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Regional Coherence Alterations in Patients with Poststroke Cognitive Impairment after Acupuncture Therapy: A Resting-State fMRI Study

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Abstract

Objective: To explore regional homogeneity (ReHo) alterations after acupuncture treatment in poststroke cognitive impairment (PSCI) patients. **Methods**: Twenty-one PSCI patients who underwent acupuncture therapy in our hospital and 12 matched healthy controls were enrolled in this study. All study subjects underwent resting-state functional magnetic resonance imaging (rs-fMRI); for PSCI patients, rs-fMRI scans were conducted before and after acupuncture therapy. Data preprocessing was performed using the DPARSF5.4 and SPM12 toolkits on the MATLAB 2022b platform. DPARSF5.4 was used to calculate the ReHo index of the preprocessed resting-state data. A two-sample t-test was used to compare the differences in ReHo between the PSCI patients group pretreatment and the control group (with sex and age as covariates), and a paired t-test was used to compare the differences in ReHo between the pretreatment and posttreatment groups of PSCI patients (without covariates). AAL_116_binary_mask.nii was used as the statistical mask, and the statistical results were corrected using family-wise error correction, with $P < 0.001$ at the voxel level and $P < 0.05$ at the cluster level considered to indicate statistical significance. Results: In the right cerebellum area 6, the ReHo of the pretreatment PSCI group was significantly greater than that of the control group; in the left middle frontal gyrus, the ReHo of the posttreatment PSCI group was significantly higher than that of the pretreatment group. **Conclusion**: PSCI patients exhibited abnormal ReHo in the resting state, and ReHo was significantly

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altered after acupuncture treatment. The results of this study suggest that ReHo might be a potential biomarker in the diagnosis and treatment of PSCI.

Keywords

Acupuncture, Post-Stroke Cognitive Impairment, Functional Magnetic Resonance Imaging, Regional Coherence

1. Introduction

Stroke is very common in middle-aged and elderly populations and is associated with high disability and mortality rates. Stroke not only causes physical dysfunction but also poses a high risk of cognitive impairment. Studies have shown that the incidence of poststroke cognitive impairment (PSCI) is as high as 80% [1], and approximately 25% of stroke patients develop vascular dementia after one year [2]. Therefore, the early diagnosis, prevention, and treatment of PSCI have become critical issues that need to be addressed.

The exact mechanism underlying PSCI remains unclear. The continuous development of brain imaging technology, especially the emergence of resting-state functional MRI (rs-fMRI), has opened new avenues for studying brain structure and function [3]. Regional homogeneity (ReHo) is a whole-brain rs-fMRI parameter that can be used to identify abnormalities in local neural activity throughout the brain and is a powerful tool for studying alterations in resting-state brain activity [4]-[13]. Abnormal ReHo may be related to an imbalance in spontaneous neural activity within and between corresponding brain regions, and this imbalance may be associated with cognitive impairment and brain injuries such as transient ischemic attack [14] [15].

Currently, acupuncture is recognized as a complementary therapy to improve the cognitive function of PSCI patients [16] and is becoming increasingly popular [11] [17]-[22]. However, to date, no studies have focused on ReHo alterations after acupuncture in PSCI patients. Therefore, the purpose of this study was to explore the ReHo alterations after acupuncture treatment in PSCI patients.

2.Materials and Methods

2.1. Clinical Data

Twenty-one PSCI patients who underwent acupuncture therapy in our hospital and 12 healthy controls (HCs) matched for age, sex, and education level were enrolled in this study. The inclusion criteria for PSCI patients were as follows: 1) first-onset PSCI and meeting the diagnostic criteria for cerebral infarction; 2) a diagnosis of unilateral basal ganglia and/or corona radiata infarction lesions on CT or MRI; 3) right-handedness; and 4) conscious with stable vital signs. The exclusion criteria were as follows: 1) hemorrhagic stroke or second stroke confirmed by imaging; 2) mental illness such as depression, hysteria, or obvious hypophrenia before this PSCI onset; 3) inability to receive acupuncture therapy or fainting during acupuncture therapy; 4) claustrophobia or contraindications to MRI scan; and 5) poor image quality or incomplete data. The same acupuncturist sequentially administered acupuncture treatment to the Neiguan (bilaterally), Baihui, and Sishenzong acupoints of the PSCI patients every morning from 8:00 to 10:00 a.m., 5 days a week, for 2 weeks. Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) scores were evaluated before and at the end of acupuncture treatment. All the subjects signed informed consent forms.

2.2 Brain MRI Acquisition

All study subjects underwent 3D-T1-weighted structural imaging (T1WI) and rs-fMRI scans using a magnetic resonance scanner with a 32-channel head-neck coil (MR750 3.0 T, GE) (**Table 1**). For PSCI patients, rs-fMRI scans were conducted at baseline and 2 weeks after acupuncture therapy.

Table 1. MRI sequences and parameters.

Sequence	TR/TE (ms)	FA (°)	Matrix (mm²)	FOV (mm²)	ST (mm)	SI	Time
T1WI	8.2/3.1	7	256 × 256	256 × 256	1	0	3 min 59 s
rs-fMRI	2000/30	90	64 × 64	230 × 230	3.5	0.7	8 min 10 s

Notes: TR, repetition time; TE, echo time; FA, flip angle; FOV, field of view; ST, slice thickness; SI, slice thickness; T1WI, T1-weighted imaging; rs-fMRI, resting-state functional MRI.

2.3. Data Processing

Data preprocessing was performed using DPARSF5.4 and SPM12 toolkits on the MATLAB 2022b platform according to a previous study [23] [24]. The main steps were as follows: 1) Data format conversion: The functional and structural images of the original data were converted to files in the NIfTI format using dcm2niix. 2) The first 10 time points were removed to ensure signal stability. 3) Time correction: All image layers of each result were aligned with the time point in the middle of the scan so that the result of each scan was close to the actual result at a certain time. 4) Head-motion correction: Subjects whose head rotated more than approximately 3˚ or moved more than 3 mm in the x, y, or z axis were excluded. 5) Spatial normalization: The brain images of the subjects were registered to the standard space of the Montreal Neurological Institute (MNI) and then resampled to a voxel size of 3 mm × 3 mm × 3 mm to obtain normalized images. 6) Linear drift removal was performed to eliminate the baseline drift caused by the machine. 7) Covariates were removed to eliminate the influences of head motion, white matter signals, and cerebrospinal fluid signals. 8) Low-frequency filtering: All data were processed with a horizontal bandwidth of 0.01 - 0.08 Hz to remove high-frequency signals and physiological noise.

According to a previous study [25], DPARSF5.4 was used to calculate the ReHo index on the preprocessed resting-state data. 1) The similarity between time series was calculated using Kendall's coefficient of concordance (KCC). For each subject, the KCC value between the time series of a specific voxel and its 26 nearest voxels was calculated to obtain the ReHo map for each participant. 2) ReHo map normalization. The KCC value of each voxel in the ReHo map of each subject was divided by the mean KCC value of all voxels throughout the brain of the subject to obtain a normalized ReHo map that eliminated individual differences. 3) Image smoothing: Spatial smoothing of the ReHo map was performed using a Gaussian smoothing kernel (full-width half maximum (FWHM) = 6 × 6 × 6 mm) to reduce spatial noise and enhance the signal-to-noise ratio (SNR) of the image.

2.4. Statistical Analysis

A two-sample t-test was used to compare the difference in ReHo between the pretreatment group of PSCI patients and the control group (with sex and age as covariates), and a paired t-test was used to compare the difference in ReHo between the pretreatment and posttreatment groups of PSCI patients (without covariates). AAL_116_binary_mask.nii was used as the statistical mask, and the statistical results were corrected using family-wise error (FWE) correction, with $P < 0.001$ at the voxel level and $P < 0.05$ at the cluster level.

3. Results

The demographic characteristics of the PSCI and HC groups are shown in Table 2. In the right cerebellum area 6 (Cerebellum_6_R), the ReHo of the pretreatment group was significantly higher than that of the control group (Table 2, Figure 1). In the left middle frontal gyrus (Frontal_Mid_L (aal)), the ReHo of the posttreatment group was significantly higher than that of the pretreatment group (Table 3, Figure 2).

In addition, before treatment, the ReHo index for the right cerebellum area 6 of the PSCI patients was negatively correlated with the MMSE score ($r = 0.874$, $p = -0.037$). After treatment, the MMSE (18.0 ± 3.2 vs. 22.2 ± 3.0, $p < 0.001$) and MoCA (15.7 ± 3.6 vs. 19.6 ± 3.9, $p < 0.001$) scores of the PSCI patients increased significantly.

Table 2. The demographic characteristics of the of the PSCI and HC groups.

Clinical characteristics	PSCI	HC	X^2/t/Z	P
Sex (males/females)	12/9	4/8	1.733	0.188
Age (years)	60.2 ± 9.2	56.8 ± 5.0	1.393	0.174
Education level (years)	6(6,9)	6(6,9)	-0.514	0.645

Table 3. Analysis of the ReHo of the pretreatment group of PSCI patients compared with that of the control group and the posttreatment group of PSCI patients. (voxel_p < 0.001, cluster_p < 0.05, family-wise error corrected)

Between-group comparison	Brain region	Coordinates of peak MNI			t value	Cluster size
		X	Y	Z		
Pretreatment group > Control group	Cerebellum_6_R (aal)	21	−54	−24	5.3199	210
Posttreatment group > Pretreatment group	Frontal_Mid_L (aal)	−27	45	18	5.898	259

Notes: MNI, Montreal Neurological Institute.

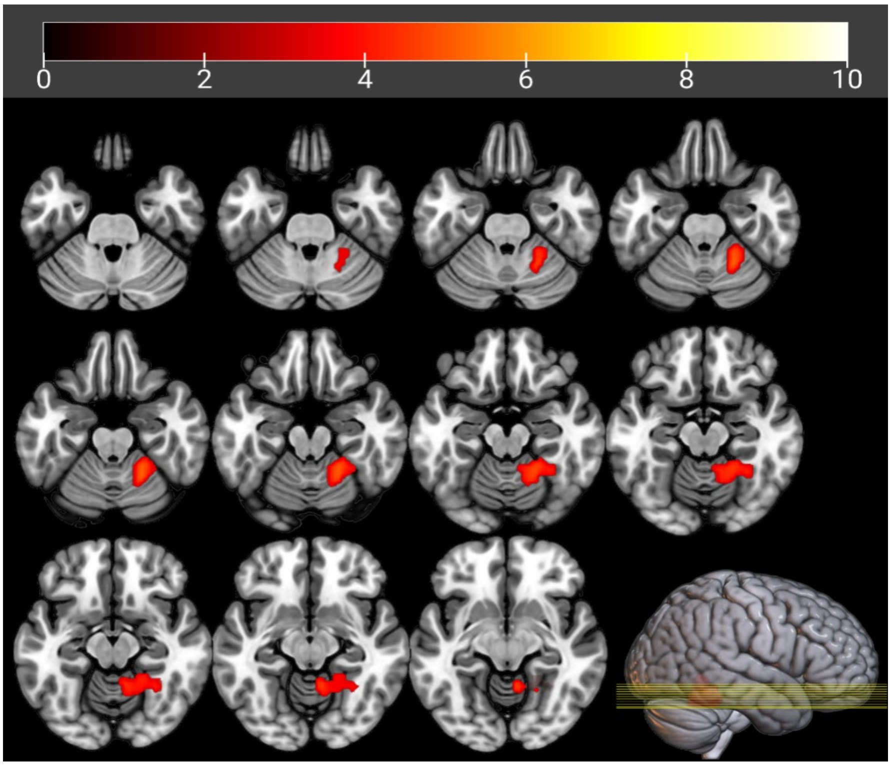

Figure 1. Brain regions with regional homogeneity (ReHo) in the pretreatment group of poststroke cognitive impairment (PSCI) patients. ReHo in the pretreatment group of PSCI patients was higher than that in control group subjects (sectional view).

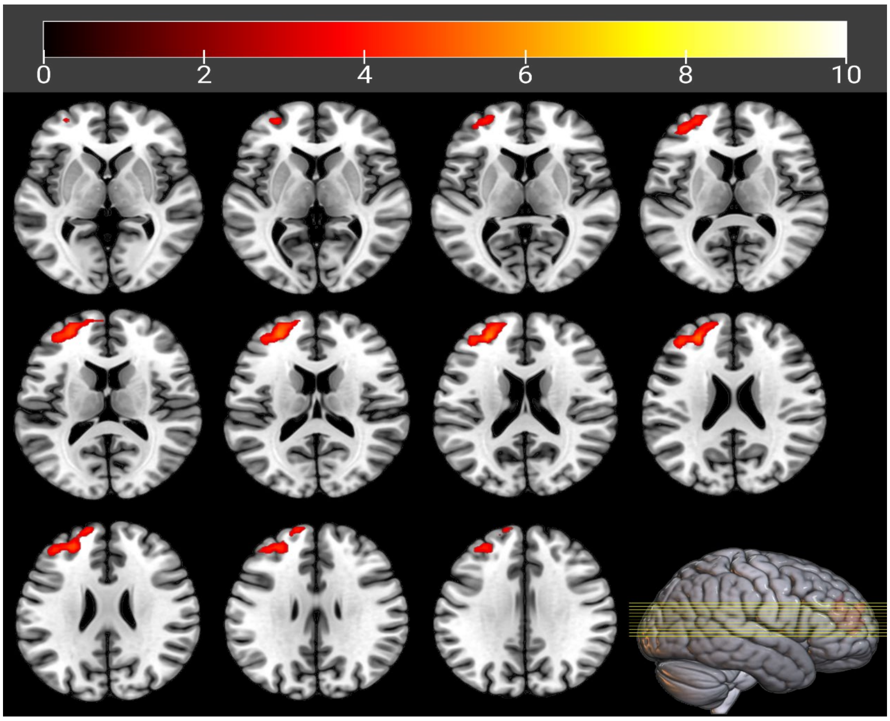

Figure 2. Brain regions with regional homogeneity (ReHo) in the posttreatment group of poststroke cognitive impairment (PSCI) patients. ReHo in the posttreatment group of PSCI patients was higher than that in the pretreatment group of PSCI patients (sectional view).

4. Discussion

In this study, the ReHo algorithm was used to investigate ReHo alterations after acupuncture treatment in PSCI patients. The results showed that the ReHo of the right cerebellum area 6 was significantly higher in the group of PSCI patients before treatment than in the HC group and that the ReHo of the left middle frontal gyrus was significantly higher in the PSCI patients after treatment than before treatment. These findings may help to elucidate the neuropathophysiological mechanisms of cognitive impairment in PSCI patients.

Thus far, studies on ReHo in PSCI patients are scarce in the literature. The existing studies focus mainly on alterations in ReHo in patients with subcortical stroke. Peng *et al.* [26] used rs-fMRI to study alterations in ReHo in patients with subcortical stroke. They showed that, compared with HCs (n = 30) and patients with good cognitive function after stroke (n = 16), patients with poor cognitive function after stroke (n = 16) had significantly reduced ReHo in the bilateral anterior cingulate cortex (ACC) and the left posterior cingulate cortex (PCC)/precuneus (PCu). Their study findings suggested that ReHo may be a promising indicator of neurobiological deficits in poststroke patients. Liu *et al.* [27] studied the relationship between alterations in default mode network (DMN) spontaneous activity in patients with chronic subcortical stroke and cognitive decline. The researchers performed multimodal MRI examinations on 18 patients with chronic subcortical stroke and 20 HCs; calculated the ReHo, resting-state functional connectivity (rsFC), and gray matter volume (GMV); and compared the ReHo in the DMN between the groups. Then, they extracted the brain regions with significant between-group differences in ReHo and calculated the rsFC and GMV of these areas. Their results showed that, compared with the HC group, the stroke patients had reduced ReHo in the PCC and reduced rsFC between the PCC and ACC. There was no significant difference in the volume of the PCC or the whole DMN between the groups. The ReHo of the PCC was associated with cognitive decline. These researchers argued that regional spontaneous activity and its interactions are impaired in stroke patients and that the reduced ReHo of the PCC may be the cause of poststroke cognitive decline. Yuan *et al.* [28] explored the brain network activities in amnesic mild cognitive impairment (aMCI) patients. They found that, compared with HCs, aMCI patients had significantly reduced ReHo areas in the right inferior parietal lobule (IPL), left PCC/PCu, left inferior temporal gyrus (ITG), right supramarginal gyrus (SMG), right fusiform gyrus (FG), bilateral lentiform nucleus (LN), and right posterior cerebellum; moreover, the ReHo areas in the right middle frontal gyrus (MFG), bilateral bilateral postcentral gyrus (PoCG), left cuneus, and right lingual gyrus (LG) increased significantly. Ye Q *et al.* investigated ReHo in subjects with white matter hyperintensities (WMHs). Their results showed that the WMH with CI group had higher ReHo in the bilateral superior parietal gyrus (SPG)/superior occipital gyrus (SOG) than both the WMH without CI group and the HC group, suggesting that CI could be related to greater local coherence of activities in the SPG/SOG [29]. The results of the present study showed that the ReHo of right cerebellum area 6 was significantly greater in the pretreatment group of PSCI patients than in the HC group, which is consistent with the results of Ye Q *et al.* [29].

Details of the underlying mechanisms of PSCI are unknown in detail. Vascular cognitive impairment (VCI) and mixed Alzheimer's disease (AD) with stroke, alone or in combination, may contribute to the pathogenesis of PSCI [30] [31]. PSCI patients benefit from not only the application of anti-dementia treatments but also measures focusing on cerebrovascular diseases. A healthy lifestyle, stress management and cognitive rehabilitation are the basic elements of successful management of mild cognitive impairment (MCI). Darviri C *et al.* developed a new non-pharmaceutical self-referring intervention called Pythagorean Self-Awareness Intervention (PSAI) that improved the elements of healthy lifestyle, stress management and cognitive rehabilitation in MCI patients [32]. Numerous studies have investigated the impact of acupuncture treatment on CI. A meta-analysis including 29 randomized clinical trials (RCTs) with 2477 PSCI patients demonstrated that the MMSE and MoCA scores were higher in the acupuncture group than in the medicine group; acupuncture was superior to conventional therapy for improving cognitive function in PSCI patients at 4 weeks after treatment. The results of that meta-analysis indicated that acupuncture therapy has potential value in ameliorating cognitive deficits in individuals diagnosed with PSCI [33]. In the present study, the MMSE and MoCA scores of the PSCI patients increased significantly after acupuncture therapy, which is consistent with these previous findings.

The above research results suggest that PSCI patients exhibit abnormal ReHo in local brain regions. In addition, the present study further revealed the trend of alterations in ReHo in PSCI patients after acupuncture treatment, which may provide a new noninvasive method for evaluating and researching PSCI treatment.

Our study has the following limitations: 1) The sample size of each group was relatively small. Future studies with larger sample sizes should be performed to validate these results further. 2) The included PSCI patients were all patients with mild cognitive impairment. In the future, further comparative analysis of the ReHo differences among patients with varying degrees of cognitive impairment should be performed. 3) For various reasons, the group of PSCI patients in this study were discharged after receiving acupuncture treatment for only two weeks in the hospital. Therefore, data on the dynamic alterations in the ReHo of patients after receiving longer durations of acupuncture treatment were not collected. A lack of long-term follow-up data may affect the generalizability of findings and the overall validity of the results. This issue will be investigated when conditions permit in the future. In addition, a placebo control group is needed to demonstrate the effectiveness of acupuncture in future studies.

In summary, PSCI patients exhibited abnormal ReHo in the resting state, and their ReHo significantly changed after acupuncture treatment. The results of this study suggest that ReHo might be a potential biomarker in the diagnosis and treatment of PSCI.

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Author Contributions

Conception, N.L., X.-H. H., L.Y., X.-M. Z.; patient recruitment and exploration, P.Z., R.W.; data analysis,P.Z., R.W., N.L.; manuscript writing and revision, P. Z., R.W., L.Y.; All authors have read and agreed to the published version of the manuscript.

Ethics Statement

This study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College (No.2020ER117-1).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

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