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Neural Mechanism of Skill Transfer in Parkinson's Disease

Submission to McGill Faculty of Medicine IRB

contents

Abbreviations

PD: Parkinson's disease

SBT: Split-belt treadmill

PwPD: Patients with Parkinson's disease

PPC: Posterior parietal cortex

TMS: Transcranial magnetic stimulation

rTMS: Repetitive transcranial magnetic stimulation

NFOGQ: New Freezing of Gai Questionnaire

MOCA: Montréal Cognitive Assessment

10MWT: 10 Meter Walk Test

MDS-UPDRS: Movement Disorder Society-Unified Parkinson’s Disease Rating Scale

FES: Falls efficacy scale

HADS: Hospital Anxiety and Depression Scale

SMA: Somatosensory motor area

APDM: Ambulatory Parkinson’s Disease Monitoring

MEPs: Motor evoked potentials

FDI: First dorsal interosseous

RMT: Resting motor threshold

TBT: tide-belt treadmill

TBS: theta burst stimulation

iTBS: intermittent theta burst stimulation

Lay summary

Parkinson's disease (PD) is a neurological degenerative disorder that shows motor impairment (Wu et al., 2015) and cognitive dysfunction (Sarter et al., 2021). Motor impairment including the decrease in motor adaptation skills results in increased falls (Jacobsen & Ferris, 2024), highlighting the importance of addressing the decline in motor adaptation skills in patients with PD (PwPD). To improve the motor adaptation in PwPD, the split-belt treadmill (SBT), where each foot is driven at a different speed, has been used. Currently, the SBT training has been shown to modulate gait in PwPD (D'Cruz et al., 2020; Hulzinga et al., 2023; Roemmich et al., 2014), but the skill transfer from the SBT training to the overground walking is poorly understood (Hulzinga et al., 2023). In terms of brain regions involved in the process of SBT adaptation, the posterior parietal cortex (PPC) has been found to play an important role in visuomotor integration and error monitoring (Shin et al., 2009) (Gwin et al., 2011), critical for overground walking. Furthermore, less activation of PPC has been reported in PwPD with freezing of gait symptom (Mitchell et al., 2019). Therefore, for this project, we propose to upregulate the PPC with non-invasive brain stimulation prior to SBT training to determine the role of the PPC on SBT gait adaptation.

Objectives

1. Determine the effect of the upregulation of PPC on SBT gait adaptation skill transfer from the treadmill to overground walking in PwPD.
2. Determine the effect of PPC upregulation on the training effects of SBT in PwPD.

Experimental approach

24 participants will participate in this study. Participants will take part in a three-visit protocol. The first visit will consist of a general clinical assessment and screening for participation. The other two visits will consist of rTMS over PPC (real or sham) + SBT training intervention, presented in random (i.e. real or sham rTMS stimulation over the PPC) order and counterbalanced among subjects. These interventions will be preceded and followed by an overground gait tests and the treadmill adaptation tests. To investigate how the rTMS over PPC affects the *gait adaptation skill transfer*, the gait parameters will be compared between the SBT adaptation tests and the overground walking tests after the intervention. Also, to investigate how the rTMS over PPC affects the *SBT training outcomes*, the gait parameters on the SBT adaptation tests and in the overground walking tests will be compared before and after the intervention.

Hypotheses

From a mechanistic point of view:

- If upregulation of PPC facilitates the skill transfer from the SBT adaptation tests to the overground walking tests, the activation of the PPC might contribute to the gait adaptation skill transfer in PwPD.
- If upregulation of PPC improves the SBT training effect, the PPC might contribute to the gait adaptation skill in PwPD.

Based on previous literature:

- Because the PPC has been shown to contribute to visuomotor integration and error monitoring required for complex walking(Gwin et al., 2011; Shin et al., 2009) and decrease its activation during steering of gait in PwPD with freezing of gait (Mitchell et al., 2019), it is hypothesized that upregulation of the PPC will facilitate the SBT training effects, as well as its transfer to overground walking.

Relevance

To define appropriate therapeutic interventions to improve the motor adaptation deficit in PwPD, it is critical to demonstrate that the skills acquired from the interventions can be transferred to real-life situations. The data gained from this protocol will allow us to investigate the skill transfer from the SBT training to real-life walking. Also, it will provide key information on the potential role of PPC on gait adaptation as well as skill transfer, that will benefit further work on discovering the brain mechanisms related to human gait and skill transfer.

Study purpose and rationale

PwPD show motor adaptation impairments that lead to increases in falls (Jacobsen & Ferris, 2024). Although training on the SBT has been proposed to improve motor adaptation skills (D'Cruz et al., 2020; Roemmich et al., 2014) and retention (Hulzinga et al., 2023) in PwPD, the investigation of skill transfer from the SBT to the overground complex walking has been limited. The PPC brain region has been proposed to integrate visuomotor information and monitor errors to guide motor programs (Shin et al., 2009) (Gwin et al., 2011), critical for complex walking. Also, we have shown that upregulation of the PPC can improve the freezing of gait symptom in PwPD (Potvin-Desrochers et al., 2023).
Therefore, the aim of this project is to:

- Investigate the effect of the upregulation of PPC on the gait adaptation skill transfer from the adaptation task on the SBT to overground walking tasks such as straight walking, steering, and turning.
- Investigate the effect of the upregulation of PPC on SBT training outcomes on the SBT as well as in the overground.

Description of study population, inclusion and exclusion criteria

For this study, 24 patients with PD will be recruited based on the following inclusion and exclusion criteria.

Inclusion criteria: 1) a confirmed diagnosis of idiopathic Parkinson's disease, 2) being aged 50 and above 3) absence of freezing of gait confirmed by a "No" answer to the second item of the New Freezing of Gait Questionnaire (NFOGQ) and no observation of FOG during a freezing provoking test, 4) no other neurological diagnosis, 5) no severe musculoskeletal/orthopedic or vestibular condition that interferes with walking and or significantly affects balance, 6) no mild cognitive impairment (MOCA $\geq$ 25), 7) able to walk independently and without assistive device for 30 minutes, 8) no previous experience with split-belt treadmill. **Exclusion criteria**: 1) severe dyskinesia that interacts with walking and balance, 2) hearing or visual impairment, 3) observed inability to walk safely on a tied-belt treadmill. 4) neurological disorders other than PD or other pathology (e.g., orthopedic) interfering with mobility. 5) contradiction for TMS, 6) implanted deep brain stimulator.

Recruitment:

Participants will first be recruited through our laboratory's bank of participants (people who participated in previous studies in our laboratory and gave their consent for future contact; IRB Studies: A10-B96-22B and A08-B49-19A), or through the Quebec Parkinson Network.

We estimate that the rate of recruitment should be at least 12 patients per month, without difficulty. Thus, the recruitment period for 24 PD patients should approximately 2 months.

Sample size and how it was determined

The sample size was calculated by using G*Power version 3.1.9.7 (Faul et al., 2007). Based on the calculation, 24 participants are required to obtain 80% power, at a level of significance of 95% (α=.05), and effect size f = 0.25 (moderate). The effect size was decided based on previous research which found the statistically significant intervention effect of the SBT with medium to high effect size in the PwPD (Hulzinga et al., 2023) (Seuthe et al., 2020).

Participants attrition: Some personal or technical issues may prevent us from collecting data (e.g., drop-out before the completion of the experiments). Therefore, we could recruit up to 3 additional participants (~10% of our desired sample size) to ensure that we reach our full sample size.

Design and description of methodology

This study is designed as a **randomized controlled crossover** and **single-blind** study. Participants will be required to visit the Human Brain Control of Locomotion Lab (HBCL) at McGill University on **three occasions**. During the **first day**, participants will go through a clinical assessment and determine their baseline walking speed using walking ability and gait speed using the 10-Meter Walk Test (10MWT). The rTMS targets will be identified and motor thresholds will be obtained. The **second and third visits**, will take place at least 48h a part to ensure that the rTMS effects are washed-out between visits. As illustrated in Figure 1, during these two visits, the participants will first perform pre-overground walking tests: straight walking, steering, and turning, followed by pre-SBT adaptation tests. After these gait tests, motor threshold validation will be conducted to determine optimal rTMS stimulation, followed the rTMS or sham intervention. The order of the sham and rTMS will be randomized and counterbalanced among subjects. Immediately after the rTMS or sham intervention, patients will move to the split-belt treadmill for the 6 blocks (5 minutes for each block) of SBT training with a 1-minute break in between to prevent the effects of fatigue. After the SBT interventions, post-SBT adaptation tests and the post-overground walking tasks will be performed. Cortical excitability will be measured to investigate the change in the excitability of PPC before and after the TMS intervention (as shown by orange arrows in Figure 1).

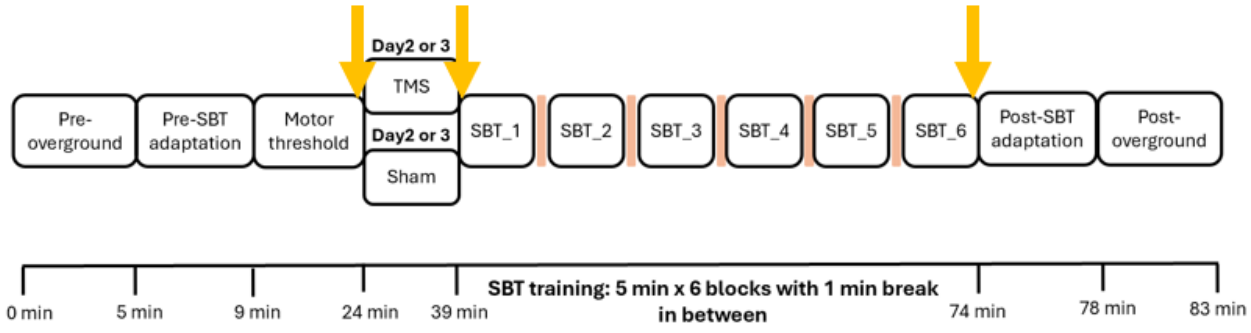


FIGURE 1. Protocol design for visits 2 and 3. Pre-overground and pre-SBT adaptation tests will be performed before the intervention. The order of the sham and rTMS will be randomized and counterbalanced among subjects. After the 6 blocks of SBT training, post-SBT adaptation and post-overground tests will be completed. Orange arrows indicate cortical excitability measurements.

Clinical assessment (first visit)

In the first visit, we will first review the consent form with the participants to ensure that participants have the capacity to consent. We will ask questions to ensure that they understand the information in the consent form and appreciate the experimental procedure and possible consequences, that they can reason, and that they can express a choice. If there are any questions concerning the ability of participants to provide consent, we will exclude the participant and terminate participation in the study. Several assessments will be performed to gain demographic information and rate the PD-associated level of impairment, which include the following:

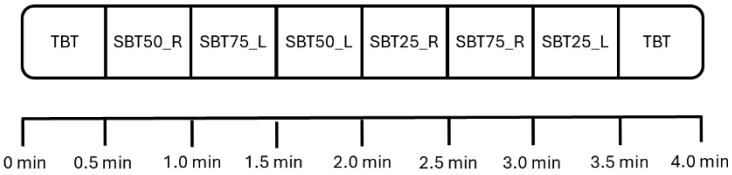
- Freezing of gait status, and severity using the New Freezing of Gait Questionnaire (NFOGQ) (Nieuwboer et al., 2009);
- Parkinson's disease severity and stage using the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS- part III)(Goetz et al., 2008) and Hoen and Yahr scale (Goetz et al., 2004);
- Global cognition using the Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005);
- Fear of falling using the Tinetti Falls Efficacy Scale (Tinetti FES) (Tinetti et al., 1990);
- Ratings of anxiety and depression using Hospital Anxiety and Depression Scale (HADS) (Snaith, 2003);
- Walking ability and gait speed using the 10 Meter Walk Test (10MWT);
- Participant demographic information, such as gender (GENESIS PRAXIS questionnaire), age, and body mass will be collected.
- PD medication and dosage to calculate the levodopa equivalent dose using established methods (Tomlinson et al., 2010).

Finally, through these clinical assessments, participants will be screened for a history of seizures, other existing neurological disorders, or other severe health conditions.

Gait tasks (second and third visit)

The **pre- and post-overground walking tests** consist of straight walking, steering, and turning tasks. Presentation of these tasks will be randomized across subjects. **For the pre-and post-SBT adaptation tests**, the three different SBT ratios; 25% (SBT25), 50% (SBT50), and 75%(SBT75) of the baseline walking speed measured on the 1 Visit will be applied to either leg, meaning there are 6 different SBT conditions (3 SBT ratios x 2 legs). These six conditions will be randomly ordered and fixed among subjects. The SBT conditions will be changed every 30 seconds and be preceded and followed by the 30 seconds of tide-belt treadmill (TBT) baseline walking, meaning two belts set at the baseline speed (fig.2). The **SBT training** consists of 6 blocks, each for 5 minutes, and 1 minute break

in between. The same 6 conditions as the ones used in the pre- and post-adaptation tests will be applied and changed every 30 seconds without notifying participants. We will change the ratio continuously to examine gait adaptation to the split-belt, a protocol we have used previously (IRB Study: A11-M109-12B and published(Hinton et al., 2019))However, the order of the ratio will differ



from the one used in the pre- and post-adaptation tests and will be fixed among subjects. During the gait tests both on the SBT and in the overground, participants will wear binaural over-ear headphones that play pure white noise while walking to prevent auditory input coming from the different speed ratios.

FIGURE 2. The example of a protocol design for the pre-and post-adaptation tests. The random order will be applied to the SBT ratios, and the order will be fixed among subjects. The ratios will be changed to another every 30 seconds. _R means the ratio will be applied to the right leg, and _L means the ratio will be applied to the left leg.

Outcome measures

Up to seven inertial sensors, specifically Ambulatory Parkinson's Disease Monitoring (APDM) (Opal, Portland, OR, USA) will be affixed to measure gait parameters; stride length, cadence, and the proportion of the gait cycle spent in dual support for the SBT adaptation tests and the overground walking tests, and gait speed, turning speed, and steps per turn for the overground walking tests.

rTMS procedure

The rTMS procedure in this study will follow the method that has been approved by McGill IRB (IRB study number: A08-B49-19A and published(Potvin-Desrochers et al., 2023)). TMS will be delivered to the participants while comfortably seated, using a Super Rapid 2 TMS system (Magstim Company, UK) connected with a 70-mm figure of eight-shaped coil. A BrainSight frameless stereotaxic neuronavigation system (Rogue Research Inc, Montreal, Canada) will be used to mark the location of the stimulation points. The right PPC will be targeted with intermittent Theta Burst Stimulation (iTBS), a patterned form of rTMS, characterized by 2-second periods of 50 Hz bursts, repeated every 10 seconds for a total of 600 pulses (Huang et al., 2005). The targeted coordinates for the PPC are 38.4, -67.2, and 46.3 (x, y, z) (Koch et al., 2011), aiming at the inferior parietal lobe. Considering that we will be setting our target on the MNI template, the exact location of stimulation will vary across

participants. During stimulation the coil will be orientated tangentially to the scalp and 10° from the midline (Ku et al., 2015). For the sham stimulation, a second 50 mm figure-of-eight coil will be placed between the scalp and the stimulating coil. The upper coil will be turned upside-down to make stimulation to the cortex negligible, while preserving the sound and some of the sensation of vibration on the head. The stimulation will be delivered at 80% of FDI AMT away from the PPC(Potvin-Desrochers et al., 2023). iTBS will be administered at 75% of RMT (Chung et al., 2018). Because the PPC is a non-motor region, we will use motor thresholds of the FDI representation as both these regions lie at a similar depth under the scalp and as we have used previously. During the first visit, the location of the FDI will be identified by probing the hand motor region of the cortex. The hotspot will be considered the location of the right primary motor cortex that elicits 2 consecutive motor evoked potentials (MEPs) in the relaxed right first dorsal interosseous (FDI) muscle with greater amplitude than the surrounding positions. Resting motor threshold (RMT) will be determined as the minimum TMS intensity required to elicit a MEP of 0.05mV in the resting FDI in at least 10 of 20 trials (Rossini et al., 2015). RMT will be quantified at each visit and used to calibrate iTBS intensity. Disposable surface electrodes (Biopac Systems, Inc.), placed in a belly-tendon mount, will be used to record the electromyographic (EMG) activity of the FDI. EMG signal will be recorded with a Biopac MP150 acquisition system, sampled at 10kHz on a 16-bit analog-to-digital board, amplified and bandpass filtered (10-5000Hz).

Cortical excitability

The 25 TMS pulses will be applied over the tibialis anterior (TA) cortical motor representation with the 50 mm dome coil. The stimulation intensity will be set to elicit 1 mV MEPs at baseline and fixed through all sessions. In 25 additional trials, a conditioning stimulus to the PPC will be added 4 milliseconds before the TM pulses with a 25 mm figure-of-eight coil in a dual coil set-up (PPC + TA). The stimulation will be set at 90% of the FDI RMT. TA and PPC + TA stimulus will be randomly intermixed and delivered using two Magstim 2002 stimulators(Potvin-Desrochers et al., 2023).
To reduce inter-session variability, each session will be carried out at the same time of the day for each participant. The use of the neuronavigation system also reduces this variability since the different stimulation sites will be saved and used during the different conditions. We will also ensure that the participants keep a similar position between the different sessions.

Definition of endpoints

The study endpoints will be differences in gait kinematics to SBT adaptation pre-post intervention for each stimulation condition.

Measurements and study instruments

TMS equipment and the SBT are available in our laboratory and we have experience with these protocols and patient population (TMS: IRB study number: A08-B49-19A and published(Potvin-Desrochers et al., 2023), SBT: IRB Study: A11-M109-12B and published(Hinton et al., 2019)) .

Clinical assessment will be conducted using a series of tests and questionnaires attached as appendices:

- Health Questionnaire (PD)
- GENESIS PRAXY Gender Questionnaire (EN/FR)
- Edingburgh Handedness Inventory (EN/FR)
- Waterloo Footedness Questionnaire
- MDS-UPDRS-part III (administered by the researcher)
- Hoen and Yahr scale (administered by the researcher)
- MOCA (administered by the participants)
- FES (administered by the participants)
- HADS (administered by the participants)
- 10MWT (gait performance)

Data analysis plan

The kinematic data of the pre-and post-SBT adaptation tests will be averaged over 4 minutes. Then, the stride length and dual support symmetry will be calculated by utilizing the following equation: symmetry = (right leg-left leg)/(right leg + left leg)(Malone & Bastian, 2010). For the cortical excitability, PPC + TA ratio will be obtained based on the following calculation(Potvin-Desrochers et al., 2023): (PPC + TA) / (TA). Factorial repeated measures ANOVA will test the change in the stride length and dual support symmetry between the SBT and the overground, and between rTMS and sham in the post-test (SBT x overground, rTMS x sham) (1), as well as the changes in the gait parameters in the overground walking tests (2) and in the SBT adaptation tests (3) between sham and rTMS (pre x post, rTMS x sham) (fig.3). The symmetry on the overground for (1) will be calculated from the first 30 seconds of the TBT treadmill. In addition, factorial repeated measures ANOVA will test the differences in PPC + TA ratio (pre x post, rTMS x sham) to verify the effect of rTMS over PPC.

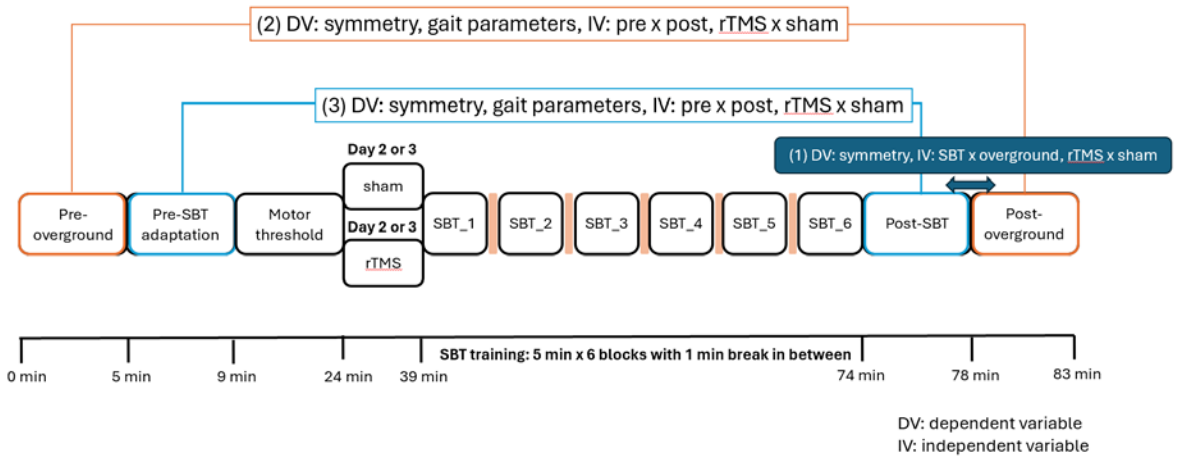


FIGURE 3. The plan for the data analysis. Factorial repeated measures ANOVA will test the differences in the stride length and dual support symmetry in the post-tests (SBT x overground, rTMS x sham) and the change in the symmetry and gait parameters: cadence, gait speed, turning speed, and steps per turn between pre-and post-interventions (pre x post, rTMS x sham).

Recruitment procedures

Firstly, we will recruit participants from our laboratory's bank of participants (people who participated in the previous study in our laboratory and gave their consent for future contact, IRB study number: A08-B49-19A and A11-M109-12B), and then from the Quebec Parkinson Network.

Details on confidentiality

At all times, participants' personal and identifying information will be kept confidential and under lock and key. During data analysis and documentation, participants will be identified only by their unique identification number. The recorded data by computers will be transferred and kept on a server located within McGill facilities with limited access to the members of the research team. All information, including the consent for the future study, will be kept for 7 years before destruction. Results from this study will be analyzed in group form. The outcomes will not contain the patient's name or any potentially identifying information and will only appear in the form of a scientific presentation.

Statement on ethical considerations

This study will be conducted according to the ethical principles stated in the Declaration of Helsinki

(2013). Ethics approval will be obtained before initiating the study. Consent forms will take into consideration the well-being, free-will and respect of the participants, including respect of privacy. We agree to respect the requirements of the McGill University Faculty of Medicine Institutional Review Board, the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 1998 (updated 2018) and the FRSQ Standards on ethics involving research and scientific integrity.

Associated risk

As mentioned before, the TMS application used in this research will follow the method used in our lab previously (Potvin-Desrochers et al., 2023) (IRB study number: A08-B49-19A). Because that study did not find any adverse effect, the risk of using rTMS with this protocol is low. Furthermore, there has been no report about the long-lasting side effects of rTMS, and the risk of TBS has been reported to be comparable and even less considerable than other high frequency of rTMS protocol (Oberman et al., 2011). Although the most common adverse effect is neck pain and transient headache, which affected 3% of the subjects undergoing TBS, the percentage is smaller compared to that for traditional high-frequency rTMS, 40% (Oberman et al., 2011).

For the SBT, our laboratory has experience with the use of the SBT and has one published paper where the ratios of the SBT are changed constantly (Hinton et al., 2019). Furthermore, to prevent participants from falling, a safety harness will be used, as previously done in our laboratory (Hinton et al., 2019).

Summary of the budget

Participants will be compensated for their transportation (i.e. bus/metro ticket, taxi, mileage) if needed, and will be given 40$ for their participation. Thus, we estimate a cost of 960$ for this research. Funds from an NSERC grant to Caroline Paquette will be used to cover these expenses.

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Appendices

- Clinical assessment questionnaires/ tests
  - Health Questionnaire (PD)
  - GENESIS PRAXY Gender Questionnaire (EN/FR)
  - Edinburgh Handedness Inventory (EN/FR)
  - Waterloo Footedness Questionnaire
  - MDS-UPDRS-part III
  - Hoen and Yahr scale
  - NFOGQ
  - MOCA
  - HADS
  - FES
  - 10MWT
- English and French consent forms
- Permission to contact (EN/FR)