

Project title:

Effects of combined repetitive transcranial magnetic stimulation and treadmill training on gait performance in Parkinson's disease – a randomised controlled trial

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1. Project Title:

Effects of combined repetitive transcranial magnetic stimulation and treadmill training on gait performance in Parkinson's disease – a randomised controlled trial

2. Project Objectives:

There are three objectives in this research study:

1. To compare short- and long-term effects of 25Hz repetitive transcranial magnetic stimulation (rTMS) with 1Hz rTMS followed by treadmill training on their gait performance during single task and dual task conditions in people with Parkinson's disease (PD)
2. To compare short- and long-term effects of 1Hz with 25Hz rTMS followed by treadmill training on corticomotor excitation and intracortical inhibition in people with PD.
3. To explore whether combined rTMS and treadmill training can be transferred to enhancement of balance performance in people with PD

3. Scope and Background of Research:

Parkinson's disease (PD) is a complex neurodegenerative disorder. The cardinal motor symptoms of PD are resting tremor, bradykinesia, rigidity and postural instability, which cause disrupted control of body movement in people with PD. There are many concomitant non-motor symptoms, including cognitive decline affecting dual tasking ability and executive functioning. The pathophysiology of PD is related to the loss of dopamine producing neurons in the substantia nigra leading to depletion of dopamine supplying the basal ganglia. The basal ganglia consist of caudate, putamen, globus pallidus, subthalamic nucleus, and substantia nigra. Voluntary movement is initiated from cerebral cortex and regulated by complex feedback loops that involve the cortex, thalamus, basal ganglia and cerebellum. Dopamine has an important role in facilitating the motor outputs in this feedback loop. In addition, the internal globus pallidus, the output nucleus of basal ganglia, sends phasic cues to the supplementary motor area to regulate movement size and hence allows well-learned movement to be performed without constant conscious attention (1). A loss of dopamine inhibits output from the thalamus to the cerebral cortex, leading to various motor manifestations including resting tremor, bradykinesia and rigidity. The defective facilitation from the basal ganglia to the motor cortices also affects the automaticity of movement control in a well-learned movement sequence such as walking. Indeed, gait difficulty was reported to be one of the most debilitating symptoms for people with PD and to be able to walk effectively and safely has significant impact on their quality of life (2). The most typical gait disorders in PD are hypokinetic gait pattern characterized by slow walking speed and short stride length. It can be accompanied by increased stride time variability associating with reduced gait stability. Apart from this continuous form of gait difficulty, PD patients may also experience some episodic gait disorders such as freezing of gait and gait festination (3). Secondary

to the effects of reduced automaticity in movement control in PD, performing an additional task while walking can be very challenging for PwPD. Dual tasking during walking provokes freezing of gait in some cases.

In terms of neurophysiology study on the central nervous system in PD, transcranial magnetic stimulation (TMS) has been used extensively in the recent decade to assess the cortical excitability and that of the corticospinal motor system via non-invasive magnetic stimulation applied to the motor cortex. Consistent findings have been reported for cortical excitability studies in PD (4-8). Cortical silent period was found to be significantly shorter and short interval intracortical inhibition was also found to be smaller in PD (5). Besides, decreased motor threshold and increased motor evoke potential at rest was reported in PD (6). These changes in the cortical excitability appears to be related to the pathophysiology of PD since levodopa can restore both cortical silent period and short interval intracortical inhibition (8).

Repetitive transcranial magnetic stimulation (rTMS) refers to the regular repeated stimuli of single pulse TMS delivered in trains. Cortical excitability can be enhanced by high frequency rTMS (with rate more than 1 Hz) (9) whereas low frequency rTMS (with rate of less than 1Hz) induces depression of cortical activity (10). These changes in cortical excitability are transient, lasting for about 10-30 minutes (11, 12). rTMS has been used to modulate the cortical excitability in PD with therapeutic effect (8). Regarding rTMS stimulation parameters, recent meta-analysis reviewed that high frequency rTMS was effective in enhancing motor symptoms of PD and low frequency has little effect on motor function (13, 14). Moreover, stimulation of cortical motor areas was also found to increase the duration of cortical silent period in PD patients (8, 15, and 16). In terms of dosage, when using high frequency rTMS in PD a single session of rTMS found to reduce PD disease severity measured by Unified PD rating scale (UPDRS). More lasting effects (up to 10 days to 1 month post-treatment) was demonstrated with multiple rTMS sessions ranging from daily treatment for 6-10 days and 8 sessions over 2.5 weeks (17,18,19). Regarding the stimulation frequency, Khedr et al. (17) compared the effects of 25Hz rTMS and 10Hz rTMS in 55 PD subjects with off levodopa for at least 1 week. They found that there were cumulative and long lasting improvements in UPDRS motor scores, walking time as well as keyboard tapping time in both 25Hz and 10Hz subject groups (17). However, PD subjects received 25Hz seemed to have greater improvement as well as faster improvement compared with 10Hz. Lomarev and colleagues (19) also demonstrated very similar results in their study using the same TMS parameters (25Hz, 100% RMT) associated with an increased in walking speed and amplitude of the motor evoked potential. These findings suggest that 25 Hz rTMS stimulation could be effective in enhancing motor performance and cortical modulation in PD patients.

In addition, high frequency rTMS was found to enhance motor learning (20). Long lasting motor learning is achieved by long-term potentiation and long-term depression, which involve synaptic plastic changes related to the new learnt task (21). The transient raised excitability of the motor cortex through high frequency rTMS is proposed to facilitate this motor learning process (20). Other

than this, the principal of activity dependent neuroplasticity suggests that motor learning has to be task specific (22). Therefore, application of rTMS before specific motor training may boost up the training effect. Yang et al (23) recently demonstrated that 12 sessions over 4 weeks of 5Hz rTMS and treadmill training compared with treadmill alone led to better improvement of walking and functional mobility performance accompanied with some positive changes in intracortical inhibition. This modulation of intracortical inhibition has also been shown after high intensity treadmill training (24). These findings are very intriguing but further randomised control trials with more sample sizes are warranted to minimise bias. In addition, it is uncertain if the rTMS stimulation protocol used in Yang et al study is optimal. The carry over effect has also not been examined.

Therefore, this research projects aim to determine a rTMS stimulation protocol that would optimise the beneficial effect of treadmill training in PD by comparing the 2 different stimulation frequency protocols i.e. 1Hz and 25 Hz. In addition, rTMS has been found to restore the intracortical inhibition in PD (23). The restoration of the cortical inhibition through rTMS may have therapeutic effect on the defective cortical-basal ganglia-cortical network in PD (8). The inhibitory signals are essential for optimal execution of motor program by inhibiting other inappropriate and competing circuits. As discussed earlier, the basal ganglia allow well-learned movement such as walking to be performed with less attention resources. Hence, it would be interesting to investigate if rTMS would enhance the automaticity of walking and thus better dual-task walking performance.

Last but not least, it will be interesting to investigate whether combined rTMS and treadmill training can be transferred to enhancement of balance performance in PD as treadmill training has been found to reduce fall rate in PD (33).

4. Research Methodology:

Study Design: A double-blinded randomised controlled trial

Participants

This study is divided into three parts. Ten healthy participants will be recruited for study part I; 5 healthy participants and 5 participants with PD will be recruited for study part II; the following inclusion criteria for study part I & II: 1) Aged 18 and above for healthy participant and aged 40 -70 above for PD. The exclusion criteria are as follow: 1) severe comorbidity that may interfere with their ability to participate in the study (e.g. chronic obstructive airway disease, angina, congestive cardiac failure, and significant renal or liver disease, malignancy) 2) significant orthopaedic or rheumatological conditions or disorders of peripheral nervous system that may interfere with tested ankle and foot strength and mobility 3) Female subjects who are pregnant 4) a score of less than 23 on the Mini-Mental State Examination 5) any auditory or visual impairment 6) History of neurosurgery 7) contraindication to TMS including personal or family history of seizure disorder, metal in the head, implants of medical devices such as cardiac pacemakers or medical pumps (Appendix 1). Informed consent in accordance with the Declaration of Helsinki will be obtained from all participants and data

collection will only be carried out after the approval of Hong Kong Polytechnic University Ethics Committee.

Fifty-one participants with PD will be recruited with the following inclusion criteria for study part III: 1) Aged 40 to 70, 2) Diagnosed with idiopathic Parkinson's disease by a neurologist 3) Hoehn & Yahr Scale Stage II to III with stable medications usage 4) ability to walk independently with or without walking aids for 10 metres. The exclusion criteria are as follow: 1) severe comorbidity that may interfere with their ability to participate in the study (e.g. chronic obstructive airway disease, angina, congestive cardiac failure, and significant renal or liver disease, malignancy) 2) significant orthopaedic or rheumatological conditions or disorders of peripheral nervous system that may interfere with mobility or balance performance 3) Female subjects who are pregnant 4) Neurological disease other than PD 5) a score of less than 23 on the Mini-Mental State Examination 6) any auditory or visual impairment 7) History of neurosurgery 8) contraindication to TMS including personal or family history of seizure disorder, metal in the head, implants of medical devices such as cardiac pacemakers or medical pumps (Appendix 1). 9) Subjects with irrepressible tremor and/dyskinesia. Informed consent in accordance with the Declaration of Helsinki will be obtained from all participants and data collection will only be carried out after the approval of Hong Kong Polytechnic University Ethics Committee.

The sample size calculation is based the significant findings of the gait speed and cortical silent period reported by Yang et al. (23). A two-way repeated measures ANOVA design with between-subject group effect (3 levels) and within-subject time effect (4 levels) determines that fifteen subjects per group are required to achieve 85% power to test the interaction effect between group and time effect with a 5% significance level and the effect size is 0.4. By assuming 10% dropout rate, 17 subjects will be required per group.

Experimental protocol

Part I & II. Mapping study and reliability study

Measures of cortical excitability including resting motor threshold (RMT) and recruitment curves will be obtained with transcranial magnetic stimulation (TMS) for 10 healthy subjects for study part I to identify the optimal site for TMS stimulation of the tibialis anterior (TA) muscles.

Magstim_200 magnetic stimulator (Magstim Company, Whitland, UK) and 90-mm double cone coil will be used to deliver TMS in this study. Each participant will be seated comfortably in a recumbent chair with arm and head supported by pillow. Small surface electromyography EMG electrodes will be attached to the belly of the TA with a ground electrode placed on the ankle. The motor evoked potential (MEP) in the TA will be recorded with surface EMG, which will be amplified with the band pass filtered between 10 and 1000Hz(Viking II Electromyography). All EMG traces will be stored for offline analysis.

Skin preparation using "3M One Step" skin prep abrasive sandpaper to reduce skin impedance will

be performed prior to the placement of the surface electrodes as well as the ground electrodes.

Resting Motor Threshold

Resting motor threshold of each participant will be determined with the following procedure: A latex swim cap will be placed on each participant's head and measurement of the vertex (Cz) will be marked on the cap. Subjects will be instructed to relax but to keep their eyes open during the whole procedure.

The coil is held centred over Cz, with a common longitudinal part of the coil along the interhemispheric fissure. Single TMS pulse will be delivered over the scalp overlying contralateral primary motor cortex that controls the TA. The MEPs of the bilateral tibialis anterior muscles will be recorded in response to TMS delivered with different coil orientation and location to determine the best coil orientation and hot spot. The site that evokes the largest and most consistent MEP amplitudes will be considered as the motor hot spot. The best coil orientation that evokes the largest and most consistent amplitudes will be adopted for subsequent TMS procedure of this study. This location with reference to Cz will be marked on the swim cap fitted for each subject. With the stimulus coil placed over the hot spot, stimulus intensity will be lowered gradually in a step-wise manner to determine the resting motor threshold (RMT). RMT is defined by minimal intensity that produces a MEP of a minimum of 50 μ V in 5 out of 10 consecutive trials.

Cortical silent period

Cortical silent period (CSP) is defined as an interruption of electromyographic (EMG) activity in the corresponding contracting muscle during a TMS (26). Subject will be asked to perform a 20% isometric maximal contraction of the TA by flexing the ankle against a belt strapped around foot. The EMG activity of the muscle will be reflected on a computer screen and visible to the subject. The subject will be asked to maintain this constant force while TMS is applied. TMS intensity at 130% of RMT will be delivered during the isometric of TA. Ten CSP measurements will be obtained within a single session. The duration of CSP will be measured from the end of the MEP to the point when the EMG level returns to the baseline value measured 50ms before the TMS stimulus (26, 27). Each CSP duration will be analysed and the mean value of 10 CSP duration will be used for further analysis. The duration of the cortical silent period (CSP) was used to examine the intracortical inhibitory mechanisms, possibly via a GABA-B mediated circuit (34).

Recruitment curve

Recruitment curve (RC) is also known as stimulus-response curve, illustrate the change in MEP size as a function of stimulus intensity. Recruitment curves of increasing intensities of 10% steps will be obtained in ten trials per step starting at 10% below RMT and increasing up to 180% of the RMT. MEP amplitudes are measured peak-to-peak and averaged off line. TA MEPs were expressed as a percentage of the TA maximum motor response (M-max). Typically TA Max is acquired by stimulating the common peroneal nerve with supramaximal stimuli by bipolar surface electrodes placed distal to the neck of the fibular.

Intracortical inhibition

A paired conditioning-test stimulus technique will be used to measure SICI in the TA muscle according to Kujirai's procedure (35). A test TMS of 120% RMT pulse will be delivered preceded by a brief conditioned pulse set at a lower intensity of 80% of the RMT with inter-stimulus interval of 2ms. For each condition, 10n trials were collected and averaged.

Measures of cortical excitability including resting motor threshold (RMT), recruitment curves, intracortical inhibition (SICI) will be obtained with transcranial magnetic stimulation (TMS) for intra-rater and test-retest reliability of all these measures will be established for Study Part II. TMS assessment will be repeated twice, at least 1.5 hour apart within the same session for each study participant to assess the intra-rater reliability. Study participants will be asked to returned 1 week after for TMS assessment to assess the test-retest reliability.

Part III. Interventions

All assessment and treatment will be carried out at the electrophysiology and Gait and balance laboratory. Participants will be randomised into three groups i.e. two experimental groups and a sham group. Participants in the experimental groups will received either 1 Hz or 25Hz real rTMS and control group will receive sham rTMS, followed by treadmill training for 16 sessions over 8 weeks.

Repetitive transcranial magnetic stimulation. Repetitive TMS will be delivered to the scalp over the leg area of the motor cortex contralateral to the more affected side by using a Magstim200 magnetic stimulator (Magstim Company, Whitland, UK) and 90mm double cone coil in this study. Each participant will be seated comfortably in a recumbent chair with legs and head supported by pillow. The experimental group will receive either a 1Hz or 25 Hz of real rTMS with an intensity of 80% resting MT, a total of 1200 rTMS pulses to both hemispheres. For 1Hz rTMS, subjects will receive 3 trains of 200s-1Hz with 10 seconds inter train intervals to each hemisphere in 20 minutes. For 25Hz rTMS, subjects will receive 3 blocks (2 minutes break) of 8 trains of 1s-25Hz with 10s inter train intervals to each hemisphere in 20 minutes. The coil is centred over vertex and laterally offset to the leg area at the optimal site for response from the contralateral tibialis anterior (TA) muscle. A latex swim cap will be placed on each participant's head and measurement of the vertex will be marked on the cap. Subjects will be instructed to relax but to keep their eyes open during the whole procedure. The location of the stimulation will be marked, referenced by vertex-centred coordinates and recorded to maintain consistency among sessions. The sham rTMS will be delivered in the same setup and parameters of that of 25 Hz rTMS, however, with the cables of the coil disconnected. Another figure-of-eight coil delivering 25 Hz of rTMS will be placed posterior to the subject's neck. Subjects in the placebo group will be told that the stimulation intensity is sub threshold for muscle contraction.

Treadmill training. All participants will walk on a motorized treadmill after rTMS for 30 minutes. The

participants will wear a safety harness without body weight support during walking on the treadmill to prevent falls. The maximum tolerated walking speed was determined before training session. Half of the maximum speed will be used for a 5-minute warm up; the training walking speed will be increased by increments of 0.6km/h every 5 minutes. When the belt speed is increased to the highest speed at which the subject could walk safely and without stumbling. This maximum – achieved belt speed will be maintained for 5 minutes and then followed by 0.6km/h decrements. The subject will maintain this speed for the rest of the treadmill session for 15 minutes. If subject is unable to maintain this speed, it will be reduced by 0.6km/h in the next phase. If subject is able to maintain this reduced speed for 5 minutes, the speed will increase during the next phase by 0.6km/h. The treadmill is not included throughout the training. The treadmill training session will last for 30 minutes.

Data Collection

Data will be collected 1 week before intervention and immediately after completion, and at 2 and 6 months after treatment completion. All subjects will be instructed to take their customary medications 1hour before each assessment. The assessor will be blinded to group assignment. During the baseline condition, demographic factors such as age, gender, duration of PD, and the number and daily dosage of anti-parkinsonian medications will be recorded. In each assessment session, the dosage of anti-parkinsonian medications will be recorded.

Outcome measures

Corticomotor excitability

The RMT, RC, CSP duration, SICI of the tibialis anterior muscle elicited by TMS will be used to evaluate motor cortex excitability and inhibition using the procedure described above.

Motor assessment and Functional mobility test

1. Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

MDS- UPDRS motor scoring will be assessed for each participant a week before the TMS measure. Motor section of the MDS-UPDRS will be used. There are total of 27 items [tremor at rest (arm and leg), action tremor (arm), rigidity (arm and leg), finger taps, hand movements, rapid alternating hand movements, and leg agility]. Each item scores from 0-4, with 0 indicates no disability and 4 maximum disabled.

2. Gait and functional Performance

Ten-meter walk test (10-meter walk test) and timed up and go test (TUG) were measured to evaluate the gait performance in both single task and dual task conditions. Gait parameter will be captured by the APDM systems. The APDM system is a valid, wearable gait and balance analysis system (28). The gait parameters measured includes gait speed, stride length, cadence, variability and asymmetry. Anticipatory postural adjustment, center of mass motion and postural sway path can be also measured with this system.

2.1 Single task test condition:

For 10-meter walk test, subjects will be instructed to walk at their comfortable speed and fast

walking speed from 2m before the start line of a 10m distance and complete the walk 2m after the end of 10m. Each subject will perform 3 trials for both comfortable and fast walking speed and data will be averaged.

For TUG, Subjects will be instructed to stand up from a standardized chair, walk 3m at a comfortable speed, turn around, walk back to the chair and sit down. Timing will be commenced on the word 'start' and stopped once the subject sits down again with the back touching the backrest of the chair. Each subject will perform 3 trials of TUG with one practice trial before testing commences. Timed up and go test (TUG) is a functional mobility test with good validity and reliability (29). Poor TUG performance is associated with high fall risk in PD patients (30).

2.2 Dual task test condition:

Subjects will be asked to repeat both 10-meter walk test and TUG 3 trials each while performing an additional task such as serial three subtractions (counting backwards by threes aloud).

3. Balance performance

MimiBESTest will be used to measure the balance performance. MiniBEST has been validated to identify fallers in PD (31). High inter-rater reliability and test-retest reliability were shown (32).

Statistical analysis

All statistical analyses were performed using SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov tests will be used to check the normality of data. One-way analysis of variance (ANOVA), Mann-Whitney U tests, and Chi-square tests will be used to compare the dependent variables (demographic data, daily dosage of levodopa, and the number of correct calculated answers/ walking time) among the 1Hz, 25Hz and sham groups. Two-way repeated measures ANOVA will be used to analyze continuous data with measurement interval (baseline, post-treatment, 2-month and 6-month post-treatment) as within-factor and group (1Hz, 25Hz, sham) as between-factor. In the case of an interaction effect between group and time being found, one-way repeated measure ANOVA and *t*-tests with Bonferroni adjustment will be used to determine the real differences. A significance level of 0.05 was employed for analysis.

5. Project Significance and Value:

The progressive and disabling features of PD are the major burden to patients themselves, their families and society as a whole. One of the most disabling motor symptoms is gait difficulty and postural instability. Beneficial long-term effects of rTMS and treadmill training suggest that this intervention could slow down motor function deterioration and maintain gait and balance performance for a relatively long period of time. To be able to walk safely and effectively will promote independence, enhance quality of life, prevent falls and reduced institutionalisation for people with PD.

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Appendix 1

Name of Participant: _____

Date: _____

Name of Investigator: _____

TMS Screening Questionnaire

	<u>Yes</u>	<u>No</u>
Have you ever:		
(1) Had TMS before?		[] []
(2) Had a seizure?	[]	[]
(3) Had an unexplained spell of loss of consciousness?		[] []
(4) Had a stroke?	[]	[]
(5) Had a serious head injury?		[] []
(6) Had a surgery to your head?	[]	[]
(7) Had any neurological illnesses?	[]	[]
(8) Had any illness that may have caused brain injury?		[] []
Do you have any:		
(9) Frequent or severe headaches?	[]	[]
(10) Metal in your head region (inside or outside)?	[]	[]
(11) Implants of medical devices such as cardiac pacemakers, or medical pumps? [] []		
(12) Are you taking any medications?		[] []
(13) Are you pregnant?		[] []
(14) Does anyone in your family have epilepsy?		[] []
(15) Do you need any further explanation of TMS or its associated risks?		[] []

For any 'YES' response, please provide detailed information underneath.
