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# Efficacy of paired associative stimulation combined with low-temperature thermoplastic orthosis in the treatment of post-stroke wrist flexor spasticity

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## *Abstract*

*Objective:* This study aims to investigate the efficacy of Paired Associative Stimulation (PAS) integrated with Low-Temperature Thermoplastic Orthosis (LTTPO) on post-stroke wrist flexor spasticity. *Methods:* This prospective randomized controlled study recruited 63 patients with post-stroke wrist flexor spasticity treated in the Neurology Department of our hospital from January 2022 to June 2023. The patients were randomly assigned in a ratio of 1:1 to receive either sham stimulation combined with LTTPO (control group) or PAS combined with low-temperature thermoplastic orthosis (study group) via a random number table, with 31 patients in the control group and 32 in the study group. The primary endpoints used to evaluate treatment efficacy were functional recovery—assessed by the Modified Ashworth Scale (MAS), Fugl-Meyer Assessment (FMA), Barthel Index (BI), and Visual Analog Scale (VAS)—and brain functional remodeling. *Results:* At treatment completion, 4 weeks post-treatment, and 8 weeks post-treatment, PAS combined with LTTPO provided a significantly higher treatment effectiveness rate than LTTPO with sham stimulation. Patients receiving PAS exhibited significantly better functional recovery of wrist joint and pain mitigation than those with sham stimulation at the aforementioned time points, as evidenced by the lower MAS scores, higher Simplified FMA scores, and lower VAS pain scores. Both groups demonstrated improvements in BI scores over time, indicating enhanced functional independence. However, they also exhibited progressively worsening joint swelling. Despite these opposing trends, the differences between the two groups in both BI improvement and joint swelling were not statistically significant.
*Conclusion:* The integration of PAS combined with LTTPO offers a viable alternative managing post-stroke wrist flexor spasticity by significantly reducing wrist flexor spasticity, improving functional recovery, alleviating pain, and promoting neural remodeling.

*Keywords:* Stroke, paired associative stimulation, transcranial magnetic stimulation, peripheral nerve electrical stimulation, wrist flexor spasticity.

## INTRODUCTION

Stroke is a common cerebrovascular disease that causes significant nervous system impairment and is a major factor in long-term disability.[1] Despite substantially enhanced survival benefits provided by evolving intervention techniques and rehabilitation treatments, the disability rate of post-stroke patients remains high. Approximately 85% of stroke survivors experience limb paralysis, within which upper limb dysfunction, particularly wrist flexor spasticity, represents the most prevalent category, accounting for 55% to 75%.[2,3] Hand dysfunction affects daily activities and personal care, leading to difficulties in routine tasks, compromised quality of life, and increased caregiving burden on families.[4]

Post-stroke recovery of fine motor function of the hand is essential in reducing patient disability, constituting a major challenge in the field of rehabilitation. To ameliorate hand function impairments, function exercises are primarily adopted to mitigate wrist flexor spasticity. Conventional rehabilitation approaches encompass physical therapy—which includes orthotic interventions and modern technologies—occupational therapy, speech therapy, physical

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agent modalities, hyperbaric oxygen therapy, acupuncture, and massage therapy.[5] Orthosis, as an external support device designed to alleviate dysfunction in the musculoskeletal system of the limbs, effectively serves to compensate for deficits, stabilize joints, and prevent complications associated with abnormal upper limb movement patterns following stroke.[6,7] Electromagnetic stimulation is a non-invasive treatment modality in stroke rehabilitation, and Transcranial Magnetic Stimulation (TMS) has been extensively employed in the rehabilitation of motor, speech, and cognitive impairments after stroke.[8,9] TMS acts on the central nervous system through pulsed magnetic fields and alters the membrane potential of cortical neurons to generate induced currents, thereby modifying brain metabolism and neural activity. It improves brain plasticity through the promotion or inhibition of synaptic transmission.[10] In addition to TMS, Peripheral Neuromagnetic Stimulation (PNS) is another treatment alternative for spasticity, urinary incontinence, swallowing difficulties, and pain using electrical stimulation through a stimulation coil placed on peripheral nerves or muscles.[11,12]

Paired Associative Stimulation (PAS) is a neuromodulation approach derived from the sensory-motor feedback loop's physiological principles. It finely regulates central motor neurons and spike-timing-dependent plasticity mechanisms by pairing PNS with TMS. This pairing enables rapid, bidirectional modulation of neural function within a limited number of stimulation cycles.[13] While prior studies have demonstrated favorable outcomes using TMS-assisted orthosis to promote normal muscle activation and maintain wrist positioning in patients with post-stroke upper limb dysfunction[14,15], research specifically investigating PAS—i.e., the combined application of TMS and PNS—remains limited.

Given this gap, the present study explores the efficacy of PAS combined with Low-Temperature Therapeutic Positioning Orthosis (LTTPO) in managing post-stroke wrist flexor spasticity. Stroke remains a major global health burden, with motor impairments often proving refractory to treatment and contributing to long-term disability.[16] Notably, more than one-third of patients experience persistent upper limb dysfunction six months after stroke onset, severely impairing self-care abilities and causing substantial physical and psychological distress for both patients and caregivers.[17,18] As the upper limb is integral to dexterity, coordination, and complex motor tasks in daily life, early and effective reduction of spasticity is essential for functional recovery. Therefore, targeted interventions that mitigate spasticity are crucial for improving rehabilitation outcomes in stroke survivors.[19]

## METHODS

### *Baseline patient profiles*

This prospective randomized controlled study recruited 63 patients with post-stroke wrist flexor spasticity treated in the Neurology Department of our hospital from January 2022 to June 2023. The patients were randomly assigned in a ratio of 1:1 to receive either sham stimulation combined with LTTPO (control group) or PAS combined with low-temperature thermoplastic orthosis (study group) via a random number table, with 31 patients in the control group and 32 in the study group. The study adhered to the ethical standards of clinical research outlined in the Helsinki Declaration and obtained approval from our hospital's ethics committee. All participants have provided written informed consent.

### *Inclusion and exclusion criteria*

*Inclusion Criteria:* (1) Patients aged between 35 to 80 years old; (2) Met the diagnostic criteria for ischemic or hemorrhagic stroke, with residual limb hemiparesis as a result of the initial cerebrovascular accident; (3) Patients with wrist flexor spasticity at level I to IV; (4) No central or peripheral stimulation therapy received within the past 3 months; (5) Stroke onset within 3 to 18 months; (6) Capable of understanding and performing movements following instructions; (7) Stable vital signs; (8) Patients strictly followed the medication instruction by the doctor during the treatment and follow-up period.

*Exclusion Criteria:* (1) Previous motor disorders, and presence of diseases such as rheumatoid arthritis, joint deformities, and spinal cord injury that directly affect motor function; (2) Previous treatment with botulinum toxin, alcohol, and phenol block; (3) Previous wrist joint orthopedic surgery; (4) Concurrent wrist extension spasticity ≥ grade II; (5) Uncontrolled hypertension, diabetes, hyperlipidemia, arrhythmia, liver or kidney dysfunction; (6) History of epilepsy; (7) Severe mental disorders; (8) Malignant tumors; (9) Previous peripheral venous thrombosis.

*Intervention methods*

The study group received PAS combined with LTTPO, while the control group received sham stimulation combined with low-temperature thermoplastic orthosis.

The specific methods are as follows:

LTTPO: The patient's maximum wrist extension range was measured, and with reference to 90% of the passive maximum range and the anterior and inferior 2/3 of the patient, the orthosis was heated in 70°C water for 5 minutes for shaping. A thick towel was wrapped around the upper limb on the affected side during the wearing of the orthosis to prevent skin damage. Throughout the rehabilitation sessions, the orthosis, when used to stabilize the joint, was taken off every two hours to allow for a 30-minute period of relaxation. The angle at which the orthosis was fixed was modified weekly based on the patient's condition. This regimen spanned a period of three weeks.

(2) PAS: The PAS mode of the TMS treatment produced by Wuhan Yiruide Company (Model: YRD CCY-IV magnetic stimulator) was employed. The stimulator was placed at the M1 area on the affected side of the skull lesion. Before treatment, the relevant information and possible adverse reactions were explained to the patient to alleviate potential negative emotions. The patient was positioned in a supine position, and the magnetic stimulation coil was fixed on the M1 area on the affected side, with the head kept still during the treatment. Peripheral electrical stimulation was applied to the median nerve in the wrist of the affected upper limb. A precise 8-shaped coil for the targeted area was used, with a magnetic stimulation intensity of 120% MT. Electrical stimulation: the intensity was set to cause slight contraction of the target muscle, with peripheral electrical stimulation followed by central stimulation, and a time interval of 25 ms. A total of 90 stimulations were performed. Fifteen sessions of TMS treatment were conducted, 5 times a week for 3 weeks.

(3) Sham stimulation: All parameters and treatment intensities were the same as those for magnetic stimulation, but the central coil was inverted, producing no effective magnetic stimulation. Peripheral nerve electrical stimulation did not emit impulses. All treatments were administered once daily, 5 times a week, for a total of 3 weeks.

*Observation indicators*

*Clinical efficacy*

Clinical efficacy was assessed by two therapists who received specialized training and were blinded to the study design and grouping. The Modified Ashworth Scale (MAS) improvement level was used to classify clinical efficacy into three categories:

*Complete response (CR):* MAS improvement level ≥ 2 or 0, indicating that the MAS rating after treatment improved by 2 or more levels compared to before treatment, or the MAS rating became 0 after treatment.

*Partial response (PR):* MAS improvement level < 2, but ≥ 1, indicating improvement of one level after treatment.

*No response (NR):* MAS improvement level < 1, indicating improvement of less than one level after treatment, or no change, or an increase in MAS rating. Clinical effectiveness rate = (PR + CR) / Total cases × 100%.

*Wrist spasticity status*

The MAS was used to assess the degree of wrist spasticity. The MAS categorizes the muscle tone of the wrist into six levels based on the completion of passive wrist extension within one second (from 120° to 0°). These levels are defined as follows[20]:

Level 0: No increase in muscle tone; the passive movement of the affected limb is unresisted throughout the entire range.
Level 1: Slight increase in muscle tone; slight resistance is encountered when the passive movement of the affected limb reaches the terminal position.
Level 1+: Slight increase in muscle tone; there is a slight feeling of "catch" in the first half of the Range Of Motion (ROM), and slight resistance in the second half of the ROM.
Level 2: Mild increase in muscle tone, there is resistance during passive movement of the affected limb in most of the ROM, but movement is still possible.
Level 3: Moderate increase in muscle tone; there is resistance throughout the entire ROM, resulting in comparatively difficult movement.

Level 4: Severe increase in muscle tone; the affected limb is rigid, and there is significant resistance, making passive movement very difficult.

A higher level indicates more severe spasticity. For the convenience of statistical analysis, the levels 0, 1, 1+, 2, 3, and 4 are respectively denoted as 0, 1, 2, 3, 4, and 5.

*Wrist joint function and quality of life*

The wrist and hand section of the simplified Fugl-Meyer assessment (FMA)[21] was used to evaluate upper limb hand motor function in patients. Scores were assigned based on the patient's performance of specified actions or elicited reflexes. Inability to perform an action or elicit a reflex was 0 points, partial completion received 1 point, and smooth completion or elicited reflex was 2 points. The total score for wrist and hand motor function was 24 points, with higher scores indicating better upper limb hand function. The Barthel Index (BI) was used to assess the quality of life of patients. The BI assessment included 10 items with a total of 100 points. The assessment score was directly proportional to the level of self-care ability, with higher scores indicating stronger self-care ability.

*Pain and swelling severity*

The Visual Analog Scale (VAS) was used to assess the degree of wrist joint pain, with scores ranging from 0 to 10. A score of 0 indicated no pain, while 10 indicated the most severe pain. Based on severity, the degree of swelling of the affected wrist joint was divided into four levels, from level 0 to level 3. These corresponded to no joint swelling, mild joint swelling with shallow skin texture changes but clear bone markers, significant joint swelling with basic disappearance of skin texture and unclear bone markers.

*Statistical analysis*

The data was organized and statistically analyzed using SPSS 25.0 software. Normality tests were conducted for measurement data. Measurement data that followed a normal distribution was described by mean ± standard deviation ($\overline{x} \pm s$). Non-normally distributed data underwent normality transformation. Count data and ordinal data were expressed as rates/percentages (%). The t-test was used to compare differences with statistical significance for measurement data, the chi-square test was employed for count data, and the rank-sum test for ordinal data. In this study, all comparisons were two-tailed tests, and a significance level of $\alpha$=0.05 was used as the threshold for statistically significant differences.

## RESULTS

*Baseline patient profiles*

The comparison of baseline information between the two groups of patients is presented in Table 1. In the control group, there were 19 males and 12 females, with a mean age of 69.17 ± 9.7 years. Sixteen patients had cerebral infarction and 15 had cerebral hemorrhage, with 7 cases of left hemiplegic and 24 cases of right hemiplegic. The mean MMSE score of the control group was 26.96±5.69. There were 20 males and 12 females in the study group, with a mean age of 68.38±9.68 years. There were 21 cases of cerebral infarction and 11 cases of cerebral hemorrhage. With 17 cases of lleft hemiplegic side and 15 cases of right hemiplegic side. The MMSE score of the study group was 27.19±6.14 points. The two groups were well-balanced in baseline profiles (P>0.05).

*Clinical efficacy*

The clinical efficacy of patients was evaluated at T1 (post-treatment), T2 (4 weeks), and T3 (8 weeks), as summarized in Table 2. At T1, the study group showed a significantly higher response rate (77%) compared to the control group (29%) ($\chi^2 = 13.34$, $P < 0.001$). By T2, the effectiveness rate in the study group increased to 97%, while the control group reached 45% ($\chi^2 = 20.63$, $P < 0.001$). At T3, the study group maintained a 97% effectiveness rate, significantly higher than the 74% seen in the control group ($\chi^2 = 6.615$, $P = 0.010$). These results suggest that PAS combined with LTTPO yields a more substantial and sustained therapeutic effect than sham stimulation combined with LTTPO.

*Wrist joint MAS scores*

The wrist flexors spasticity was assessed using the MAS scale at T0, T1, T2, and T3, as shown in Figure 1A. In the control group, the MAS score was 3.95±0.76 at T0, 3.31±0.53 at T1, 2.96±0.44 at T2, and 2.41±0.35 at T3. In the study group, the MAS score was 3.85±0.87 at T0, 2.96±0.48 at T1, 2.58±0.41 at T2, and 2.11±0.37 at T3. Patients receiving PAS showed significantly greater reductions in wrist flexor spasticity compared to those receiving sham stimulation at the assessed time points ($P < 0.05$), as measured by the MAS.

**Table 1: Baseline patient profiles**

| Index | Category | Control Group | Study Group | $t/\chi^2$ | P |
|---|---|---|---|---|---|
| **Age** | – | 69.17 ± 9.70 | 68.38 ± 9.68 | 0.625 | 0.749 |
| **Gender** | Male | 12 (38.7%) | 20 (62.5%) | 3.566 | 0.059 |
| | Female | 19 (61.3%) | 12 (37.5%) | – | – |
| **Type of Stroke** | Cerebral infarction | 16 (51.6%) | 21 (65.6%) | 1.416 | 0.259 |
| | Cerebral hemorrhage | 15 (48.4%) | 11 (34.4%) | – | – |
| **Hemiplegic Side** | Left | 7 (22.6%) | 17 (53.1%) | 2.04 | **0.013** |
| | Right | 24 (77.4%) | 15 (46.9%) | – | – |
| **Disease Course (days)** | ≤30 | 7 (22.6%) | 4 (12.5%) | 1.276 | 0.514 |
| | 31–90 | 11 (35.5%) | 17 (53.1%) | – | – |
| | 91–180 | 9 (29.0%) | 8 (25.0%) | – | – |
| | >180 | 4 (12.9%) | 3 (9.4%) | – | – |
| **Brunnstrom Stage – Upper Limb** | **Stage** | | | 0.4 | 0.377 |
| | 1 | 1 (3.2%) | 1 (3.1%) | | |
| | 2 | 13 (41.9%) | 11 (34.4%) | | |
| | 3 | 10 (32.3%) | 14 (43.8%) | | |
| | 4 | 4 (12.9%) | 6 (18.8%) | | |
| | 5 | 3 (9.7%) | 0 (0%) | | |
| **Brunnstrom Stage – Hand** | **Stage** | | | 0.154 | 0.361 |
| | 1 | 1 (3.2%) | 0 (0%) | | |
| | 2 | 19 (61.3%) | 24 (75.0%) | | |
| | 3 | 11 (35.5%) | 8 (25.0%) | | |
| **Motor Power – Lower Limb (MRC Grade)** | **Grade** | | | 2.342 | 0.698 |
| | 1 | 0 (0%) | 1 (3.1%) | | |
| | 2 | 3 (9.7%) | 4 (12.5%) | | |
| | 3 | 18 (58.1%) | 15 (46.9%) | | |
| | 4 | 8 (25.8%) | 11 (34.4%) | | |
| | 5 | 2 (6.5%) | 1 (3.1%) | | |
| **Other Baseline Measures** | | | | **t** | **P** |
| MAS at T0 | – | 2 (1) | 2 (1) | 1.879 | 0.731 |
| FMA at T0 | – | 6.48 ± 1.81 | 7.06 ± 1.37 | 2.113 | 0.156 |
| VAS at T0 | – | 1.42 ± 1.29 | 0.81 ± 1.12 | 0.655 | 0.051 |
| Swelling at T0 | – | 1.29 ± 0.78 | 1.03 ± 0.82 | 1.567 | 0.205 |
| Barthel Index at T0 | – | 45.16 ± 17.34 | 48.13 ± 14.91 | 2.767 | 0.469 |

Note: Brunnstrom Stages: Range from Stage 1 (flaccid paralysis) to Stage 6 (near-normal movement). Used to assess motor recovery for upper limb and hand.
Motor Power – Lower Limb: Evaluated using the Medical Research Council (MRC) scale, with grades 0 – 5; higher grades indicate stronger muscle power. Please specify joint(s) assessed (e.g., hip flexion, knee extension) in the Methods.
MAS: Modified Ashworth Scale (0 – 4+), assessing spasticity.
FMA: Fugl-Meyer Assessment (24-point subset for wrist/hand function).
VAS: Visual Analog Scale (0 – 10) for pain.
Barthel Index: Scale of 0 – 100 measuring activities of daily living.

**Table 2: Clinical efficacy at different time points**

| Group | n | Time Point | CR | PR | NR | Clinical Efficacy (CR + PR) | $\chi^2$ | P |
|---|---|---|---|---|---|---|---|---|
| **Control Group** | 31 | T1 (Post-Treatment) | 0 | 9 | 22 | 9 (29%) | 13.34[a] | <0.001 |
| | | T2 (4 Weeks After) | 0 | 14 | 17 | 14 (45%) | 20.63[b] | <0.001 |
| | | T3 (8 Weeks After) | 1 | 22 | 8 | 23 (74%) | 6.615[c] | 0.01 |
| **Study Group** | 32 | T1 (Post-Treatment) | 1 | 23 | 8 | 24 (77%) | | |
| | | T2 (4 Weeks After) | 7 | 24 | 1 | 31 (97%) | | |
| | | T3 (8 Weeks After) | 12 | 19 | 1 | 31 (97%) | | |

Note: [a]At T1 point, Control Group vs Study Group; [b]At T2 point, Control Group vs Study Group; [c]At T3 point, Control Group vs Study Group
T1: Immediately after all treatments T2: End of the 4th week after treatment T3: End of the 8th week after treatment; CR (Complete Response): MAS improvement ≥ 2 levels or to 0; PR (Partial Response): MAS improvement of 1 level; NR (No Response): MAS improvement <1 level; Clinical Efficacy = (CR + PR)/Total × 100%

*Comparison of wrist joint FMA and BI*

The functional status of the wrist joint was assessed using the FMA at T0, T1, T2, and T3, as shown in Figure 1B-C. The FMA score for the control group was 6.48±1.81 at T0, 8.06±2.34 at T1, 8.55±2.79 at T2, and 9.23±2.91 at T3. In the study group, the score was 7.06±1.37 at T0, 9.69±2.55 at T1, 10.91±2.36 at T2, and 11.72±3.04 at T3. The level of functional independence for both groups was assessed using the BI. In the control group, the BI scores were 45.16 ± 17.34 at T0, 51.77 ± 20.48 at T1, 55.32 ± 19.53 at T2, and 58.39 ± 18.32 at T3. In the study group, the BI scores were 48.13 ± 14.91 at T0, 51.56 ± 18.68 at T1, 57.34 ± 16.21 at T2, and 59.66 ± 16.30 at T3. Although both groups demonstrated a gradual increase in BI scores over time, the intergroup differences were not statistically significant (P > 0.05). In contrast, significantly higher FMA scores for wrist joint function were observed in the study group, indicating superior motor function recovery following PAS combined with LTTPO compared to sham stimulation (P < 0.05)."

*VAS score and swelling of wrist joints*

The VAS score was used to assess the patients' wrist joint pain and the edema of the wrist joint at T0, T1, T2, and T3, as depicted in Figure 2. In the control group, the VAS score was 2.42±0.49 at T0, 2.13±0.36 at T1, 1.85±0.25 at T2 and 1.45±0.18 at T3. VAS in the study group was 2.51±0.52 at T0, 1.87±0.38 at T1, 1.68±0.27 at T2 and 1.21±0.19 at T3. Wrist swelling score was 1.29±0.58 at T0, 1.03±0.35 at T1, 0.84±0.29

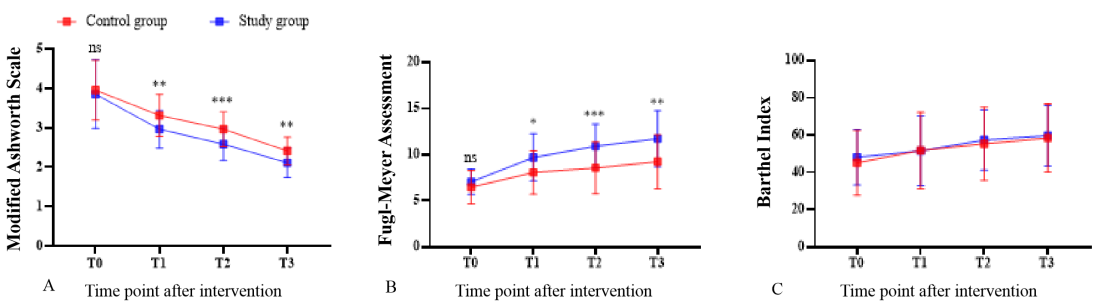


Figure 1. Comparison of MAS score, f FMA and BI
ns, no significance, ** indicated P<0.01, *** indicated P<0.001

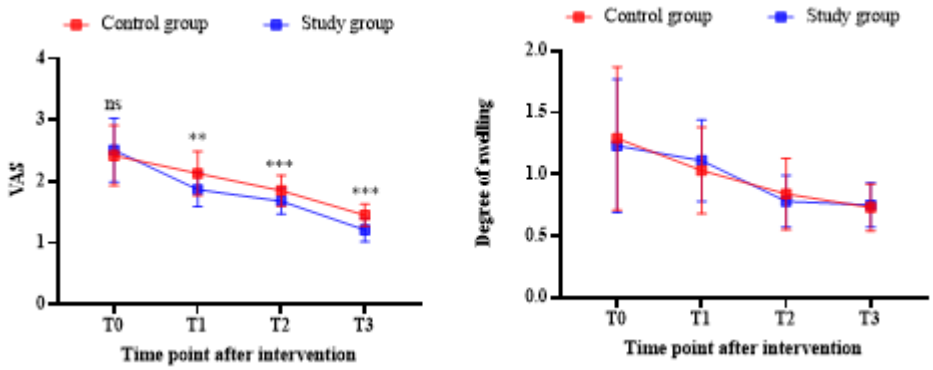


Figure 2. Comparison of VAS and swelling score
ns, no significance, ** indicated P<0.01, *** indicated P<0.001

at T2, and 0.73±0.19 at T3 in the control group. Wrist swelling score was 1.23±0.54 at T0, 1.11±0.33 at T1, 0.78±0.21 at T2, and 0.75±0.18 at T3 in the study group. Patients receiving the combined intervention of PAS with LTTPO had significantly better pain mitigation than those with sham stimulation (P<0.05). Both groups showed increasingly severe joint swelling over time, yet no statistical significance was observed in this intergroup distinction (P>0.05).

*fMRI results*

Functional MRI analysis showed no significant baseline differences in whole-brain Amplitude of Low-Frequency Fluctuation (ALFF) between the two groups (P > 0.05). After 3 weeks of intervention, the study group exhibited significantly increased ALFF values in multiple brain regions associated with motor and cognitive processing, including the right superior frontal gyrus/precentral gyrus, left superior frontal gyrus, bilateral medial prefrontal lobes, bilateral median cingulate gyrus, bilateral supplementary motor area, left precuneus, right thalamus, left superior temporal gyrus, and left cerebellar hemisphere, compared to the control group (Table 3). These findings suggest enhanced brain functional remodeling associated with PAS combined with LTTPO.

## DISCUSSION

The application of PAS has demonstrated notable improvements in post-stroke wrist flexor spasticity, concurrent with enhancements in motor function and the alleviation of postoperative pain. In this study, the MAS was employed to gauge

**Table 3: Brain regions showing increased ALFF in the study group compared to control group after 3 weeks of treatment**

| Brain Region | MNI Coordinates (x, y, z) | T Peak | Cluster Size (voxels) |
|---|---|---|---|
| Right superior frontal gyrus / precentral gyrus | (32, 12, –41) | 5.06 | 34 |
| Left superior frontal gyrus / frontal gyrus | (–21, 4, –22) | 4.48 | 38 |
| Bilateral medial prefrontal lobes | (14, –68, –37) | 4.06 | 20 |
| Bilateral median cingulate gyrus | (14, 16, 29) | 4.99 | 18 |
| Bilateral supplementary motor area (SMA) | (–11, 35, 42) | 3.71 | 29 |
| Left precuneus lobe | (0, –71, 24) | 4.26 | 23 |
| Right thalamus | (–41, 0, 33) | 4.12 | 26 |
| Left superior temporal gyrus | (–35, 26, –26) | 3.71 | 20 |
| Left cerebellar hemisphere | (–5, –51, 36) | 3.71 | 29 |

Note: MNI: Montreal Neurological Institute coordinates; ALFF: Amplitude of Low-Frequency Fluctuation. The table presents clusters where ALFF values were significantly higher in the study group than in the control group after 3 weeks of treatment (T1). Baseline fMRI showed no significant differences between groups. These regions are associated with motor planning (SMA, precentral gyrus), sensory integration (precuneus, thalamus), and cognitive control (medial prefrontal cortex), suggesting enhanced brain remodeling in the study group.

spasticity levels in patients, while the FMA scale was utilized to appraise wrist joint functionality. The results evidenced that the MAS scores in the PAS group were substantially lower than those in the control group, and the FMA scores were correspondingly superior. This indicates that PAS efficaciously mitigates spasticity in the early stages and ameliorates wrist joint functionality. Although transcranial magnetic stimulation and peripheral nerve stimulation stand as non-invasive neuroregulatory techniques capable of promoting functional recovery in post-stroke spasticity patients, research on PAS remains relatively nascent.[22] As a non-invasive brain stimulation modality, TMS not only induces cortical neuroplasticity and bolsters inter-neuronal connections within the cortex but also transiently augments cerebral blood flow. This enhances corticospinal tract functionality, thereby facilitating the alleviation of limb spasticity and the promotion of motor function recovery.[23] Animal studies have shown that TMS enhances the compensatory effect of synaptic interface and dendritic structures in undamaged sensorimotor cortex regions and increases the underlying mechanism of synaptic plasticity, promoting the improvement of neurological function in cerebral ischemic rats.[24] In the ischemic penumbra cortex following a stroke, TMS and exercise training can both increase the plasticity of synaptic ultrastructure. These alterations in synaptic ultrastructure are closely linked to PAS, which facilitates the recovery of motor function as well as learning and memory skills following ischemic brain injury.[25]

Furthermore, PNS intervention modulates proprioceptive nerve transmission, thereby impacting proprioception and somatosensory input. This serves to fortify the central feedback and input of sensory and motor control patterns, improving motor control for stroke patients. PAS involves stimulating the central and peripheral nervous systems both in an ascending and descending manner, exerting a synergistic effect between the two types of stimulation. This enhances the inhibitory signals from the affected cortical motor center downward, thus suppressing overactive stretch reflexes and reducing the degree of muscle spasticity in the limbs.[26] PAS by integrating TMS and PNS, can induce timing-dependent plasticity and regulate cortical excitability in the brain, enhancing motor function.[25] In addition to integrating the effects of TMS and PNS, PAS can also establish new associations between action perception and its corresponding motor programs.[27] Pain emerges as a prevalent symptom following stroke, with an incidence rate reaching up to 50%.[28] Upper limb pain represents the most common manifestation, with its intensity remaining unaltered over time. The potential benefits of TMS for post-stroke pain patients have been substantiated, and paired associative stimulation has yielded promising results.[29] Research has demonstrated that TMS can prevent neural stem cells and hippocampal neurons in rats that have experienced cerebral infarction from undergoing apoptosis; this can enhance the rats' capacity for learning and memory, and it may also be associated with B-cell lymphoma/leukemia gene 2, inhibition of proteins related to the Bcl gene, and the p-CREB pathway.[30] PNS can also have a neuroprotective effect by slowing down the rate at which neurons undergo apoptosis; and PAS, a novel neural modulation technique that combines PNS and TMS, ought to have neuroprotective effects. Its suppression of neuronal apoptosis is one of its symptoms.

Additionally, this study conducted an amplitude of low-frequency fluctuations analysis to probe into the potential neural correlates of PAS.[31] This study introduces a pioneering application of PAS within post-stroke patients afflicted by wrist flexor spasticity. It substantiates the efficacy of the regimen in both motor function improvement and neural reshaping. Nevertheless, this study was confined to a single center, featured a modest sample size, and entailed a relatively brief follow-up duration. Further analysis regarding its central mechanism is presently underway.

In conclusion, the integration of PAS combined with LTTPO offers a viable alternative to the management of post-stroke wrist flexor spasticity by significantly alleviating the spasticity of patients, improving functional recovery, alleviating pain, and promoting neural remodeling.

## DISCLOSURE

Ethics: The study obtained approval from our hospital's ethics committee. All participants have provided written informed consent.

Data availability: The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support: None

Conflict of interest: None

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