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# rTMS for poststroke pusher syndrome: study protocol for a randomised, patient-blinded controlled clinical trial

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## ABSTRACT

**Introduction** Poststroke pusher syndrome (PS) prevalence is high. Patients with PS require longer rehabilitation with prolonged length of stay. Effective treatment of PS remains a challenge for rehabilitation professionals. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that is effective and recommended in the clinical guidelines of stroke rehabilitation. However, the role of rTMS for PS has not been examined. The study is to assess the efficacy of a specific rTMS programme for patients with PS in reducing pushing behaviour, enhancing motor recovery and improving mobility, as well as testing the safety of rTMS for patients with PS.

**Methods and analysis** A randomised, patient and assessor blinded sham-controlled trial with two parallel groups will be conducted. Thirty-four eligible patients with PS will be randomly allocated to receive either rTMS or sham rTMS for 3 weeks. The primary assessment outcome is the pushing behaviour measured by the Burke Lateropulsion Scale and Scale for Contraversive Pushing. The secondary outcomes are the motor functions and mobility measured by the Fugl-Meyer Assessment Scale (motor domain) and Modified Rivermead Mobility Index, and any adverse events. Assessment will be performed at baseline and 1 week, 2 weeks and 3 weeks after intervention. Repeated-measures analysis of variance will be used for data analysis with the level of significance level set at 0.05.

**Ethics and dissemination** The protocol has been approved by the Biomedical Ethics Committee of West China Hospital, Sichuan University on 23 March 2022 (2022-133). The trial findings will be published in peer-reviewed journals.

**Trial registration number** Chinese Clinical Trial Registry (ChiCTR2200058015).

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial is the first randomised controlled clinical trial to explore the clinical efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in patients with poststroke pusher syndrome (PS).
⇒ The patients and assessors blinded trial with sham stimulation can reduce bias and confirm the role of rTMS in the treatment of PS.
⇒ The design of endpoint measurements of 1 week, 2 weeks and 3 weeks enables us to examine the optimal treatment duration of rTMS for PS.
⇒ This trial has the limitation of not assessing the long-term effect of rTMS for PS.

## INTRODUCTION

Pusher syndrome (PS) or lateropulsion, is a common impairment after stroke.[1] It is characterised by patients actively pushing toward their hemiparetic side and exhibiting resistance to passive correction of the body to the vertical upright position.[2] PS was recently reported in 41% of patients who had stroke.[3] In 21% of patients with PS, pushing behaviour persisted at 3 months, with motor recovery and functional abilities significantly poorer than non-pushers.[4] Although patients with PS can finally achieve similar improvement in function as non-pushers, longer duration of rehabilitation[1] and more supplemental care after discharge from an inpatient rehabilitation setting[4 5] are required. This implies an increase in the burden of care on the health system.

Various interventions for PS have been reported in the literature but their efficacy remains uncertain.[6] The majority of the existing studies prevalently based on observational reports show that the intervention focusing on conscious visual feedback is beneficial for patients with PS.[7–11] Hypothesising that PS results from a mismatch between the visual and postural perception of the vertical, the use of visual feedback might be considered as a compensatory approach.[6 11] Furthermore, these trainings are applied as conscious strategies that would be inefficient for postural control, which normally works under automatic unconscious feedback system. Within controlled trials, robotic or machine-assisted somatosensory cues training showed better outcomes than the visual feedback ones[12–14] or general postural training.[15] Nevertheless, study showed that somatosensory input plays a relatively minor role in PS.[16] Four studies used transcranial direct current stimulation, a type of brain stimulation applied over the

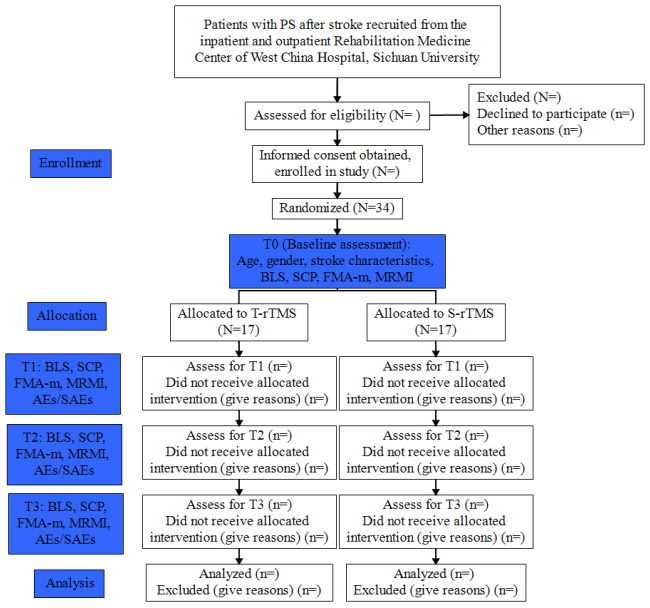


**Figure 1** The flow diagram of the study. T0, baseline assessment; T1: after 1 week of intervention; T2: after 2 weeks of intervention; T3: after 3 weeks of intervention. AEs, adverse events; BLS, Burke Lateropulsion Scale; FMA-m, Fugl-Meyer Assessment Scale-motor domain; MRMI, Modified Rivermead Mobility Index; PS, pusher syndrome; S-rTMS, sham repetitive transcranial magnetic stimulation group; SAEs, serious adverse events; SCP, Scale for Contraversive Pushing; T-rTMS, true repetitive transcranial magnetic stimulation group.

cortex or mastoid, showed positive effect on improved posture.[17–20] However, these studies were based on observational reports and non-randomised controlled trials. Further in-depth investigation is needed on the treatment approaches based on brain stimulation for PS, as a direct way to modulate input to the network of brain centres responsible for the egocentric postural reference system for vertical upright.

The disagreement exists among researchers with regard to the brain stimulation for PS partly because of unclear neuroanatomy. Previous lesion studies associated with PS have inconsistent results of establishing the neuroanatomical basis from small sizes and unmatched samples.[21–23] A recent case–control design study with a large sample size, a matched comparison group, and a sophisticated multivariate statistical approach for lesion symptom mapping led to the identification of the specific brain lesion location most associated with PS. The authors found that the inferior parietal lobe (IPL) at the junction of the postcentral gyrus (Brodmann Area 2, BA 20) and Brodmann Area 40 (BA 40) was a key neuroanatomical determinant of developing PS.[24] Applying brain stimulation over IPL may be feasible to ameliorate pushing behaviour for patients with PS.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique using a high-intensity magnetic field generated by an electric current passing through an inductive coil to modulate the cerebral cortex's excitability.[25] rTMS has been used in the field of neurorehabilitation for the treatment of a diversity of neurological disorders and can augment functional recovery.[26 27] The current literatures converge on the positive effect of rTMS in the rehabilitation of most of all clinical manifestations of stroke.[28] rTMS is considered to ameliorate neglect symptoms similar as PS with evidence of class IIb, level B.[29] However, there is no clinical trial study of rTMS for PS. rTMS may be effective for PS if its application is guided by underlying neuroanatomical mechanisms reported by Babyar and associates.[24] Therefore, we will conduct a randomised controlled trial with patients and assessors blinded to provide preliminary evidence on the clinical efficacy and safety in patients with PS who receive rTMS applied over the IPL compared with sham rTMS. The primary objective of this trial is to examine a specific rTMS programme for patients with PS in reducing pushing behaviour. The secondary objectives are to assess the efficacy of a specific rTMS programme for patients with PS in enhancing motor recovery and mobility; to determine the safety of rTMS application. We hypothesise that rTMS applied over the IPL is an effective and safe method in reducing pusher behaviour and improving functional outcomes in patients with PS in the short term.

## METHODS

### Trial design

A patient and assessor blinded randomised controlled clinical trial is used in this study with a repeated measures design. This study protocol is developed in compliance with the Standard Protocol Items of the Recommendations for Interventional Trials guidelines. The flow diagram to be followed in this study is shown in figure 1. In this trial, patients are randomly assigned to either the rTMS group or the sham rTMS group, aiming to explore the efficacy of inhibitory rTMS applied over the intact IPL on pushing behaviour, motor recovery and mobility. Outcome data will be collected before intervention (T0), after 1 week of intervention (T1), after 2 weeks of intervention (T2), and after 3 weeks of intervention (T3).

### Participants

Patients with ischaemic or haemorrhagic stroke will be recruited by an independent researcher (YG) from the inpatient and outpatient rehabilitation medicine centre of West China Hospital, Sichuan University, China, from 26 March 2022 to 31 December 2022. Patients are eligible for this study if they meet the inclusion and exclusion criteria listed in table 1. Written informed consent will be obtained from all participants or caregivers. The English example of the patient consent form is provided in online supplemental file 1. Potential participants or caregivers are informed of study details, including procedures, risks and benefits, confidentiality and voluntary nature of the participation, before signing the consent form.

### Sample size calculation

Sample size is calculated using the G*Power software V.3.1.9.2. An effect size of 1.0 for comparing the change

Table 1 Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| ► Ages:18–80 years<br>► ≤6 months following an ischaemic or haemorrhagic stroke<br>► Patients with PS defined as BLS scores ≥3 during the initial examination<br>► Ability to follow two-step commands<br>► Ability to provide informed consent<br>► No other neurological disorders | ► Have visual field deficits or eye muscle paralysis<br>► Orthopaedic conditions limiting participation, for example, fracture, severe osteoporosis, contractures of the lower extremities<br>► Having an unstable medical condition, or being unable to safely perform mild to moderate exercise<br>► Metal implants, cardiac pacemaker, brain tumour, meningitis or epilepsy |

BLS, Burke Lateropulsion Scale.

scores of Burke Lateropulsion Scale (BLS) using independent t-test between the two groups, with a two-tailed level of significance of 0.05 and a statistical power of 80%. A total of sample size of 34 with 17 participants per group is estimated.

### Randomisation, allocation concealment and blinding

Participants will be randomly allocated into either the rTMS group or the sham rTMS group. The random sequence is generated by using randomly permuted blocks with a size of 4 per block. Blocks are specified as AABB, ABAB, ABBA, BBAA, BABA, BAAB (A=rTMS and B=sham rTMS). Considering the type of stroke can be a possible confounding factor, stratified blocked randomisation[30] is performed to balance the number of ischaemic stroke or haemorrhagic stroke in both groups with two separate allocation sequences generated for patients who had ischaemic stroke and patients who had haemorrhagic stroke. An independent researcher (LM) will randomly select the blocks with replacement of block for both the ischaemic and haemorrhagic patients to generate two sets of allocation sequence with at least 36 participants in each sequence. The recruitment of participants will be stopped when the total number of participants reaches the estimated sample size of 34. After the allocation sequences are generated, the researcher will place them in sequentially numbered sealed opaque envelopes and store them in a locked cabinet. When an eligible participant is recruited into the trial, the therapist will contact the independent researcher to open the sealed envelope to determine the allocation of the participant.

The assessors and patients will be blinded to group assignment. In case of serious adverse events (SAEs) or suspected unexpected serious adverse reactions, patient blinding status will be broken after consultation with the principal investigator (PI). Subsequently, these events will be reported to the Medical Ethical Committee.

### Interventions

Patients with poststroke PS participate in this randomised controlled trial in which the experimental group will receive the rTMS in addition to the usual rehabilitation services. In the control group, the sham rTMS will be delivered with the usual rehabilitation services. The intervention allocation will be performed by an independent researcher (LH of research team).

Patients in the rTMS group will receive rTMS sessions over the intact IPL at the junction of the postcentral gyrus (BA 2) and BA 40. rTMS is performed by using a rapid magnetic stimulator (YIREUIDE, Wuhan, China). A figure-eight coil is oriented at a tangent to the target scalp. Since there is no previous study on rTMS for PS, the parameters of a continuous theta burst stimulation (cTBS) protocol, an inhibitory rTMS used for neglect, are referred to.[27 31–33] Fifteen sessions of cTBS will be administered over 3 weeks (15 work days), and the detailed parameters used in each session will be set as follows:

- Non-lesional IPL as the target area, corresponding to the CP3-CP4 sites of the international EEG 10–20 system for the location.
- The intensity is set at 80% of the resting motor threshold (RMT) of the contralateral first dorsal interosseus muscle identified under electroneuromyography control. The RMT of each patient will be determined before treatment, which is defined as the minimum stimulation intensity required to evoke motor evoked potentials of more than 50 µV in at least five of 10 trials at rest to the nearest 1% stimulator output.
- The cTBS protocol comprises 801 pulses delivered in a continuous train of 267 bursts. Each burst consists of three pulses at 30 Hz, repeated at 6 Hz. The duration of one single cTBS train is therefore 44 s.
- Eight cTBS protocols with an interval of 30 s are applied per session per day. Sessions are performed with patients lying on the plinth.

Patients in the sham rTMS group will be given pseudostimulation for 3 weeks. The treatment parameter of the sham group is the same as that of the experimental group, except the coil is horizontally turned backward, with the back of the coil facing toward the stimulation point of the patients' head, with patients hearing the stimulator sound without receiving stimulation.

All patients will receive the usual rehabilitation programme according to the guidelines for adult stroke rehabilitation.[29] The usual rehabilitation lasts approximately 4 hours per day, with exercise graduated according to their impairments and recovery. The usual

rehabilitation includes (1) physiotherapy and occupational therapy consisting of training of bed and wheelchair mobility, transfer, sit-to-stand, balance, pregait and gait training and activities of daily living with visual feedback, (2) speech-language therapy, (3) treatment of dysphagia, (4) cognitive rehabilitation. The detailed usual rehabilitation programme is shown in online supplemental file 2.

Incentive of reducing therapy fees will be provided for the participants to comply with the treatment protocol and complete the 3 weeks of intervention. If a participant chooses to withdraw, they will be asked to provide the reasons which will be recorded.

## Outcome measures

All outcome data will be collected by two independent researchers (SY and QW of research team) who are blinded to the group assignment and not involved in the delivery of interventions to the participants. The assessors have more than 10 years of working experience in stroke rehabilitation and in using the outcome measures, especially BLS and Scale for Contraversive Pushing (SCP). Baseline characteristics will be collected in both groups, such as age, sex, stroke characteristics (duration, type, lesion side and lesion location), handedness, BLS scores and presence of neglect or aphasia. Baseline assessment and preintervention assessments (T0) will be performed before randomisation. The primary outcome measures are the BLS and SCP to assess pushing behaviour. The secondary outcome measures are the Fugl-Meyer Assessment Scale-motor domain (FMA-m) and the Modified Rivermead Mobility Index (MRMI) to assess motor functions and mobility, and adverse events. To improve the reliability of scoring, all the assessment scales will be administered jointly by the two independent researchers.

### Burke Lateropulsion Scale

The BLS was recently recommended as the preferred tool to evaluate PS.[34] The BLS is both a reliable and a valid assessment of lateropulsion following stroke and has sound clinimetric properties.[35–37] BLS is an appropriate alternative to the widely used SCP to follow-up patients with pushing behaviour. It might be more sensitive to detect mild pushing behaviour in standing and walking.[36] The BLS uses a 17-point ordinal scale to evaluate the postural alignment according to how much resistance met by the examiner while the patient performs the functional activities: rolling, sitting, standing, transferring and walking.[37] The score for each item is rated on a scale from 0 to 3 (0 to 4 for standing) and is based on the severity of resistance or the tilt angle when the patient starts to resist the movement. The greater the resistance noted by the therapist, the higher the score. Scores range from 0 for those without lateropulsion to a maximum score of 17. The cut-off for the diagnosis of pusher behaviour is ≥3 points.[38] BLS is considered significant when the change value was more than 1 point.[13] Without the availability of minimal clinically important difference (MCID) of BLS from the literature, the most common and well-described distribution-based formula for MCID calculation using half SD (MCID=0.5×SD) of baseline scores will be adopted.[39]

### Scale for Contraversive Pushing

The SCP has the most extensive testing of clinimetric properties.[35] The validity of the SCP has already been established, and the interrater reliability of the SCP has been reported to be good to excellent with regard to both each subscore and the total score. The internal consistency was very high, along with correlations between subscore and total score of the scale.[40] The construct validity of the SCP was demonstrated by significant moderate to high correlations with mobility, functional and balance scores.[41] Moreover, there was almost perfect agreement with clinical diagnosis with a cut-off >0 in each category.[41] The SCP includes three components with a total score ranging from 0 to 6: (1) the symmetry of spontaneous body posture (rated with 0, 0.25, 0.75 or 1 point), (2) the use of non-paretic extremities to push away from the unaffected side of the body (0, 0.5 or 1 point) and (3) the resistance to passive correction of the tilted posture (0 or 1 point).[42] Lateropulsion is scored 0.25 for a mild contraversive body tilt without falling, 0.50 for a severe contraversive body tilt without falling, and one for a severe contraversive body tilt with falling to the contralesional side. Each component is tested in sitting and standing positions, yielding a maximum score of 2 per component. The half SD of SCP scores at baseline is set as the MCID.

### Fugl-Meyer Assessment Scale-motor domain

The FMA is a well-designed, feasible and efficient clinical examination method that has been tested widely in the stroke population.[43] The FMA scale is divided into five domains: motor functions, sensory functions, balance, joint range of motion and joint pain. The motor domain is highly recommended as a clinical and research tool for evaluating changes in motor impairment following stroke.[43] The FMA-m includes items measuring movement, coordination and reflex action about the shoulder, elbow, forearm, wrist, hand, hip, knee and ankle. Each item is scored on a 3-point ordinal scale (0=cannot perform, 1=performs partially, 2=performs fully). The motor score ranges from 0 (hemiplegia) to a maximum of 100 points (normal motor performance), divided into 66 points for the upper extremities and 34 points for the lower extremities.

### Modified Rivermead Mobility Index

MRMI is a short and simple test of mobility in routine clinical practice. MRMI has good to excellent measurement properties with good content validity, high responsiveness, adequate predictive validity, excellent test–retest reliability, high internal consistency and unidimensionality.[44] The MRMI consists of eight items, including turning over, changing from lying to sitting, maintaining sitting balance, going from sitting to standing, standing,

transferring, walking indoors and climbing stairs. The MRMI score ranges from 0 to 40. Scores are assigned based on direct observations of the patient's performances in the items.

### Adverse events/SAEs assessment and management

Safety will be reported as adverse events (AEs) or SAEs. The collected data for AEs/SAEs are: start date, stop date, description, severity and amount. The researchers are obliged to take necessary measures to protect the safety of the participants. The rTMS has been shown to be safe and well tolerated when applied to patients who had stroke with different clinical and rehabilitative conditions.[28] Nonetheless, before undergoing the rTMS procedure, patients should always be screened according to the safety guidelines[45] to rule out possible contraindications. If AEs/SAEs occur during the trial, the investigator should immediately take the appropriate treatment measures as follows. If SAEs occur, the investigator should report to the Ethics Committee in a timely manner. In addition, the investigator will record them in the case report form (CRF) and explain whether they are related with the intervention. If the treatment is suspended, the reason for the suspension will be reported in the CRF. Data on AEs/SAEs will be analysed appropriately and included in the study's final report. The potential AEs/SAEs of rTMS[45] and the estimated frequencies of AEs[46] are listed as follows:

- Transient headache (common, ≥1% and <10%): transient headache usually does not require any treatment. If requested by the patient, analgesics will be administered.
- Local annoyance in the stimulated area (very common, ≥10%): it rarely requires the suspension of rTMS. If the discomfort is reported to be excessive, the session will be suspended until the discomfort subsides within 2 hours. Then the intervention will be resumed if the patient agrees.
- Temporary loss of hearing (rare, ≥0.01% and <0.1%): in such a case, the session will be suspended until the discomfort subsides within 24 hours. Then the intervention will be resumed if the patient agrees.
- Epileptic crises (rather rare, ≤0.01%): they may occur in predisposed individuals with a history of epileptic seizures. To minimise this risk, participants who have suffered from seizures during the acute phase or have a diagnosis of epilepsy will be excluded from the trial (exclusion criterion). If a convulsive episode occurs during treatment with rTMS despite the above precautions, the latter will be immediately suspended, and the patient will be treated according to the standard hospital protocols for epileptic seizures.

### Data management and safety monitoring

All baseline data and raw data will be recorded on CRFs in a complete, accurate and clear manner immediately on data acquisition. The two assessors cross-check to ensure the accuracy and cleanliness of the data. A database (Microsoft Excel spreadsheet) will be used to manage the data. All research data will be entered into this electronic database on the last day of the month. Data input and proofreading will be performed by two independent researchers (QGuo and JY of research team), leading to double data entry and storage. For this database, data will be imported directly into the IBM SPSS V.25.0 for ease of statistical analysis.

On enrolment, each participant will be assigned a unique numeric study number so that they can be tracked anonymously throughout the study. Only the PI will have access to identifiers that can link the data to the individual participant. Consent forms and hard copy data collection forms will be stored in a locked cabinet at the research centre. Access to them can only be made available through the PI.

### Statistical analyses

Categorical variables are expressed as frequencies and percentages. Continuous variables are expressed as means and SD. Demographics and baseline clinical characteristics of patients will be compared between groups using independent t-tests (for continuous variables) or $\chi^2$ tests (for categorical variables). The normality of continuous data will be examined using the Shapiro-Wilk test. Two-way repeated-measures analysis of variance (ANOVA) will be used to examine any interaction effects in those outcome variables between the two groups over the four time points. The Mauchly's test of sphericity will be used to examine the assumption of sphericity of the repeated-measures ANOVA. If the interaction effect is significant, posthoc multiple comparisons with Bonferroni correction will be applied to examine the simple effects between groups at different time points and among different time points in each group. If there is an obvious or important baseline difference, continuous variable will be added as the covariate in the repeated-measures analysis of covariance. Categorical variable will be added as the independent variable in repeated-measures ANOVA. All analyses will be performed using IBM SPSS Statistics for Windows V.25.0 (IBM Corp). Following the Consolidated Standards of Reporting Trials statement, all our analyses will adhere to the intention-to-treat principle. In case there is any missing value of a variable in T1 to T3, missing data will be replaced with the mean value of the variable in that particular group. The level of significance will be set at 0.05 for all analyses.

## ETHICS AND DISSEMINATION

### Ethics and trial registration

This study will be performed in accordance with the Declaration of Helsinki. Ethics approval was obtained from the Biomedical Ethics Committee of West China Hospital, Sichuan University (approval no. 2022-133) on 23 March 2022. The study has been registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/searchprojen.aspx) on 26 March 2022.

## Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## Dissemination plan

The results on the efficacy and safety of rTMS in patients with PS are expected in December 2022. These findings will be submitted and published in international peer-reviewed journals in 2023.

## DISCUSSION

This randomised controlled trial is designed to examine the efficacy of rTMS in reducing pushing behaviour and improving motor recovery and mobility in patients who had stroke with PS. We will also investigate the safety of rTMS for PS by monitoring AEs. Finally, this trial may provide a key target area-IPL for neuromodulation therapy of PS.

PS is a strong and negative predictor of the general functional outcome of patients after stroke. The search for effective therapy for PS remains a challenge. To date, the role of rTMS in the recovery of PS has not been tested. Studies have shown the benefits of using rTMS for neglect, which is a perceptual defect,[27 31 47] resulting from interhemispheric imbalance.[48 49] Pérennou *et al* suggested that a major component in the PS is an implicit active body postural alignment with the perceived vertical.[50] A tilted perception of postural vertical in patients with PS leads to tilted body posture and loss of lateral balance. This tilted perception of postural vertical is probably the consequence of interhemispheric imbalance. The parietal cortices are part of an interhemispheric and intrahemispheric frontal-parietal pathway. Thus, damage to one parietal cortex causes disinhibition of the other parietal cortex with pathological overactivation of the latter. Recent research suggests that cortical strokes causing PS localise primarily to the IPL.[24] The IPL appears to hold a central role in the pathway for evaluating and integrating somatosensory, visual and vestibular inputs. This cortical area may be important for the perception of postural vertical and for compiling the egocentric reference system. From a clinical perspective, improving the function of this area might improve recovery from PS, which, in turn, would allow patients to focus on relearning activities of daily living during their rehabilitation. Based on the current understanding of the IPL, one may speculate that modulating IPL activity via rTMS may be a rational therapeutic strategy for PS.

## Strengths and limitations of this study

This trial has several strengths. First, this is the first randomised controlled clinical trial to explore the efficacy of a neuromodulation approach in patients with PS after stroke, which may provide a novel and more effective treatment strategy for PS. Second, the IPL is selected as the therapeutic target for neuromodulation in order to explore the underlying structure and mechanism responsible for PS. Third, the design of endpoint measurements of 1 week, 2 weeks and 3 weeks will enable us to examine the optimal treatment duration of rTMS for PS. Fourth, the trial will provide the stimulation parameters as reference for future studies of rTMS in designing more effective rTMS programme for PS. The study has several limitations. There is no objective measurement of pushing behaviour of the patients. The generalisability of the study results may be reduced when some patients are excluded owing to safety concerns. There is no follow-up to investigate the long-term effects of rTMS on the recovery of pushing behaviour and general functions of the patients.

**Contributors** All authors were involved in the study design, and read and approved the final manuscript. LM, RCCT and QGao contributed to conception and design of this study. LM and YG drafted the manuscript. RCCT, QGuo and QGao reviewed and revised the manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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## REFERENCES

1 Nolan J, Godecke E, Singer B. The association between contraversive lateropulsion and outcomes post stroke: a systematic review. *Top Stroke Rehabil* 2022;29:92–102.
2 Karnath H-O. Pusher syndrome--a frequent but little-known disturbance of body orientation perception. *J Neurol* 2007;254:415–24.
3 Dai S, Lemaire C, Piscicelli C, *et al*. Lateropulsion prevalence after stroke: a systematic review and meta-analysis. *Neurology* 2022;98:e1574–84.
4 Danells CJ, Black SE, Gladstone DJ, *et al*. Poststroke "pushing": natural history and relationship to motor and functional recovery. *Stroke* 2004;35:2873–8.
5 Abe H, Kondo T, Oouchida Y, *et al*. Prevalence and length of recovery of pusher syndrome based on cerebral hemispheric lesion side in patients with acute stroke. *Stroke* 2012;43:1654–6.
6 Paci M, Macchioni G, Ferrarello F. Treatment approaches for pusher behaviour: a scoping review. *Top Stroke Rehabil* 2022:1–18.
7 Yang Y-R, Chen Y-H, Chang H-C, *et al*. Effects of interactive visual feedback training on post-stroke pusher syndrome: a pilot randomized controlled study. *Clin Rehabil* 2015;29:987–93.

8 Paci M, Nannetti L. Physiotherapy for pusher behaviour in a patient with post-stroke hemiplegia. *J Rehabil Med* 2004;36:183–5.
9 Karnath H-O, Broetz D. Understanding and treating "pusher syndrome". *Phys Ther* 2003;83:1119–25.
10 Broetz D, Johannsen L, Karnath H-O. Time course of 'pusher syndrome' under visual feedback treatment. *Physiother Res Int* 2004;9:138–43.
11 Broetz D, Karnath H-O. New aspects for the physiotherapy of pushing behaviour. *NeuroRehabilitation* 2005;20:133–8.
12 Krewer C, Rieß K, Bergmann J, *et al*. Immediate effectiveness of single-session therapeutic interventions in pusher behaviour. *Gait Posture* 2013;37:246–50.
13 Yun N, Joo MC, Kim S-C, *et al*. Robot-Assisted gait training effectively improved lateropulsion in subacute stroke patients: a single-blinded randomized controlled trial. *Eur J Phys Rehabil Med* 2018;54:827–36.
14 Bergmann J, Krewer C, Jahn K, *et al*. Robot-Assisted gait training to reduce pusher behavior: a randomized controlled trial. *Neurology* 2018;91:e1319–27.
15 An C-M, Ko M-H, Kim D-H, *et al*. Effect of postural training using a whole-body tilt apparatus in subacute stroke patients with lateropulsion: a single-blinded randomized controlled trial. *Ann Phys Rehabil Med* 2021;64:101393.
16 Lee JH, Kim SB, Lee KW, *et al*. Somatosensory findings of pusher syndrome in stroke patients. *Ann Rehabil Med* 2013;37:88–95.
17 Nakamura J, Kita Y, Yuda T, *et al*. Effects of galvanic vestibular stimulation combined with physical therapy on pusher behavior in stroke patients: a case series. *NeuroRehabilitation* 2014;35:31–7.
18 Babyar S, Santos-Pontelli T, Will-Lemos T, *et al*. Center of pressure speed changes with tDCS versus GVS in patients with lateropulsion after stroke. *Brain Stimul* 2016;9:796–8.
19 Babyar S, Santos T, Will-Lemos T, *et al*. Sinusoidal transcranial direct current versus galvanic vestibular stimulation for treatment of lateropulsion poststroke. *J Stroke Cerebrovasc Dis* 2018;27:3621–5.
20 Yamaguchi T, Satow T, Komuro T, *et al*. Transcranial direct current stimulation improves pusher phenomenon. *Case Rep Neurol* 2019;11:61–5.
21 Ticini LF, Klose U, Nägele T, *et al*. Perfusion imaging in pusher syndrome to investigate the neural substrates involved in controlling upright body position. *PLoS One* 2009;4:e5737.
22 Karnath H-O, Johannsen L, Broetz D, *et al*. Posterior thalamic hemorrhage induces "pusher syndrome". *Neurology* 2005;64:1014–9.
23 Baier B, Janzen J, Müller-Forell W, *et al*. Pusher syndrome: its cortical correlate. *J Neurol* 2012;259:277–83.
24 Babyar SR, Smeragliuolo A, Albazron FM, *et al*. Lesion localization of poststroke lateropulsion. *Stroke* 2019;50:1067–73.
25 Pell GS, Roth Y, Zangen A. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: influence of timing and geometrical parameters and underlying mechanisms. *Prog Neurobiol* 2011;93:59–98.
26 Cortes M, Black-Schaffer RM, Edwards DJ. Transcranial magnetic stimulation as an investigative tool for motor dysfunction and recovery in stroke: an overview for neurorehabilitation clinicians. *Neuromodulation* 2012;15:316–25.
27 Lefaucheur J-P, Aleman A, Baeken C, *et al*. Evidence-Based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). *Clin Neurophysiol* 2020;131:474–528.
28 Fisicaro F, Lanza G, Grasso AA, *et al*. Repetitive transcranial magnetic stimulation in stroke rehabilitation: review of the current evidence and pitfalls. *Ther Adv Neurol Disord* 2019;12:175628641987831–22.
29 Winstein CJ, Stein J, Arena R, *et al*. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2016;47:e98–169.
30 Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 2005;20:187–91.
31 Nyffeler T, Vanbellingen T, Kaufmann BC, *et al*. Theta burst stimulation in neglect after stroke: functional outcome and response variability origins. *Brain* 2019;142:992–1008.
32 Nyffeler T, Cazzoli D, Hess CW, *et al*. One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. *Stroke* 2009;40:2791–6.
33 Cazzoli D, Wurtz P, Müri RM, *et al*. Interhemispheric balance of overt attention: a theta burst stimulation study. *Eur J Neurosci* 2009;29:1271–6.
34 Koter R, Regan S, Clark C, *et al*. Clinical outcome measures for lateropulsion poststroke: an updated systematic review. *J Neurol Phys Ther* 2017;41:145–55.
35 Babyar SR, Peterson MGE, Bohannon R, *et al*. Clinical examination tools for lateropulsion or pusher syndrome following stroke: a systematic review of the literature. *Clin Rehabil* 2009;23:639–50.
36 Bergmann J, Krewer C, Rieß K, *et al*. Inconsistent classification of pusher behaviour in stroke patients: a direct comparison of the scale for contraversive pushing and the Burke lateropulsion scale. *Clin Rehabil* 2014;28:696–703.
37 D'Aquila MA, Smith T, Organ D, *et al*. Validation of a lateropulsion scale for patients recovering from stroke. *Clin Rehabil* 2004;18:102–9.
38 Bergmann J, Krewer C, Müller F, *et al*. A new cutoff score for the Burke lateropulsion scale improves validity in the classification of pusher behavior in subactue stroke patients. *Gait Posture* 2019;68:514–7.
39 Sedaghat AR. Understanding the minimal clinically important difference (MCID) of patient-reported outcome measures. *Otolaryngol Head Neck Surg* 2019;161:551–60.
40 Baccini M, Paci M, Rinaldi LA. The scale for contraversive pushing: a reliability and validity study. *Neurorehabil Neural Repair* 2006;20:468–72.
41 Baccini M, Paci M, Nannetti L, *et al*. Scale for contraversive pushing: cutoff scores for diagnosing "pusher behavior" and construct validity. *Phys Ther* 2008;88:947–55.
42 Karnath H-O, Brötz D. Instructions for the clinical scale for contraversive pushing (SCP). *Neurorehabil Neural Repair* 2007;21:370–1.
43 Rech KD, Salazar AP, Marchese RR, *et al*. Fugl-Meyer assessment scores are related with kinematic measures in people with chronic hemiparesis after stroke. *J Stroke Cerebrovasc Dis* 2020;29:104463.
44 Tsang RC-C, Chau RM-W, Cheuk TH-W, *et al*. The measurement properties of modified Rivermead mobility index and modified functional ambulation classification as outcome measures for Chinese stroke patients. *Physiother Theory Pract* 2014;30:353–9.
45 Rossi S, Hallett M, Rossini PM, *et al*. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–39.
46 Marodin G, Goldim JR. [Confusions and ambiguities in the classification of adverse events in the clinical research]. *Rev Esc Enferm USP* 2009;43:690–6.
47 Yang W, Liu T-T, Song X-B, *et al*. Comparison of different stimulation parameters of repetitive transcranial magnetic stimulation for unilateral spatial neglect in stroke patients. *J Neurol Sci* 2015;359:219–25.
48 Corbetta M, Patel G, Shulman GL. The reorienting system of the human brain: from environment to theory of mind. *Neuron* 2008;58:306–24.
49 He BJ, Snyder AZ, Vincent JL, *et al*. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron* 2007;53:905–18.
50 Pérennou DA, Mazibrada G, Chauvineau V, *et al*. Lateropulsion, pushing and verticality perception in hemisphere stroke: a causal relationship? *Brain* 2008;131:2401–13.

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# Informed Consent Form

You are invited to participate in the study "rTMS for poststroke pusher syndrome: a randomised, patient-blinded controlled clinical trial". This study will be conducted in the West China Hospital, Sichuan University and a total of 34 participants will be voluntarily invited to participate. Ethical approval for this study has been obtained from the Biomedical Ethics Committee of West China Hospital, Sichuan University (approval No. 2022-133).

## 1. Why do we carry out this study?

Poststroke pusher syndrome (PS) severely affects the posture and balance of stroke patients, resulting in limited mobility and increased risk of falls. Studies have shown that pushing behaviours persisted at three months, with motor recovery and functional abilities significantly poorer than non-pushers. Patients with PS require longer duration of rehabilitation and more supplemental care after discharge from the inpatient rehabilitation setting. Therefore, patients with PS should be treated as early as possible. However, various interventions for PS have been reported but their efficacy remains uncertain. A more effective intervention needs to be developed. The study is to assess the efficacy and safety of repeated transcranial magnetic stimulation (rTMS) for patients after stroke with PS.

## 2. What do you need to do if you participate in this study?

If you agree to participate in this study, the information of your age, sex, stroke characteristics (duration, type, lesion side and lesion location) and handedness will be collected before treatment commencement, and you will be assessed with 4 measurement scales. Then you will be assigned to either the rTMS or sham stimulation

group. You will receive the rTMS or sham stimulation once a day during weekdays for about 9-10 minutes for a total of 15 sessions in three weeks, with 5 sessions per week. In addition, you will receive usual rehabilitation with exercise therapy provided according to your impairments and recovery, including (1) physioherapy and occupational therapy, (2) speech-language therapy, (3) treatment of dysphagia, (4) cognitive rehabilitation. The usual rehabilitation lasts approximately 4 hours daily on weekdays for 3 weeks.

Outcome data on efficacy of safety will be collected after 1 week, 2 week and 3 week of both groups.

**3. What are the treatment options available?**

(1) Balance training by using balance board, balance ball, balance master and other instruments to improve balance;

(2) postural training performed by the therapist to correct posture to the upright position.

**4. Who should not participate in this study?**

If you have any of the following conditions, you are not eligible to participate in this study.

(1) Have visual field deficits or eye muscle paralysis;

(2) Orthopaedic conditions limiting your participation, e.g., fracture, severe osteoporosis, contractures of the lower extremities;

(3) Having an unstable medical condition, or being unable to safely perform mild to moderate exercise;

(4) Metal implants, cardiac pacemaker, brain tumor, meningitis or epilepsy.

**5. What are the risks of participating in this study?**

The rTMS has been shown to be safe and well tolerated when applied to stroke patients. You may experience the following discomfort after rTMS therapy:

(1) Transient headache (common): It usually does not require any treatment.

(2) Local annoyance in the stimulated area (very common): It does not require any

treatment and rarely requires the suspension of rTMS. If the discomfort is reported to be excessive, the session will be suspended until the discomfort subsides.

(3) Temporary loss of hearing (rare): In such a case, the session will be suspended until the discomfort subsides within 24 hours. Then the intervention will be resumed if the patient agrees.

(4) Epileptic crises (rather rare): They may occur in predisposed individuals with history of epileptic seizures. To minimize this risk, participants who have suffered from seizures during the acute phase or have a diagnosis of epilepsy will be excluded from the trial (exclusion criterion). If a convulsive episode occurs during treatment with rTMS despite the above precautions, the latter will be immediately suspended, and the patient will be treated according to the standard hospital protocols for epileptic seizures.

During the study period, we will closely monitor these adverse effects and take appropriate action in a timely manner.

**6. What are the possible benefits of participating in this study?**

Your condition may improve if you participate in this study. This study will help determine whether rTMS can be used as a more effective and safer method to treat other patients with similar conditions.

**7. Do I need to pay any fees to participate in this study?**

There is no payment required to participate in the study. Incentive of reducing other therapy fees will be provided for you. You will be provided corresponding treatment and compensation in accordance with relevant national regulations in case of any injury occurred in relation to the study.

**8. Is personal information confidential?**

All your information will be kept confidential in the West China Hospital, Sichuan University. Your medical record will only be accessible to the researchers, research authorities and the ethics committee. Your personal identity will not be disclosed in any

public report of this study. We will make every effort to protect the personal data privacy of each participant in accordance to the requirements of the ethics committee and legal authorities.

**9. Do I have to participate in the study?**

Participation in this study is completely voluntary. You may refuse to participate or withdraw from the study at any stage of the study without being subjected to any discrimination or retaliation. Your rights to appropriate medical treatment will not be affected. If you decide to withdraw from the study, please contact your doctor for proper treatment.

**Participant declaration:** I have read the above information of this study. The researcher has fully explained to me the purpose, the procedures, the possible risks and potential benefits of this study, and answered all my relevant questions.

I volunteer to participate in the study.

**I agree** ☐ **or refuse** ☐ to use my research data and biological specimens for research other than this study.

Name of participant in block letters:

Participant 's signature: Date:

Phone number of participant:

Legal representative name in Block letters: (if applicable)

Relationship with participant:

Legal representative signature: Date:

Reasons for signing by legal representative:

Name of Witness in block letters: (if applicable)

Signature of witness: Date:

Reasons for signing by witnesses:

**Physician statement:** I have explained the study details to the participant and provided him/her with an original signed informed consent form. I confirm that I have explained this study to the subject in detail, especially the ethical principles and information of risks and benefits, fee and compensation, injury and compensation, voluntariness and confidentiality that may arise from participating in the study.

Doctor's signature: Date:

Contact number of the doctor:

**Biomedical Ethics Committee of West China Hospital, Sichuan University**

**Contact number: 028-85422654, 028-85423237**

## Usual Rehabilitation Programme

All patients will receive the usual rehabilitation with exercise therapy according to their impairments and recovery. The usual rehabilitation programme is consistent with the clinical guidelines for adult stroke rehabilitation published by the American Heart Association/American Stroke Association. The usual rehabilitation programme is administered by the multidisciplinary team including physiotherapist, occupational therapist and speech therapist. Each treatment is delivered by the same therapists with more than 5 years of working experience in stroke rehabilitation and familiarity with the treatment of PS. The usual rehabilitation lasts approximately for 4 hours daily on weekdays for 3 weeks. The usual rehabilitation programme includes:

1. **Physiotherapy**

Physiotherapy (administered by JZ) in the context of task-specific training with visual feedback consisting of:

(1) bed and wheelchair mobility training;

(2) bed-wheelchair transfer training;

(3) sit-to-stand;

(4) sitting and standing balance training;

(5) pre-gait and gait training performed by robot-assisted treadmill training

2. **Occupational therapy**

Occupational therapy (administered by XM) in the context of task-specific training with visual feedback consist of:

(1) task-oriented hand and upper limb training in which the tasks are graded to challenge individual capabilities, practised repeatedly and progressed in difficulty on a frequent basis;

(2) activities of daily living and instrumental activities of daily living training tailored to individual needs and eventual discharge setting

**3. Speech-language therapy**

Speech-language therapy (administered by YL) includes:

(1) physiological support for speech and target impairments in respiration, phonation, articulation, and resonance;
(2) behavioural treatments including strategies to increase the precision of articulation, to modify the rate and loudness of speech, and to improve prosody;
(3) augmentative and alternative communication devices such as simple picture boards or spelling boards;
(4) supplemental strategies such as gesture or writing

**4. Treatment of dysphagia**

The management and treatment of dysphagia (administered by LW) includes:

(1) swallowing exercises;
(2) environmental modifications such as upright positioning for feeding;
(3) safe swallowing advice and appropriate dietary modifications;
(4) pharyngeal electric stimulation;
(5) physical stimulation such as ice stimulation

**5. Cognitive rehabilitation**

Cognitive rehabilitation (administered by RZ) includes:

(1) activities practice requiring attention;
(2) planning or working memory with pencil and paper or computerized activities;
(3) treatment of visual neglect;
(4) executive functioning training;
(5) teaching of compensatory strategies;
(6) memory rehabilitation interventions:

a. for patients with mild memory impairments, memory strategy training, including the use of internalized strategies (eg, visual imagery, semantic organization or spaced practice) and external memory compensations (eg, notebooks, computers or other prompting devices), is recommended

b. for patients with severe memory deficits, errorless learning techniques and the use of external compensations, including assistive technology, with direct application to

functional activities is recommended