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

Lijiao Meng [1,2] Raymond C C Tsang,[3] Yanlei Ge,[1,2] Qifan Guo,[4] Qiang Gao[1,2]

[1] Rehabilitation Medicine Center, Sichuan University West China Hospital, Chengdu, Sichuan, China
[2] Key Laboratory of Rehabilitation Medicine in Sichuan Province, Sichuan University West China Hospital, Chengdu, Sichuan, China
[3] Physiotherapy Department, MacLehose Medical Rehabilitation Centre, Hong Kong, China
[4] Department of Rehabilitation Sciences, West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

Correspondence to
Dr Qiang Gao;
gaoqiang_hxkf@163.com

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.

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

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
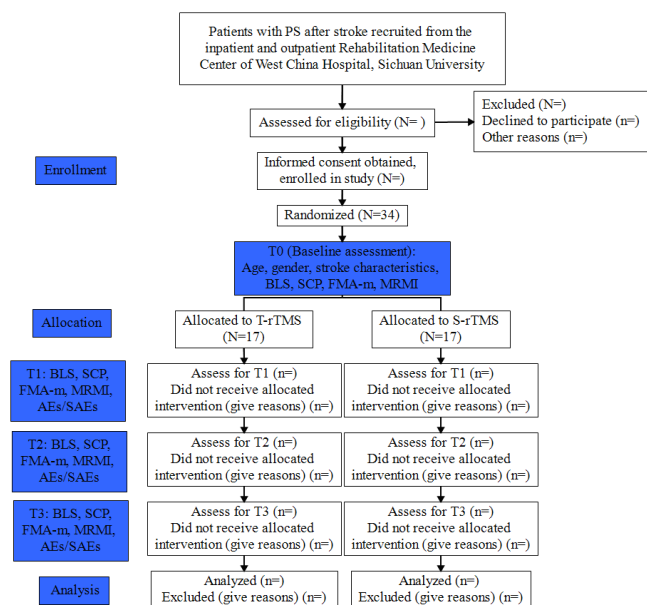
Figure 1 The flow diagram of the study. T0, baseline assessment; T1: after 1 week of intervention; T2: after 2 weeks of intervention; T3: after 3 weeks of intervention. AEs, adverse events; BLS, Burke Lateropulsion Scale; FMA-m, Fugl-Meyer Assessment Scale-motor domain; MRMI, Modified Rivermead Mobility 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 ▶ ≤6 months following an ischaemic or haemorrhagic stroke ▶ Patients with PS defined as BLS scores ≥3 during the initial examination ▶ Ability to follow two-step commands ▶ Ability to provide informed consent ▶ No other neurological disorders	▶ Have visual field deficits or eye muscle paralysis ▶ Orthopaedic conditions limiting participation, for example, fracture, severe osteoporosis, contractures of the lower extremities ▶ Having an unstable medical condition, or being unable to safely perform mild to moderate exercise ▶ 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 χ^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.

ORCID iD
Lijiao Meng http://orcid.org/0000-0002-5890-338X

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