significant extension effect on the length of the intracranial ICA and MCA and the distal MCA, and a significant increase in the number of branches of the MCA was found. Although acupuncture tended to increase the total volume of the intracranial ICA and the volume of the MCA, no statistical significance was reached. The total intensity was not altered, but the intensity and diameter of the M1 segment were significantly increased, whereas the intensity of the MCA was decreased. A positive correlation between M1 intensity changes and UPDRS-III changes was found.

Conclusions: Angiographic evaluation suggested that acupuncture had a significant effect on intracranial blood vessels, which is one possible mechanism for acupuncture improving the motor symptoms of PD.

Address correspondence to Yu Ma, lymayu@163.com

http://bua.tsinghuauniversity.com  journals.sagepub.com/home/BSA
**1 Introduction**

Parkinson’s disease (PD) is the second-most common degenerative disease of the central nervous system after Alzheimer’s disease. It causes an increasingly heavy social and economic burden, affecting more than 1% of adults older than 60 years of age in European and American countries [1, 2]. The prevalence can increase to 4% in even older individuals [1, 2]. By contrast, the incidence of PD in Asian regions is relatively low (0.6%), which may be related to differences in geographical environments, genes, lifestyles, and statistical methods. The use of traditional medical therapies for prevention and treatment was also reported to be an important reason for differences [3]. In the United States, 40% of PD patients have utilized supplementary and alternative medical treatment methods to supplement or even replace conventional medications [4]. The use of traditional Chinese medicine (TCM) accounts for 52.7% of these cases [5]. There is increasing evidence suggesting that TCM can effectively improve nonmotor symptoms, prolong the duration of drug effects, and reduce motor complications [6, 7].

With good compliance and minor side effects, acupuncture has become one of the most commonly used TCM methods in clinics. Studies have shown that acupuncture could relieve motor symptoms [8–12] of PD, such as tremors, stiffness, and bradykinesia, finger movements, and gait and balance disorders [13]. It is associated with good effects on nonmotor symptoms as well, such as fatigue [14], sleep disorders [15], and gastrointestinal dysfunction. Acupuncture can also improve the efficacy and reduce the toxicity of dopaminergic medications when prescribed together [11, 16]. Increasing numbers of physicians and patients are accepting acupuncture in the treatment of PD worldwide [17–20].

However, controversy regarding the effectiveness of acupuncture and its mechanisms remains. Acupuncture is generally applied on the basis of syndrome differentiation under the guidance of the holistic classical TCM theory [21, 22]. It is an advantageous factor that cannot be replaced in the medical field at present. Inconsistent results, however, have been reported [23–25]. Some suggested that acupuncture did not achieve a significant effect with PD [8]. Although studies found that the clinical effect of acupuncture in combination with drugs was superior to that of drugs alone, it was also claimed that the placebo effect could not be ruled out when assessing the effectiveness of acupuncture [26]. The underlying modern medicine basis for how acupuncture takes effect remains not fully understood. There is still a need for a technical approach that can provide more rigorous insight and guidance for the clinical treatment of PD with acupuncture.

The blood system plays an important role in TCM theory, and blood flow improvement was considered as a vital effect for acupuncture to achieve symptom relief and disease treatment. In the meantime, a growing body of evidence has indicated that various aspects of neurodegenerative diseases are closely associated with changes in cerebrovascular function. Studies have shown that patients with PD have significant decreases in cerebral blood flow (CBF) [27] that are associated with the severity of the disease. Additionally, the change in CBF induced by Madopar had a negative correlation with the Unified Parkinson Disease Rating Scale (UPDRS) scores, suggesting that the improvement of symptoms was associated with the increase in CBF in related areas [28]. Changes in
CBF could be used as important markers for disease diagnosis, mechanism investigation, and treatment assessment [29]. In recent years, there have been studies that explored the CBF regulatory effects of acupuncture in Alzheimer’s disease, stroke, and other diseases. Results on acupuncture treatment for PD remain very limited [30–32].

Several methods can be used to measure CBF, such as rheoencephalography, transcranial Doppler imaging, and near-infrared spectroscopy. In comparison, magnetic resonance angiography (MRA), which uses methods such as arterial spin labeling (ASL), provides a powerful means for extensive inspection, including not only quantitative measurement of CBF but also structural observation of the vessels. Recently, a new MRA method was developed, called simultaneous noncontrast angiography and intraplaque hemorrhage MRA (SNAP-MRA) [33]. It can perform three-dimensional (3D) intracranial angiography and plaque imaging simultaneously in a single scan and has high sensitivity for intraplaque hemorrhage, intramural hematoma, and thrombus [34]. Since it is optimized for intracranial artery imaging [35], SNAP-MRA has high accuracy in testing lumen stenosis, enables the visualization of smaller arteries, and shows good ability in testing distal vessels [36]. Furthermore, with the newly developed analysis tool of iCafe software to trace the vessels, quantitative intracranial vascular features can be extracted [37]. It provides a new opportunity to look deeper into the effects and mechanisms of acupuncture on the symptoms of PD.

In this study, we applied acupuncture to PD patients and motor symptoms were assessed. Before and after acupuncture, pseudo-continuous ASL (PCASL) and SNAP-MRA were performed to evaluate the changes in CBF and vascular features, such as the length, volume, distal length, proximal length, diameter of the M1 segment, signal intensity of large vessels, and signal intensity of the intracranial internal carotid artery (ICA) and middle cerebral artery (MCA). The impact and effects of acupuncture on PD were therefore analyzed.

## 2 Methods

### 2.1 Ethics statement

This study was conducted according to the ethical standards of the Declaration of Helsinki and applicable national regulations. It was registered on ClinicalTrials.gov under the number NCT03501004 and approved by the ethics committee of Tsinghua University Yuquan Hospital (Approval No. QHDXQYY 20180001). All participants provided written informed consent.

### 2.2 Subjects

Fifteen PD patients diagnosed by the neurologists of Tsinghua University Yuquan Hospital were enrolled from September 2017 to October 2018. Inclusion criteria were: (1) age from 40 to 70 years; (2) meeting the new standard for clinical diagnosis of PD introduced by the International Parkinson and Movement Disorders Society in 2015 [38]; (3) stage 2 to 3 via the Hoehn–Yahr (H–Y) scale; (4) having received a stable dose of anti-Parkinson medication for at least 3 months without any adverse events; (5) having education level of junior high school or above; (6) having a correct understanding of the significance of clinical studies on acupuncture; and (7) displaying good compliance with the researchers’ observations and evaluations. Exclusion criteria were patients with (1) secondary Parkinson's syndrome; (2) Parkinson's syndrome; (3) central and peripheral infectious...
diseases; (4) dysarthria; and (5) severe psychiatric disorders that affect expression, malignancies, disability, and other severe somatic disorders. All patients maintained anti-Parkinson medications with no changes during the study as advised. Demographic information, including gender, age, stage via the H–Y scale, duration of the disease, and daily dose of anti-Parkinson drugs of all participants were recorded.

2.3 Assessment and intervention procedure

Patients were instructed to refrain from anti-Parkinson medication for at least 12 h before the test. Before acupuncture, their motor symptoms were evaluated using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III). The overall subjective feeling of comfort caused by motor and nonmotor symptoms was evaluated using the Visual Analog Scale (VAS) with 0 representing “no discomfort” and 10 for “unbearable discomfort”. An MRI scanning session followed, after which the patients were removed from the scanner and rested for 30 min. Then, they were treated with acupuncture for 30 min, followed by a reevaluation of UPDRS-III and VAS, and a second MRI scanning session.

2.4 Acupuncture intervention

Acupuncture intervention was undertaken according to the Standards for Reporting Interventions in Clinical Trials of Acupuncture [39]. All interventions were performed by the same acupuncturist who had more than 5 years of clinical experience. Disposable sterile acupuncture needles (Suzhou Medical Products Co. Ltd., Suzhou, China) measuring 0.25 mm × 25 mm were used. Dazhui (DU14) and bilateral Fengchi acupoints (GB20) were selected that had previously shown therapeutic effects with PD patients [40–44]. The Dazhui acupoint (DU14) is located beneath the spinous process of the seventh cervical vertebrae. The Fengchi acupoints (GB20) are located beneath the occiput and in the depression between the sternocleidomastoid muscle and the upper end of the trapezius muscle.

Operation procedures were as follows: routine disinfection of the acupoints was performed, and the needles were inserted 15–18 mm deep at the Dazhui acupoint (DU14) and 15–20 mm deep at the bilateral Fengchi acupoints (GB20). A twist and turn supplement method was implemented by rubbing the needle with the thumb in the forward direction and index finger in the backward direction, twisting it clockwise, and rubbing it firmly to reach a fixed depth and angle. The needles were left in for 30 min before removal.

2.5 MRI data acquisition

MRI scans were performed using an Achieva 3.0-Tesla TX MRI scanner with a 32-channel head coil (Philips, Amsterdam, Netherlands). The subjects rested flat on the examination table and were asked to breathe calmly with eyes closed and remain awake. The void between the subject's head and the coil was stuffed with sponges to minimize head movement. Scanning started after the subject became familiar with the environment. 3D-SNAP-MRA was performed with field of view (FOV) = 160 × 160 × 60 mm3, matrix = 200 × 200, 150 slices, repetition time (TR) = 10.0 ms, echo time (TE) = 5.6 ms and flip angle (FA) = 11°. PCASL was performed with FOV = 230 × 230 × 132 mm3, matrix = 64 × 64, 22 slices, thickness = 6.0 mm, and TR/TE = 3673/11 ms and FA = 90°. T1WI 3D TFE was performed with FOV = 256 × 256 × 160 mm3, voxel = 1.0 × 1.0 × 2.0, matrix = 256 × 256 × 160, 160 slices, NSA = 1. TR/TE/FA = 7.5/3.7/8, technique = 3D fast field echo (FFE), short interval = 2800 ms, and time = 3 min 46 s.
2.6 CBF determination

The CBF values were processed using MatLab software (MathWorks, Natick, MA, USA) with in-house written and developed scripts. The mean perfusion-weighted imaging was converted to CBF in physiological units with a well-recognized model [45]. This model used pseudo-continuous labeling, background suppression, a segmented three-dimensional readout without vascular crushing gradients, and calculation and presentation of both label/control difference images and CBF in absolute units. The mean CBF of the whole brain was calculated using a subject-specific mask of voxels containing at least 50% gray matter that was generated by segmentation of T1-weighted imaging with the SPM8 toolbox [46].

2.7 Vascular feature extraction

SNAP-MRA data were analyzed with iCafe software to extract the vascular features [37]. To enhance the capacity to distinguish vessels in close proximity, a modified open-curve active contour model was used to trace the vessels. Modifications included reslicing, intensity normalization, rudimentary segmentation before tracing, and a combined tracing approach with both the original image and the Frangi vesselness-filtered image [37]. Then, the arteries were labeled and the features were calculated. It was a semi-automated process that allowed human supervision and correction to ensure optimal tracing quality. Further details on the implementation can be found in a previous publication [37].

Extracted features included total length, the intracranial artery segment visualized in the ICA and MCA, total volume, the volume of the visualized ICA and the intracranial MCA with the calculation based on a cylindrical model with a varying radius along the centerline, total intensity, the mean intensity of an artery with a relatively large radius and vertical orientation including the ICA and MCA, the length of the intracranial segment of the MCA, the volume of the intracranial MCA, the mean signal intensity at each centerline point of all MCA arteries, proximity length (the length of the main artery near the circle of Willis or the length of the M1 segment; distal length), the lengths of M2, M3, and the distal artery, mean of the M1 radius, the mean of the radius of the M1 segment of the MCA, and the number of branches in the artery from the bifurcation to the end of the branch.

2.8 Statistical analysis

All statistics and calculations were performed using the SPSS version 22.0 statistical analysis program (IBM Corp., Armonk, NY, USA). The measurement data were expressed as the mean ± standard deviation (SD). Statistical analysis was performed primarily on the basis of the comparison of efficacy. When the indicators were normally distributed, a t-test was used; otherwise, nonparametric methods, such as the Wilcoxon rank-sum test or Kruskal–Wallis H test, whichever was suitable, were used. Regression analysis was based on linear regression analysis. All statistical analyses were performed with α = 0.05 as the significant limit of difference.

3 Results

3.1 Demographic characteristics

Table 1 details the demographic data for the 15 subjects. The effect of acupuncture treatment on motor symptoms was evaluated with UPDRS-III. The UPDRS-III score before acupuncture was 44.4 ± 9.1 and significantly decreased to 38.6 ± 11.0 (P ≤ 0.001) after acupuncture (Table 2). The VA5 was 7.25 ± 0.24 before acupuncture and
Table 1  Demographic data for the 15 PD patients.

| Characteristics     | Data                         |
|---------------------|------------------------------|
| Gender (n), male/total | 3/12                        |
| Age (years), average (min–max) | 58.13 (43–71)              |
| Duration (months), average (min–max) | 111.6 (71–228)           |
| H-Y scale, average (min–max) | 2.23 (2–3)                |

Table 2  Motor symptoms and subjective comfort data.

|                      | Before acupuncture, mean ± SD | After acupuncture, mean ± SD | P value |
|----------------------|-------------------------------|------------------------------|---------|
| UPDRS-III            | 44.37 ± 9.10                 | 38.61 ± 10.99               | 0.000***|
| VAS                  | 7.25 ± 0.24                  | 5.96 ± 0.35                 | 0.001***|

* The P value of the paired sample t-test using mean ± SD.
** The P value of the Wilcoxon test statistic designed with median pairing.
*** P < 0.01.

5.96 ± 0.35 after acupuncture. The decrease was significant (P = 0.001; Table 2).

3.2 CBF changes after acupuncture

After acupuncture, obvious changes in signal intensity, shown in gray levels, were frequently noted in SNAP-MRA images, especially in the ICA and MCA M1 segments. Two typical examples are shown in Fig. 1.

However, the mean global CBF was 31.70 ± 2.97 before acupuncture and 31.55 ± 3.00 after acupuncture, showing no statistically significant difference (P = 0.847).

3.3 Cerebrovascular feature changes after acupuncture

Through vessel tracing, lengthening of intracranial blood vessels, especially the distal MCA, could be seen in most patients after acupuncture. A typical example is shown in Fig. 2.

Table 3 lists all the quantitative values of the extracted cerebrovascular features. Among the general cerebrovascular features, the total length

Fig. 1  SNAP-MRA images of two PD patients (patient 1: 63 years, female; patient 2: 57 years, female) before and after acupuncture showing that the signal intensity and grayscale of the ICA and MCA M1 segments were significantly different. The signal intensity increased after acupuncture, and the grayscale became higher.

Fig. 2  Sagittal and axial views of SNAP-MRA images of a 60-year-old female PD patient. The length of intracranial blood vessels changed significantly before and after acupuncture, and the distal length of the MCA after acupuncture was significantly increased (as shown in the red circles).
Table 3  Total and local cerebral blood flow and vascular data.

|                          | Before acupuncture, mean ± SD | After acupuncture, mean ± SD | P value |
|--------------------------|-------------------------------|-------------------------------|---------|
| Total length             | 3,509 ± 814                   | 3,900 ± 935                   | 0.012**|
| Total volume             | 58,135 ± 16,984               | 64,479 ± 12,419               | 0.098*  |
| Total intensity          | 2,146 ± 471                   | 2,095 ± 402                   | 0.541†  |
| MCA length               | 3,196 ± 805                   | 3,580 ± 933                   | 0.012*  |
| MCA volume               | 33,322 ± 10,788               | 35,575 ± 11,463               | 0.370   |
| MCA intensity            | 1,680 ± 280                   | 1,518 ± 245                   | 0.005** |
| MCA branches             | 35.60 ± 11.21                 | 40.93 ± 9.06                  | 0.020†  |
| Proximal length          | 92.36 ± 26.60                 | 92.98 ± 26.03                 | 0.913   |
| Distal length            | 3,104 ± 814                   | 3,487 ± 937                   | 0.011‡  |
| M1 radius                | 3.75 ± 0.40                   | 3.82 ± 0.38                   | 0.043*  |
| M1 intensity             | 89.04 ± 48.03                 | 262.0 ± 139.9                 | 0.000** |

* The P value of the paired sample t-test using mean ± SD.
† The P value of the Wilcoxon test statistic designed using median pairing.
‡ P < 0.05, ‡‡ P < 0.01.

showed a significant increase (P = 0.012) from 3,509 ± 814 before acupuncture to 3,900 ± 935 after acupuncture. The total volume (P = 0.098) and the total intensity (P = 0.541) did not show a significant difference.

Among the local cerebrovascular features, MCA length (P = 0.012) and branches (P = 0.020), distal length (P = 0.011), M1 radius (P = 0.043), and M1 intensity (P ≤ 0.001) showed a significant increase, whereas the MCA intensity (P = 0.005) showed a significant decrease. The other features, namely, the MCA volume (P = 0.370) and the proximal length (P = 0.913), showed no difference.

Correlations between the changes in the distal length and proximal length with the changes in the total length and the MCA length were examined (Fig. 3). There was a linear relationship between the distal length changes and the total length (r = 0.921, P ≤ 0.001) as well as the MCA length changes (r = 0.971, P ≤ 0.001) before and after acupuncture. This correlation was not found with the proximal length changes (P = 0.567 and P = 0.621, respectively).

3.4 Correlation between the vascular characteristics and clinical outcomes

Linear regressions were performed to analyze the correlations between changes in cerebrovascular characteristics before and after acupuncture and changes in clinical symptoms and subjective comfort feelings (Table 4). The results showed that there was a positive correlation between the changes in signal intensity of the M1 segment and the changes in the UPDRS-III score (r = 0.911, P ≤ 0.001, Fig. 4). Changes in the other vascular characteristics showed no correlation with the changes in UPDRS-III nor VAS scores.

4 Discussion

In this study, PCASL and SNAP-MRA were used to visualize the changes in the intracranial blood vessels before and after acupuncture in a real-time and quantifiable manner. These are groundbreaking results. With the newly developed quantitative analysis tool iCafe, brain vessels were traced and various features were extracted and analyzed. These methods helped
to clearly and intuitively display the physiological and pathological mechanisms of acupuncture, which is of great importance for further exploration of TCM and acupuncture in the field of brain science.

After acupuncture at the Dazhui and Fengchi acupoints, the PD patients showed improvement in both movement performance and subjective feelings evaluated with UPDRS-III and VAS scales, respectively. During the procedure, various cerebrovascular characteristics changed.

Table 4  Linear regression analysis of vascular characteristics changes with UPDRS-III and VAS changes before and after acupuncture.

|                        | UPDRS changes | VAS changes |
|------------------------|---------------|-------------|
|                        | $r$           | $t$         | $p$         | $r$           | $t$         | $p$         |
| Total length           | 0.378         | 2.168       | 0.165       | 0.462         | 3.530       | 0.083       |
| Total volume           | 0.304         | 1.324       | 0.271       | 0.460         | 3.497       | 0.084       |
| Total intensity        | 0.114         | 0.173       | 0.685       | 0.282         | 1.121       | 0.309       |
| MCA length             | 0.351         | 1.831       | 0.199       | 0.438         | 3.452       | 0.086       |
| MCA volume             | 0.190         | 0.489       | 0.497       | 0.368         | 2.041       | 0.177       |
| MCA intensity          | 0.154         | 0.314       | 0.583       | 0.019         | 0.005       | 0.946       |
| MCA branches           | 0.448         | 3.273       | 0.094       | 0.298         | 1.265       | 0.281       |
| Proximal length        | 0.037         | 0.018       | 0.926       | 0.082         | 0.087       | 0.772       |
| Distal length          | 0.350         | 1.819       | 0.200       | 0.455         | 3.396       | 0.088       |
| M1 radius              | 0.135         | 0.240       | 0.632       | 0.082         | 0.087       | 0.772       |
| M1 intensity           | 0.911         | 63.369      | 0.000**     | 0.282         | 1.121       | 0.309       |

** $P < 0.01$.  

Fig. 3  (A) Linear relationship between the distal length changes and the total length changes. (B) Linear relationship between the distal length changes and the MCA length changes. (C) Linear relationship between the proximal length changes and the total length changes. (D) Linear relationship between the proximal length changes and the MCA length changes.
It was revealed that acupuncture significantly increased the total length of the intracranial ICA, the total length of the MCA, and the distal length of the M3 segment. Since the increase in the proximal length of the MCA was not significant, the increase in the total length of the intracranial ICA and total valid length of the MCA resulted from the increase in the distal length of the M3 segment. The M3 segment of the MCA provides blood to most parts of the dorsolateral side of the cerebral hemisphere, including the anterior central gyrus, posterior central gyrus, middle frontal gyrus, inferior frontal gyrus, superior parietal lobule, supramarginal gyrus, and temporal lobe. These regions are important components of the cortex–striatum circuit, which plays a decisive role in the control of a patient's sensation and movement. Previous studies showed that blood flow in frontal and parietal lobes was reduced in patients with PD, whereas dopamine had a therapeutic effect by improving blood flow in the corresponding brain regions [28]. There is direct contact between the cerebral microvascular system and dopaminergic nerve endings, which is considered to be one of the mechanisms for the improvement of CBF responses and motor symptoms caused by anti-PD drugs. Lengthening of the distal M3 segment blood flow implied blood supply improvement to these regions, which could lead to functional enhancement. This could be the reason behind acupuncture improving the motor symptoms of PD patients.

Additionally, blood flow in the striatum, globus pallidus, and other basal ganglia regions of the dopaminergic pathway was decreased in patients with PD. It primarily depends on the deep perforating branch in the horizontal segment of the MCA [47]. Our results revealed that acupuncture significantly expanded the diameter of the M1 horizontal segment and increased the number of vessel branches. This could also contribute to the therapeutic effect of acupuncture.

Despite the visible differences in local image signal intensities being observable, especially in the ICA and MCA M1 segment (Fig. 2), the quantified CBF of the whole brain showed no significant difference before and after acupuncture. This implied that acupuncture modulated and balanced the distribution of the cerebral blood supply rather than increasing the whole brain CBF. Thus, whole brain CBF might not be a sensitive indicator of the effect of acupuncture. Analysis of regional CBF might be needed to further demonstrate the influence of acupuncture on brain functions [48].

Among the cerebrovascular features that were altered by acupuncture, changes in the intensity of the MCA M1 segment showed a linear relationship with that of UPDRS-III scores. It again implied that the local blood flow improvement likely plays an important role in acupuncture treatment. The other features demonstrated no quantitative improvement in movement performance or subjective feelings, as revealed by linear regressions, and this might be due to confounding factors, such as individual variation or limitations in the sample size. Further systematic and comprehensive studies should be carried out to elucidate the...
quantitative role of these features. Moreover, improvement in analysis methods might also be needed.

There were certain limitations in this study, including the relatively small sample size. Because of the cost of vascular-neuroimaging research, most neuroimaging studies have a small sample size. Some researchers suggested [49, 50] that the statistical power of neuroimaging studies could be obtained with 12–15 subjects in each group. This study only included PD patients with moderate symptoms. Whether acupuncture would have the same effect in patients with severe conditions requires further research. The lack of a control group was another limitation of this study. This is also a general challenge to current acupuncture studies. An appropriate control group that would not receive any treatment or treatment with sham needles having a puncture effect could be applied to specify the effects of acupuncture and rule out the placebo effect.

5 Conclusions

In this study, acupuncture at the Dazhui and Fengchi acupoints improved movement performance and subjective feelings of PD patients. As revealed by quantitative analysis based on SNAP-MRA, various cerebrovascular features were altered by the treatment, which might account for the therapeutic effects. Moreover, blood flow in the M1 segment showed a correlation with improvement in motor scores. These findings shed new light on the application of acupuncture to treat PD.

Ethical approval

This study was conducted according to the ethical standards of the Declaration of Helsinki and applicable national regulations. It was registered on ClinicalTrials.gov under the number NCT03501004 and approved by the ethics committee of Tsinghua University Yuquan Hospital (Approval No. QHDXY QYY 20180001).

Consent

A written informed consent was obtained from all participants.

Conflicts of interests

The authors declare that there is no conflict of interests regarding the publication of this article.

References

[1] de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol 2006, 5(6): 525–535.
[2] Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm: Vienna 2017, 124(8): 901–905.
[3] Bega D, Zadikoff C. Complementary & alternative management of Parkinson's disease: an evidence-based review of eastern influenced practices. J Mov Disord 2014, 7(2): 57–66.
[4] Rajendran PR, Thompson RE, Reich SG. The use of alternative therapies by patients with Parkinson's disease. Neurology 2001, 57(5): 790–794.
[5] Yang Y, Miao SH, Zhou RS, et al. Analysis and policy recommendations of current status of traditional Chinese medicine treatment on Parkinson's disease. Chin Med Herald 2019, 16(35): 44–47.
[6] Zhang G, Xiong N, Zhang Z, et al. Effectiveness of traditional Chinese medicine as an adjunct therapy for Parkinson's disease: a systematic review and meta-analysis. PLoS One 2015, 10(3): e0118498.
[7] Wei W, Chen HY, Fan W, et al. Chinese medicine for idiopathic Parkinson's disease: a meta-analysis of randomized controlled trials. Chin J Integr Med 2017, 23(1): 55–61.
[8] Cristian A, Katz M, Cutrone E, et al. Evaluation of
acupuncture in the treatment of Parkinson's disease: a double-blind pilot study. *Mov Disord* 2005, 20(9): 1185–1188.

[9] Jiang M, Huang Y, Zhao Y, et al. Therapeutic effect of scalp electroacupuncture on Parkinson disease. *J South Med Univ* 2006, 26(1): 114–116.

[10] Yang DH, Shi Y, Jia YM. Influence of acupuncture plus drug in the amelioration of symptoms and blood antioxidant system of patients with Parkinson disease. *Chin J Clin Rehabil* 2006, 10(19): 14–16.

[11] Yong Z. Clinical observation on acupuncture treatment of Parkinson's syndrome. *J Acupuncture Tuina Sci* 2006, 4(4): 211–212.

[12] Chau Y, Lee H, Kim H, et al. Parsing brain activity associated with acupuncture treatment in Parkinson's diseases. *Mov Disord* 2009, 24(12): 1794–1802.

[13] Lei H, Toosizadeh N, Schwenk M, et al. A pilot clinical trial to objectively assess the efficacy of electroacupuncture on gait in patients with Parkinson's disease using body worn sensors. *PLoS One* 2016, 11(5): e0155613.

[14] Kong KH, Ng HL, Li W, et al. Acupuncture in the treatment of fatigue in Parkinson's disease: a pilot, randomized, controlled, study. *Brain Behav* 2018, 8(1): e00897.

[15] Aroxa FH, Gondim IT, Santos EL, et al. Acupuncture as adjuvant therapy for sleep disorders in Parkinson's disease. *J Acupuncture Meridian Stud* 2017, 10(1): 33–38.

[16] Yuan Y, Chen F, Yang JS. Forty-nine cases of Parkinson's disease treated by acupuncture adjacent therapy. *Chin Acupuncture Moxibust* 2014, 34(1): 53–54.

[17] Ferry P. Use of complementary therapies and non-prescribed medication in patients with Parkinson's disease. *Postgrad Med J* 2002, 78(924): 612–614.

[18] Pecci C, Rivas MJ, Moretti CM, et al. Use of complementary and alternative therapies in outpatients with Parkinson's disease in Argentina. *Mov Disord* 2010, 25(13): 2094–2098.

[19] Tan LC, Lau PN, Jamora RD, et al. Use of complementary therapies in patients with Parkinson's disease in Singapore. *Mov Disord* 2006, 21(1): 86–89.

[20] Løkk J, Nilsson M. Frequency, type and factors associated with the use of complementary and alternative medicine in patients with Parkinson's disease at a neurological outpatient clinic. *Parkinsonism Relat Disord* 2010, 16(8): 540–544.

[21] Xian XL, Xiao XR. Re-discussion about holism of traditional Chinese medicine (In Chinese). *Alin J Tradit Chin Med* 2015, 35(2): 113–115.

[22] Chen J, Yang DX, Cao Y, et al. Syndrome differentiation and treatment algorithm model in traditional Chinese medicine based on disease cause, location, characteristics and conditions. *IEEE Access* 2018, 6: 71801–71813.

[23] Kim HJ, Jeon BS. Is acupuncture efficacious therapy in Parkinson's disease? *J Neurol Sci* 2014, 341(1/2): 1–7.

[24] Lee MS, Shin BC, Kong JC, et al. Effectiveness of acupuncture for Parkinson's disease: a systematic review. *Mov Disord* 2008, 23(11): 1505–1515.

[25] Lam YC, Kum WF, Durairajan SSK, et al. Efficacy and safety of acupuncture for idiopathic Parkinson's disease: a systematic review. *J Altern Complement Med* 2008, 14(6): 663–671.

[26] Chen Y, Feng WJ, Zhang XL. Parkinson's disease combined with overactive bladder syndrome treated with acupuncture and medication. *Chin Acupuncture Moxibust* 2012, 32(3): 215–218.

[27] Pelizzari L, Laganà MM, Rossetto F, et al. Cerebral blood flow and cerebrovascular reactivity correlate with severity of motor symptoms in Parkinson's disease. *Ther Adv Neurol Disord* 2019, 12: 1756286419838354.

[28] Chen YF, Pressman P, Simuni T, et al. Effects of acute levodopa challenge on resting cerebral blood flow in Parkinson's disease patients assessed using pseudo-continuous arterial spin labeling. *PeerJ* 2015, 3: e1381.

[29] Taguchi S, Tanabe N, Niwa JL, et al. Motor improvement-related regional cerebral blood flow changes in Parkinson's disease in response to antiparkinsonian drugs. *Parkinsonism Dis* 2019, 2019: 7503230.

[30] Ding N, Jiang J, Xu AP, et al. Manual acupuncture regulates behavior and cerebral blood flow in the SAMP8 mouse model of Alzheimer's disease. *Front Neurosci* 2019, 13: 37.

[31] Kim YI, Kim SS, Sin RS, et al. Study on the cerebral blood flow regulatory features of acupuncture at
acupoints of the governor vessel. *Med Acupunct* 2018, 30(4): 192–197.

32. Ratmansky M, Levy A, Messinger A, et al. The effects of acupuncture on cerebral blood flow in post-stroke patients: a randomized controlled trial. *J Altern Complement Med* 2016, 22(1): 33–37.

33. Chen S, Zhao HL, Li JF, et al. Evaluation of carotid atherosclerotic plaque surface characteristics utilizing simultaneous noncontrast angiography and intraplaque hemorrhage (SNAP) technique. *J Magn Reson Imaging* 2018, 47(3): 634–639.

34. Li Q, Wang J, Chen H, et al. Characterization of craniofascial artery dissection by simultaneous MR noncontrast angiography and intraplaque hemorrhage imaging at 7T. *AJNR Am J Neuroradiol* 2015, 36(9): 1769–1775.

35. Xiong YH, Zhang Z, He L, et al. Intracranial simultaneous noncontrast angiography and intraplaque hemorrhage (SNAP) MRA: Analyzation, optimization, and extension for dynamic MRA. *Magn Reson Med* 2019, 82(5): 1646–1659.

36. Wang J, Guo M, Yamada K, et al. In vivo validation of simultaneous non-contrast angiography and intraplaque hemorrhage (SNAP) magnetic resonance angiography: an intracranial artery study. *PLoS One* 2016, 11(2): e0149130.

37. Chen L, Mossa-Basha M, Balu N, et al. Development of a quantitative intracranial vascular features extraction tool on 3D MRA using semiautomated open-curve active contour vessel tracing. *Magn Reson Med* 2018, 79(6): 3229–3238.

38. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson’s disease. *Mov Disord* 2015, 30(12): 1591–1601.

39. MacPherson H, White A, Cummings M, et al. Standards for reporting interventions in controlled trials of acupuncture: the STRICTA recommendations. *Complement Ther Med* 2001, 9(4): 246–249.

40. Zeng BY, Salvage S, Jenner P. Current development of acupuncture research in Parkinson’s disease. *Int Rev Neurobiol* 2013, 111: 141–158.

41. Cho SY, Lee YE, Doo KH, et al. Efficacy of combined treatment with acupuncture and bee venom acupuncture as an adjunctive treatment for Parkinson’s disease. *J Altern Complement Med* 2018, 24(1): 25–32.

42. Leem J. Acupuncture for motor symptom improvement in Parkinson’s disease and the potential identification of responders to acupuncture treatment. *Integr Med Res* 2016, 5(4): 332–335.

43. Wang F, Sun L, Zhang XZ, et al. Effect and potential mechanism of electroacupuncture add-on treatment in patients with Parkinson’s disease. *Evid Based Complement Alternat Med* 2015, 2015: 692795.

44. Sun ZL, Jia J, Gong XL, et al. Inhibition of glutamate and acetylcholine release in behavioral improvement induced by electroacupuncture in parkinsonian rats. *Neurosci Lett* 2012, 520(1): 32–37.

45. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med* 2015, 73(1): 102–116.

46. Ashburner J, Barnes G, Chen CC, et al. SPM8 manual. *Functional Imaging Laboratory* 2012: 41.

47. Li YL, Xu JP, Niu R, et al. The clinical significance of transcranial Doppler (tcd) evaluated on the patients with idiopathic Parkinson’s disease and vascular Parkinson’s syndrome (In Chinese). *Acta Acad Med Shandong* 2000, 38(3): 284–285, 288.

48. Huang Y, Zhao Y, Jiang XM, et al. Effect of scalp acupuncture on regional cerebral blood flow in Parkinson’s disease patients (In Chinese). *China J Tradit Chin Med Pharm* 2009, 24(3): 305–308.

49. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *J Neurosci Methods* 2002, 118(2): 115–128.

50. Hayasaka S, Peiffer AM, Hugenschmidt CE, et al. Power and sample size calculation for neuroimaging studies by non-central random field theory. *Neuroimage* 2007, 37(3): 721–730.
Yuan Yang received her Ph.D. degree in acupuncture and moxibustion from Beijing University of Chinese Medicine in June 2017. She is currently working in preventive treatment of disease department in Tsinghua University Yuquan Hospital. In recent years, she has published more than 10 articles in Chinese core journals. Her research focuses on the effect and mechanism of traditional Chinese medicine and acupuncture on neurodegenerative diseases and nervous system tumors. E-mail: ciisy198811@163.com

Le He received the Master’s degree in radiology from, Xinjiang Medical University in July 2003. She was a resident physician radiologist at Affiliated No. 1 Hospital of Xinjiang Medical University (1995–2000 and 2003–2004), and an MRI senior application engineer in PHILIPS (2005–2012). She has been an MRI application technologist in Center for Biomedical Imaging Research Department, Biomedical Engineering School of Medicine, Tsinghua University since 2012. Her research focuses on MRI sequence optimized and clinical application of cardiovascular and nervous system. E-mail: hele0806@aliyun.com

Suhua Miao received her Master’s degree from Capital Medical University, majoring in neuroelectrophysiology. At present, she is engaged in clinical and basic research related to neuroelectrophysiology in the Neural Regulation Center of Tsinghua University Yuquan Hospital. She has carried out intraoperative electrophysiological monitoring and systematic electrophysiological evaluation of various diseases such as brain, spinal cord and peripheral nerve. She has published 3 core Chinese journal articles and 4 SCI articles in this research field. E-mail: zuohc0415@163.com

Rongsong Zhou received his Bachelor’s degree from Shandong First Medical University in July 2011. Since in April 2012, he has been working at the Department of Neurosurgery in Tsinghua University Yuquan Hospital. He has published one article in World Neurosurgery Journal. Currently, he focuses on the Parkinson’s disease and other movement disorders, and is specializing in multimodal post-processing of imaging data of motor disorders. E-mail: rongsong0925@163.com
Yuqi Zhang is a tenured professor, Ph.D. supervisor and chief doctor at School of Medicine, Tsinghua University. He is also the president of Tsinghua University Yuquan Hospital. He works and studies in the field of pediatric neurosurgery, mainly dealing with cerebrovascular diseases like hydrocephalus and brain tumor. He is holding some positions including the 3rd committee member of CMDA (China Medical Doctor Association), editor-in-chief of Brain Science Advances, Chinese Journal of Neurosurgery, and Chinese Journal of Pediatric Surgery, chairman of WCCMF (Wang Chungcheng Medical Foundation). His prolific research results in about 180 papers with prominent impact factor.

Yu Ma received her Ph.D. in neurosurgery from China Medical University. She is the director of Neuromodulation Center of Tsinghua University Yuquan Hospital. Her expertise is surgical treatment for movement disorders such as Parkinson’s disease and dystonia. She has more than 10 years of clinical experience in deep brain stimulation (DBS) surgery, including pre-operative evaluation, intraoperative electrophysiological recording, implantation, post-operative programming and medication adjustment. She has treated more than 1000 patients using DBS and offered over 10000 times outpatient service for postoperative programming. She has published over 30 articles and participated in 3 monographs. E-mail: lymayu@163.com