Protocol for the project titled:

Transcranial direct current stimulation as a treatment for motor function in participants living with Progressive Supranuclear Palsy, Corticalbasal syndrome degeneration, or Parkinson's Disease

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Background and rationale

In 2021, we published a case report (Roncero et al., 2021) where a participant with progressive supranuclear palsy completed a series of 20-minute walking sessions accompanied with transcranial direct current stimulation (tDCS). Anode electrodes were placed over the motor cortex and cathode electrodes over the deltoid muscle to pass the tDCS current through midbrain areas. Using this setup, we began a longitudinal A-B-A study with alternating real and sham sessions. The participant received eight 20-min sessions (4 mA) over two weeks while walking 24 m during stimulation and completing a computer-based Flanker task to engage motor systems. Walking speed improved significantly after stimulation. Monthly follow-ups without stimulation showed gradual slowing until a plateau, after which tDCS was reapplied—again improving walking speed. These results suggest tDCS can enhance gait in PSP.

Proposed Study

Our preliminary results are sufficiently impressive to suggest that tDCS stimulation does have the potential to improve motor function when that ability is trained during stimulation. In the proposed study, we aim to conduct a study similar to the case study that we conducted, but with additional measures of motor function: gait, articulation, eye gaze, and motor dexterity. In addition, we wish to examine if such results can be replicated in people with other conditions, such as cortical basal syndrome (CBD), and Parkinson's disease (PD). The rationale for including people living with these conditions is the overlap in motor and cortical network dysfunction observed across these disorders. Like PSP, both CBS and PD involve impairment of motor initiation, gait, coordination, and executive motor control due to degeneration in frontal–subcortical pathways.

Because our preliminary findings in PSP suggest that tDCS can enhance motor performance when combined with active task engagement, extending the protocol to CBS and PD will help determine whether these effects generalize to other neurodegenerative movement disorders that share similar pathophysiological mechanisms. This extension will also allow for comparison of stimulation responsiveness across related diagnostic groups and provide insight into disease-specific factors influencing motor recovery potential.

Previous tDCS studies, including from our lab (Roncero et al., 2015) have found significant results with sample sizes between 10-20 participants for a two-round study comparing training sessions with real tDCS versus sessions done without tDCS. However, we plan to recruit 30 participants living with each condition as this will allow us to examine results per group, but also how the individual groups compare; for example, if improvements is seen for all three groups or only one diagnostic category (e.g. PSP).

Methods

The following is a flowchart displays the study schedule planned for each participant:

Round 1

Monday	Tuesday	Wednesday	Thursday
Baseline Evaluation	Stimulation Session	Stimulation Session	Stimulation and Evaluation Session
Stimulation Session	Stimulation Session	Stimulation Session	Stimulation Session
Stimulation Session	Stimulation Session	Stimulation Session	Stimulation and Evaluation Session

Two Weeks Later

Monday	Tuesday	Wednesday	Thursday
			Evaluation Session

Two Months Later: Round 2

Monday	Tuesday	Wednesday	Thursday
Baseline Evaluation	Stimulation Session	Stimulation Session	Stimulation and Evaluation Session
Stimulation Session	Stimulation Session	Stimulation Session	Stimulation Session
Stimulation Session	Stimulation Session	Stimulation Session	Stimulation and Evaluation Session

Two Weeks Later

Monday	Tuesday	Wednesday	Thursday
			Evaluation Session

Two Months Later

Monday	Tuesday	Wednesday	Thursday
			Evaluation Session

Each participant will undergo two rounds of stimulation, two months apart, each consisting of twelve tDCS sessions over three weeks (four sessions a week). These sessions are planned from Monday to Thursday each week. We designed the schedule in this format so if a participant misses a session during the week, the participant will be allowed to have a make-up session on Friday of that week. In the first week of both rounds, sham tDCS (i.e., placebo) will be given to establish a pre-stimulation baseline. Scores obtained in the final session of that week (i.e., Thursday) will be used as the baseline scores. In this manner, we can obtain scores that already reflect some accumulated practice from having completed a few sessions, but before actual stimulation has begun. Real tDCS stimulation will be given in weeks two and three of each round. The scores obtained in the final session of the second week of stimulation will be recorded as the stimulation scores. These scores will be taken as the result of the tDCS effect because it represents two weeks of stimulation, which should be sufficient for producing a reliable effect. Thus, the scores from the final session of week 1 and the final session of week 3 will be compared to check for an immediate effect of stimulation on performance. This comparison will be observed as the *immediate tDCS effect.* To examine possible maintenance effects from stimulation, or delayed and continued improvement from stimulation, we will also ask participants in both rounds to return two weeks later to repeat the same tasks without stimulation, which can then also be compared to scores obtained in week 1, and it will be observed as the *post tDCS effect.* An additional post-stimulation evaluation will happen two months later, again compared to week 1. At this time-point, we actually expect tDCS effects to have effectively washed-out, and the participant will have a condition similar to baseline (i.e. pre-stimulation). Comparing this result at two-months to week 1 will be observed as the *wash-out tDCS effect*. To make it convenient for participants, and reduce the amount of study time required from them, we will use scores recorded in the first session of week 1 of the second round (while participants are receiving SHAM stimulation) which is scheduled to occur approximately two-months post-stimulation. In the second round, because there is no third round, participants will simply return for a single session two months after their final

stimulation session to record their performance levels two months post-stimulation.

Each round will effectively be identical (SHAM in Week 1, real tDCS in weeks 2 and 3), but a different montage will be different in each round (counter-balanced across participants). In one montage, two anode electrodes over the left and right deltoid muscles, and two cathode electrodes over the left and right motor cortex at C3 and C4. In the other montage, two anode electrodes placed over the left and right motor cortex at C3 and C4, and two cathode electrodes over the left and right deltoid muscles. In both montages, stimulation will be given at an intensity of 4 mA for 20 minutes; thus, the only difference between montages will be the relative position of the anode and cathode electrodes. In our case study, we had found the montage with the anode electrodes over the deltoid muscles and the cathode electrodes over the motor cortex at the top of the head was superior. Our explanation for this result is that when the anodes are placed on the deltoid muscles, the electricity better travels to the motor cortex via the spinal cord rather than entering through the skull, which shunts (reduces) a great of the electricity passing the skull bone. Indeed, when electricity must enter the brain via the skull, dispersion is expected first when it hits the bone matter, and again when the electricity reaches vascular fluid which typically surrounds the brain in older adults. This double dispersion leads to the electricity received being less intense and diluted when it reaches the key brain regions. By having electricity pass through the spinal cord, these dispersion effects are avoided and ensures a sufficient dose of electricity will reach the key brain regions. Furthermore, the electricity entering the brain will be driven towards the motor cortex due to the exit point being produced by the two cathode electrodes. This is our current hypothesis, and by having participants complete both rounds with different montages, we will be able to examine if one of the montages is superior.

The tDCS stimulation will be administered via a Sortex tDCS device which allows the intensity of the stimulation to be amped up and down at any time during the session to the participants' comfort. This machine also indicates the contact quality throughout the session. The current belief regarding tDCS is that its effect is more pronounced when performed with training. The training performed during tDCS stimulation produces neuronal oscillations in relevant brain areas, which in turn attracts the tDCS current to that area which then reduces the resting threshold of those neurons. In turn, these neurons begin to fire easier, which behaviorally

results in training being more effective and symptom reduction in that impaired behavior. These neurons are also prone to greater amounts of long-term potentiation and plasticity, leading to the consolidation of improvements in the tasks that were trained in the individual during stimulation. In other words, the improvements can be observed for a limited time post-stimulation. Consistent with these arguments, this study will have participants complete tasks while receiving tDCS or SHAM stimulation. First, they will be asked to walk from the half-way point of a 24m gait mat (i.e., at the 12m mark) to the end of the gait mat, and back again, which will measure the participant's speed and additional gait-related measures. They will complete this task twice. Next, they will walk a 12m hallway from base to end and back again. For this second measure, only total time and interval times (every 3m) will be collected from the participant. They will also complete this task twice. In addition, stimulation will be continued when they walk from the gait mat to the hallway. This protocol is being used to maximize the amount of time participants are walking while receiving stimulation. However, if a participant wishes to do each activity once, this will be allowed to ensure participants aren't feeling overly fatigued to complete the study. Also, during these walks, there will be two additional research assistants present whose only task will be standing near the participant, one at the side and one at the front that will walk with the participant to ensure they can catch the participant if they fear a fall is about to occur.

Next, and while the tDCS stimulation completes (approximately the final 10 minutes of stimulation), the participants will be asked to do read words outload, followed by a FLANKER decision-making task. They will complete the FLANKER task twice: once where they verbally give the correct answer, and a second time where they will need to press one of two buttons depending on the image on the screen. Script rehearsal is done with the goal of improving articulation, while the FLANKER task is aimed at improving both articulation and motor dexterity. Finally, an eye gaze task will be administered where they will be asked to look in each cardinal direction, and then asked to maintain focus on an object while the experimenter moves their head in each cardinal direction. This task will allow us to check for improvement in eye motor control.

Outcome measures.

As previously mentioned, we have three critical time-points: *immediate, post-stimulation, and wash-out tDCS effect.* This time-points compare any improvement from tDCS to the baseline scores obtained on the final

sessions of week 1. In addition, there are two rounds representing two different montages. To examine these results, we will first use generalize estimation equations that compare the results for each time-point and the effect of round. In this manner, we can examine if results were significantly better at any time-point compared to the baseline, and if this result was affected by a particular montage. Our primary outcome measures will be those found for gait: compared to the baseline scores obtained in a round at the end of week 1, did scores improve (i.e., did they become faster) after receiving stimulation (measured at the end of week 3 in a round). As an exploratory analysis, we will also produce difference scores between baseline and the evaluation point where the walking speed was most improved (e.g., Eval 2 Score minus Baseline Score). A multiple regression will then be run with sex, age, and diagnosis as predictors to examine if these variables were predictive of the improvement observed. We may lack the numbers for the power required to examine these effects, but will still present means for groups by sex, age, and diagnosis to allow readers to examine the differences among the demographic groups (if any). A similar set of analyses will be done for the additional tasks (e.g., FLANKER), but these results represent secondary outcomes in the study as our primary focus is gait.

Inclusion and Exclusion Criteria

Participants must be able to walk unassisted, or with the assistance of a walker or cane, and be individuals who walk daily. To be clear, walking on a daily basis is defined as being able to walk around the house or surrounding area if desired. For example, a person who is unable to ever walk, even if assisted with a walker or cane, and effectively restrained to their wheelchair, would be excluded because the study is primarily focused on whether tDCS improves walking ability. Lastly, participants should have a sufficient level of English to be able to express themselves verbally to be included in this study. For safety reasons, participants need to inform us whether they are finding the tDCS received tolerable. Also, due to the reading tasks, participants should be able to read words in English. Finally, as the study requires the passage of electricity through the participants' brain, individuals with metal implants within the brain such as shunts will be excluded.

Confidentiality

A research study file as well as medical records identifying participants will be maintained within Dr. Howard Chertkow's lab. Names and identifying information will be replaced with a code, and the information

will be kept on file for 10 years after the end of the study. Data collected from participants' who withdraw from the study will also be kept, unless participants withdraw consent for its use.

Feasability

Participants will be studied in two rounds over the course of four months. Participants will be individuals with PSP or CBD recruited through the participant database at Baycrest or from individuals that receive our brochure. We will also be receiving referrals through colleagues at Toronto Western Hospital, via our brochure, who are otherwise not associated with our research. Our colleagues at Toronto Western have already received prior REB approval to give potential participants our brochure, and people then call or email our lab if they are interested. Colleagues at Toronto Western have no involvement other than distributing our brochure. Due to these resources, we anticipate no difficulty in recruiting participants for this project

Safety

The tDCS protocol for this experiment was determined according to the best practices observed in previous research using tDCS stimulation (Kuo, Paulus & Nitsche, 2014). Furthermore, tDCS is safe, has virtually no side effects, is technically easy to carry out, and is not uncomfortable to undergo (Hsu et al, 2015; Freitas et al, 2011). Multiple studies have also reported that the administration of 4 ma tDCS has no more adverse effects than 2 ma tDCS (see Nitsche & Bikson, 2017). No incidence of seizure has been recorded, although side effects could include headache, drowsiness, itching sensation, nausea, and, in rare cases, disorientation. One study reported a single incidence of a 1st degree burn (Auvichayapat et al., 2012). Another single study of treating depression using tDCS treatment reported a single incidence of hypomania (Loo et al., 2012), but it remains to be seen if this rare side effect has ever been observed in patients being treated for neurodegenerative diseases. In our experiences, the only observed and reported side-effect has been temporary redness post-stimulation where the sponge was placed, and the occasional report of headaches. For headaches, we recommend participants take Tylenol. As we will be working with a population that is susceptible to falls, the portion of the session that includes walking will be carried out in the presence of the experimenter and two assistants who will walk in front of and behind the patient.

Significance and Importance of the study

Currently there is no effective symptomatic therapy available for PSP or CBD, while no therapy has been shown to effectively decrease freezing in Parkinson's disease. Our preliminary data indicates that 10 sessions of tDCS will produce improvement in motor function, especially for walking speed and walking stability, as well as less freezing (measured as stance %). Considering the extensive motor impairments present in these conditions, an improvement in motor function would be quite beneficial. Furthermore, we will also examine if tDCS can improve other areas of impairment known to be related to these conditions (i.e., articulation and eye-gaze), and undertake post-stimulation follow-ups to determine the durability of the stimulation effect. Ultimately, we hope to produce a novel therapy feasible for many individuals with PSP, CBD, or PD.

Yours truly, Dr. Howard Chertkow, Dr. Carlos Roncero,

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