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The Role of Cerebellar Hyperactivity in Parkinson's Disease

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1. Abstract

- a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Gait and balance disturbances are one of the most incapacitating symptoms of Parkinson's disease (PD) (Boonstra et al. 2008). They can cause falls and are therefore associated with the negative spiral of (near) falls, fear of falling, fractures, reduced mobility and social isolation; hence, having a profound negative impact on quality of life (Lin et al. 2012). Originally, symptoms of PD were ascribed to dopamine deficiency and basal ganglia dysfunction (Wu et al. 2013). However, in the last decades it has become clear that other brain structures are also involved in the pathophysiology of PD (Snijders et al. 2011; Stefani et al. 2007). An intriguing, emerging insight is that the cerebellum may be involved in the pathophysiology of PD (Wu et al. 2013). That is, the cerebellum is hyperactive in PD patients during different motor tasks (Yu et al. 2007; Hanakawa et al. 1999; del Olmo et al. 2006). However, whether cerebellar hyperactivity is pathological or compensatory and how it affects gait and balance in PD patients remain open questions. Here, we aim to elucidate the role of the hyperactive cerebellum in gait dysfunction in PD patients by modulating cerebellar excitability with state-of-the-art non-invasive brain stimulation techniques and investigate the effects on gait.

2. Objectives (include all primary and secondary objectives)

In this project we will study the effects of transcranial direct-current stimulation (tDCS) on gait and the connection between the cerebellum and the motor cortex to ask: 1) Does cerebellar hyperactivity play a pathological or compensatory role in gait dysfunction in PD? 2) Can tDCS be used to reduce gait impairments in PD patients?

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The cerebellum plays an important role in generating well-coordinated locomotion, voluntary limb movements and eye movements (Morton et al. 2004). It is particularly important for balance and

limb coordination needed to generate a stable gait pattern (Morton et al. 2006). Specific roles of the cerebellum for gait include coordinating the two legs to produce a stable rhythmic pattern, dynamic regulation of balance, and adaptation of the pattern through practice (Morton et al. 2004). Though the core deficits of PD patients are largely different than those of cerebellar patients, they do show decreased bilateral coordination (Plotnik et al. 2008) and a fundamental disturbance in stride length regulation (Morris et al. 1998) during walking.

Recent work has shown that the cerebellum is hyperactive in PD patients, though it is not known whether this activity is compensatory (i.e. reduces motor impairments) or pathological (i.e. causes motor impairments). One idea is that increased cerebellar activity, affecting cerebral motor areas, compensates for the reduced drive from the basal ganglia (Wu et al. 2013). Alternatively, it is possible that cerebellar hyperactivity is pathological, as recent work suggests that cerebellar activity may be partially responsible for the generation of Parkinsonian tremor (Helmich et al. 2012). One approach to answer this question is to use non-invasive brain stimulation techniques to decrease the activity of the cerebellum in PD patients and determine if they improve or worsen their gait pattern.

Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are able to alter the excitability of brain pathways. Applying these techniques over the motor cortex, improved motor function in different patient groups, including stroke and PD (Benninger et al. 2010). Only two studies have investigated the effect of modulation of cerebellar-motor cortex excitability on motor function in PD patients. That is, 1 Hz repetitive TMS (inhibitory rTMS) over the cerebellum improved gross arm movements, but worsened fine motor skills¹⁷. Furthermore, a two-week continuous theta burst stimulation TMS protocol decreased levodopa-induced dyskinesias (Koch et al. 2009). These studies only investigated the effects on the upper extremities. The cerebellum is also hyperactive during gait (Hanakawa et al. 1999; del Olmo et al. 2006), but whether modulation of cerebellar excitability can improve gait deficits in PD patients is currently unknown.

Non-invasive brain stimulation can also be used to study the connection between the cerebellum and the motor cortex via using paired-pulse TMS. Specifically, cerebellar stimulation 5 ms before motor cortex stimulation leads to a reduction in the amplitude of motor-evoked potentials (MEPs), a phenomenon referred to as cerebellar-brain inhibition (CBI) (Pinto et al. 2001). This measure of CBI is abnormal in PD patients—it is reduced at rest, but increases with muscle contraction (Ni et al. 2010).

Gait impairments in PD are often resistant to treatment, particularly as the disease progresses. Therefore, insight in the pathophysiology of gait disturbances is essential for improving treatment options and quality of life for PD patients. Our study will answer the question of whether cerebellar hyperactivity alleviates or worsens gait deficits in PD patients. If cerebellar hyperactivity in PD is compensatory, anodal (i.e. excitatory) tDCS should improve gait in PD patients, whereas cathodal (i.e. inhibitory) tDCS will make matters worse. In contrast, if cerebellar hyperactivity is pathological, cathodal tDCS will improve gait and anodal tDCS will worsen it. Hence, our study will improve our fundamental understanding of gait pathophysiology in PD patients. We will focus on the aspects of gait that are particularly affected in PD and associated with fall risk, such as stride length and gait speed (Paul et al. 2013). In this way, our study may identify the cerebellum as a potential new target for treatment, opening up new possibilities improving gait and balance disturbances in PD.

4. Study Procedures

- a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Subjects will be screened prior to enrollment by a study team member. The initial screening will be done over the phone to assess diagnosis and basic inclusion/exclusion criteria. Next, subjects will be asked to participate in an additional in-person screening during which participants will be asked to give written consent to participate in the study. After providing consent, the screening session will include:

1. Evaluations to determine the severity of PD symptoms based on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al. 2007).
2. Evaluations of cognitive function based on the Montreal Cognitive Assessment and the Frontal Assessment Battery (Nasreddine et al. 2005; Dubois et al. 2000).
3. A questionnaire to determine self-reported symptoms of PD-related motor impairment.

If the subject is a patient of co-investigator (Dr. Mari), the in-person screening may take place in the Johns Hopkins Parkinson's Disease and movement Disorder Center. Otherwise, it will take place in the Motion Analysis Lab at Kennedy Krieger Institute.

Subjects who meet the inclusion/exclusion criteria for participation in the study will subsequently be asked to come to the Motion Analysis Lab at Kennedy Krieger Institute for 6 separate visits separated by one week. Each session will include an initial assessment of *Gait* and *Cerebellar Brain Inhibition (CBI)* measures preceding one 20-minute period of *tDCS*, followed by a second assessment of *Gait* and *CBI*. If participants experience discomfort due to *tDCS* or *TMS* and choose to discontinue the stimulation (see Section 8 for risks of discomfort due to these stimulation techniques), they will be allowed to continue the study with *Gait* assessments only.

Patients will be tested on and off their anti-Parkinson's medication (dopamine replacement or agonist). For the off testing, patients will abstain from taking their morning dose of medication and will have been off their medications for 12 hours. This is standard procedure for studies assessing PD patients (Bordelon et al. 2011).

Gait Testing

Prior to testing, small (dime sized) markers will be placed bilaterally on the foot (5th metatarsal head), ankle (lateral malleolus), knee (lateral joint space), hip (greater trochanter), pelvis (iliac crest) and shoulder (acromion process). These markers emit an infrared light which our sensors can track in 3D. A Northern Digital OPTOTRAK movement measurement system (with 2, 3-D position sensors) will be used to collect the 3-dimensional location of each marker. Marker position and analog data (treadmill belt speeds) will be time locked using OPTOTRAK software, and sampled simultaneously at 100 Hz and 1000 Hz, respectively.

Overground walking will be assessed using the Timed-Up-And-Go test (TUG) and 10 meter walk test. Next, subjects will walk on a treadmill for 2 minutes at their self-selected comfortable walking speed. During treadmill walking, subjects will wear a safety harness, have 2 safety cutoff switches (one large button to press, one magnetic cutoff tethered to them which stops the treadmill if they move too far back on it), and will have the option to hold onto a handrail if needed.

Additionally, standing balance will be assessed using Kistler force plates which allow measurement of the motion of the center of pressure. We will ask subjects to stand for 20 seconds in the following conditions: eyes open feet together and eyes closed feet together.

Transcranial Magnetic Simulation: Cerebellar Brain Inhibition

To assess the neurophysiological effect of tDCS (see below for tDCS protocol), we will use a standard paired-pulse Transcranial Magnetic Stimulation (TMS) technique, referred to as Cerebellar Brain Inhibition (CBI) (Ugawa et al. 1995). We will first measure the subject's head with a tape measure and calculate scalp landmarks based on the 10-20 EEG system (Niedermeyer and Lopes da Silva, 2004). These landmarks will be coregistered with the Brainsight Frameless software/hardware system to track the trajectory of the TMS coil in real time over a 3D surface model of the participant's brain.

A Magstim Super Rapid system will be used for TMS stimulation. First, the motor foot area will be localized by finding the location on the scalp where a single pulse of TMS effectively elicits a response in the tibialis anterior muscle. The motor threshold will then be determined by finding the minimum output of the stimulator necessary to reliably elicit a motor-evoked potential (MEP). Electromyographic activity from the muscle will be recorded using standard surface electrodes to determine the threshold for stimulation.

To obtain CBI measurements, a conditioning TMS pulse will be given on the cerebellum 5 ms prior to a test pulse on the motor cortex. The conditioning pulse will have an inhibitory effect on the amplitude of the MEP.

Transcranial Direct-Current Stimulation (tDCS)

For the tDCS component, weak DC current (2 mA) will be delivered through surface electrodes (TransQE from IOMED®, surface area: 25 cm²) using a Chattanooga Ionto™ dual channel iontophoresis system (Chattanooga Group, Hixson, TN)). We will use tDCS to modulate cortical excitability of cerebellum. Two tDCS electrodes will be applied – one over the cerebellum ipsilateral to the most affected body side (i.e. 3 cm lateral to the inion) and the other on the ipsilateral buccinators muscle (Jayaram et al. 2012). Current will be delivered for 20 minutes. The current will be increased in a ramp-like manner to reduce appearance of transient phosphenes usually present with rapid on-off applications (Wu et al, 2006; Mathiowitz et al, 1984).

For sham tDCS, the electrodes will be placed in the same way as for real tDCS but in the absence of real stimulation. This means stimulation will be increased to a current strength near the perception threshold and will be decreased afterwards and set to 0 mA output for the stimulation period. With this procedure participants are usually unable to differentiate between tDCS and sham stimulation (Gandiga et al. 2006).

b. Study duration and number of study visits required of research participants.

Each subject will be asked to participate in 6 sessions, each taking 1.5-2 hours, separated by one week. Sessions will differ in the type of tDCS stimulation applied (sham, anodal, or cathodal), as well as levodopa medication state (on or off). Thus, the 6 sessions will include: OFF medication, ON mediation, OFF-SHAM, ON-SHAM, OFF-ANODAL, ON-ANODAL, OFF-

CATHODAL, and ON-CATHODAL. All sessions will take place in the morning. The order of the sessions will be randomized and counterbalanced between participants.

- c. Blinding, including justification for blinding or not blinding the trial, if applicable.
N/A
- d. Justification of why participants will not receive routine care or will have current therapy stopped.
N/A
- e. Justification for inclusion of a placebo or non-treatment group.
N/A
- f. Definition of treatment failure or participant removal criteria.

A participant may be removed from the study if:

- They are unable to participate due to fatigue or discomfort
- Staying in the study would be harmful
- They are unable to follow directions
- The study is cancelled
- They become pregnant during the course of the experiment

- g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

There are no risks to the participant for ending the study prematurely.

5. Inclusion/Exclusion Criteria

Inclusion

Mild-moderate (Hoehn and Yahr scale: 1.5-3) idiopathic, akinetic-rigid type Parkinson's disease.

Capable of walking for 5 minutes.

Age 18-85.

Exclusion

Severe dyskinesia

Congestive heart failure.

Peripheral artery disease with claudication.

Cancer.

Pulmonary or renal failure.

Unstable angina.

Uncontrolled hypertension (> 190/110 mmHg).

Brain injury.

History of seizure or a family history of epilepsy.

Metal anywhere in the head except the mouth.

Cardiac pacemakers.

Cochlear implants.

Implanted medication pump.

Heart disease.

Intracardiac lines.

Increased intracranial pressure, such as after infarctions or trauma.

Currently taking tricyclic anti-depressants or neuroleptic medication.

History of head trauma.

History of respiratory disease.

Dementia (Montreal Cognitive Assessment < 26; Frontal Assessment Battery < 13).

Orthopedic or pain conditions.

Pregnancy.

It is possible for an individual to be more susceptible to seizures than normal without being aware of the fact. Before giving their consent to participate, the participants will be questioned about their recent alcohol intake, and excluded if they have drunk more than 3 units of alcohol or taken other recreational drugs in the 24 hour period prior to testing, or if they are sleep deprived, all factors known to reduce cortical levels of inhibition and increase the risk of a seizure. The information gathered will be used exclusively for determination of inclusion/exclusion criteria and research, and will not be made public.

6. Drugs/ Substances/ Devices

- The rationale for choosing the drug and dose or for choosing the device to be used.

TMS and tDCS are non-invasive brain stimulation techniques used in an increasing number of studies in the last 20 years to understand cortical physiology or modulate brain function. These forms of stimulation are considered to be safe and of non-significant risk due to the short duration and the very low stimulation intensity. Dosage of tDCS is selected to safely elicit changes in motor-evoked potentials or behavioral outcome based on prior literature (Nitsche and Paulus, 2000; Nitsche et al., 2003a; Galea et al., 2011).

- Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

- Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

- Primary outcome variable.

1. Stride length and gait speed during walking

2. Measures of corticomotor excitability (TMS)

- Secondary outcome variables.

Interlimb coordination during walking, variability of gait, cadence

- Statistical plan including sample size justification and interim data analysis.

We estimate needing 15 participants based on aiming for a moderate effect size of approximately 0.5 (comparable to the effects of physiotherapy (Tomlinson et al. 2013)), alpha set at 0.05, and a power of 0.8. To allow for possible dropouts, we will recruit 20 PD patients.

- Early stopping rules.

None.

8. Risks

- Medical risks, listing all procedures, their major and minor risks and expected frequency.

See Section 8b.

- Steps taken to minimize the risks.

TMS

There is no reason to believe that single pulse TMS, itself, poses any hazard. Extensive use in our laboratory has not resulted in any difficulties with the device that could pose a hazard to patients. TMS has been found to produce hearing loss in experimental animals (Counter et al, 1990; Counter et al, 1991) by means of the click produced by the stimulating coil when the inducing current is passed through it. However, we found no evidence of chronic hearing loss in several of our normal subjects who had been extensively studied with TMS, nor did we find transient changes in several subjects tested before, and immediately after, stimulation (Pascual-Leone et al, 1992). TMS does not appear to pose any hazard to the brain beyond that of electric stimulation, which has been in clinical use for decades. The procedure appears to be safe and without any side effects (Barker et al, 1985; Barker et al, 1987). Some of the original subjects have been stimulated many thousands of times. The World Health Organization task group and the Food and Drug Administration concluded that brief exposure to static magnetic fields up to 2 Tesla would have no adverse effects on human health. Currently available single-pulse stimulators are unable to produce thermal damage to tissues. No significant changes could be documented in cortisol or prolactin levels after TMS (Bridgers and Delaney, 1989). We have also shown that the EEGs of normal volunteers do not change following TMS. The induction of seizures, a concern with any type of brain stimulation, is very rare with single-pulse TMS, even when studying epileptic patients. After studying thousands of patients world-wide, only 3 seizures have been reported that were possibly related to single pulse TMS, none in our laboratory. These occurred in patients with underlying epileptogenic brain lesions. The only known transient side effect is headache, which usually fade over a few hours and responds well to non-steroidal anti-inflammatory drugs.

TMS makes a loud clicking sound and may cause a twitch of muscles in the hand or face. It is not, however, painful. The sound produced by the stimulator is actually quite loud; however, because the sound is so brief, it is not perceived as being loud. The use of ear protection will make the sound less bothersome and eliminate any risk of hearing impairment. Therefore, participants and experimenters are asked to wear ear protectors.

Direct activation of scalp muscles and nerve by TMS can be uncomfortable although this usually presents little problem for most subjects. Contractions can be minimized by slight changes in coil position or orientation, or by support of the head to relax muscles. Subjects will be told they can terminate the experiment at any time if they find contractions uncomfortable.

Some people may experience a mild headache from the stimulation. The headache, if it occurs, is usually mild and only lasts a few minutes beyond the end of the test. However, participants with a history of migraine or other types of severe or frequent headaches are excluded from the experiment. Although some participants may experience discomfort at the time of TMS, there is no reason to anticipate that any participant will experience persisting symptoms that will require medical attention.

tDCS

Weak direct currents can be applied non-invasively, transcranially and painlessly (Nitsche et al. 2003a, Priori 2003). Such application leads to transient changes in corticomotor excitability that are fully reversible (Nitsche et al. 2003a, Priori 2003).

Human Data

There are no known risks of percutaneous, DC stimulation of the brain or spinal cord, other than mild local discomfort at the electrode sites (much less than TMS for example). In the current

published studies on humans (Nitsche and Paulus 2000, Nitsche et al. 2003a, Priori 2003, Uy and Ridding 2003, Hummel et al. 2005, Nitsche et al. 2004a, Paulus 2003, Nitsche et al. 2004b, Fregni et al. 2005, Gandiga et al. 2006, Boggio et al. 2006a), the following objective safety data were reported:

- No heating of electrodes.
- No demonstrable changes in the skin underlying electrode placement after a stimulation period similar to the one proposed in this protocol.
- Mild itching sensation in the absence of pain. Never led to stopping a study in any of the previous reports.
- No change in serum neuron-specific enolase (NSE, marker for neuronal damage) in 5 subjects immediately and 1 hour after exposure to 13 min of 1 mA anodal DC to motor cortex
- No change in serum NSE in 5 subjects immediately and 1 hour after exposure to 15 min of 2.5 mA anodal DC to the spinal cord
- No changes in diffusion weighted or contrast-enhanced MRI and in EEG after exposure to tDCS (Nitsche et al. 2004a).

Nitsche et al. have studied several hundred subjects so far without reporting any side effects apart from a slight itching under the electrode and a short phosphene if the stimulation was switched on or off abruptly (Nitsche et al. 2003a, Nitsche et al. 2003b). In his own work and in his review of the modern literature, Priori (2003) found no evidence or mention of adverse effects using this technique. Additionally, several months' use of this technique at NIH in approximately 30 subjects (Drs. Wassermann and Lomarev) was done in the absence of any deleterious side effects. All these reports are in accordance with our experiences in a recently performed study in elderly healthy volunteers and chronic stroke patients. Furthermore, the NINDS IRB approved recently a protocol of Drs M. Hallett and Lomarev (03-N-0116) to apply tDCS repetitively (8 sessions) in Parkinson patients. Additionally, previous protocols of Dr L. Cohen (05-N-0149, 04-N0212, 03-N-0267) to apply tDCS in stroke patients have also been approved. Both anodal and cathodal tDCS have been successfully applied during 20 minutes in 12 stroke patients, including 2 patients with cortical stroke, without any adverse effects (Hummel et al. 2005, Fregni et al. 2005, Lang et al. 2004).

Animal Data

The existing literature indicates that 30 min of anodal DC in the mA range leads to fully reversible increases in norepinephrine-stimulated cyclic AMP accumulation in brain slices, transient increases in c-fos immunoreactivity, and increased calcium content (Islam et al. 1995, Moriwaki et al. 1991, Moriwaki et al. 1995). In one study 3 or 30 μ A anodal DC was applied either once or five times for 30 min or 3 h to the surface of the sensorimotor cortex of rats through 1 mm^2 electrodes (current density = 0.3 or 3.0 mA/cm 2). There were no abnormalities noted in animals killed 1 month after application of the stimulating technique and no behavioral abnormalities were identified (Islam et al. 1995). It is unlikely that intracranial DC stimulation cause electrochemical injury to neurons near the electrodes due to hydrolysis and the formation of potentially noxious chemical species (Dr. D. McCreery). Weiss et al. (1998) showed that intracranial DCS stimulation applied to the amygdala for 15 minutes daily over 7-14 days in rats resulted in decreased cortical excitability for weeks (it became more difficult to elicit a seizure) (Werhahn et al. 2002). It should also be noted that the magnitude of stimulation in animal studies has been much larger than those used in any human studies. This is because of the very small electrode size required for focal stimulation of the rat cortex and the lack of current diffusion by the human scalp and skull. For instance, a 1-mm 2 electrode will produce a 2500fold increase in density over our proposed 25-cm 2 electrodes.

Recent publications have shown that it is also possible to use 2mA intensities without significant risk or complications (current density of 0.095 mA/cm², total charge of 0.086 C/cm²) over the cerebellum or prefrontal cortex for 15 to 20 minutes (Ferrucci et al. 2008, Fregni et al. 2006, Iyer et al. 2005). The generated current density and total charge resulting from this intensity are known to be well below the threshold of tissue damage (Boggio et al. 2006b). Of note, the majority of the current delivered by tDCS is dissipated through the scalp, because the impedance of the skull is higher than that of the scalp (Miranda et al. 2006).

Experimental sessions will be performed in a laboratory with easy accessibility to reduce risk of falls. A researcher will accompany participants at all times. We do not expect that a discontinuation will occur once a subject meets the admission criteria. However, the following reasons may motivate termination of a subject's participation in the protocol: the subject's poor compliance with protocol evaluations or examinations, or a subject's request to withdraw.

Other risks

The risks of withholding Parkinson's medication are feeling uncomfortable due to exacerbated Parkinson's symptoms (e.g. postural instability, bradykinesia, rigidity, etc.). Since we will only recruit patients with mild-moderate impairment, we anticipate that this discomfort in the off-medicated state will be minimal.

The risks of being harmed by the treadmill, overground walking assessments, or Optotrak markers is very low. Subjects may become fatigued or lose their balance during overground or treadmill walking, and have slight muscle soreness after walking. Other than that, the risks are no greater than normal walking. There is a small risk of the subject being allergic to the adhesive tape used to secure the Optotrak markers. There is potential risk of loss of confidentiality, as well as a potential risk for lost time from work. Additionally, there is a risk of getting tired or bored during questioning/answering of questionnaires.

Subjects will be placed in a safety harness that is connected to a ceiling mounted safety track during all testing on the treadmill so that they cannot fall. Subjects also will be tethered to a magnetic safety cut-off switch, which when pulled, stops the treadmill (e.g. if they move too far back on the treadmill). Additionally, subjects have a safety stop button mounted to the front handrail of the treadmill. All subjects are allowed to hold on to the handrail through the duration of all experiments and are asked to practice stopping the treadmill with the safety button. Recent data has shown that holding onto the handrail can create an unnatural walking pattern. Since we are studying walking patterns, individuals who are comfortable walking on a treadmill without holding onto the handrail may be asked not to hold on. An experimenter will stand next to the subject on the treadmill at all times and will have a safety cutoff button too.

We will also stop the treadmill and give a rest break when subjects feel fatigued, short of breath, or simply want a break. They will be allowed to stop any test at any time, or rest between tests. We also do not recruit subjects who have medical conditions that would make walking dangerous or uncomfortable. We will put a gait belt on all subjects as they walk overground and 1-2 investigators will walk behind them in case they lose their balance.

To reduce the risk of irritation from the tape we will ask before applying the tape to be if they have any known allergy. If they think they may have an allergy we will attempt to use athletic tape or co-band wrap to hold the markers in place during the experiment.

To reduce the risk of loss of confidentiality we give every subject a code that will connect them to their personal health information (PHI) that will be locked in our file cabinets. Only the researchers and PI will know where the key is. Any experimental information will only have the code name attached to it and will be locked in our password database on our computers.

To reduce the risk associated with loss of time from work or school we will be as flexible as possible with scheduling.

c. Plan for reporting unanticipated problems or study deviations.

Adverse events and protocol deviations will be reported to the primary investigator, to the KKI Office of Research Compliance, and to the JHM IRB using the appropriate adverse event reporting form.

Expected adverse events due to TMS or tDCS that will be reported in annual reviews:

1. Slight discomfort lasting less than a second on the scalp near the TMS coil.
2. Twitching of the face and jaw due to the magnetic pulse, which may be unpleasant but usually not painful.
3. Transient headache.
4. Itching sensation under the electrode (tDCS)
5. Phosphene-like visual phenomenon if the DC stimulation will be switched on or off rapidly

Exceptional adverse events due to TMS or tDCS that will be reported immediately:

1. Skin burn
2. Seizures have been reported using repetitive TMS in about 10 human subjects, out of several thousands tested all over the world. The appearance of a seizure during application of TMS with stimulation parameters regarded as safe cannot be excluded, therefore we defined appearance of a seizure as an exceptional adverse event.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

We see minimal risk to confidentiality—data are coded and no identifying information is used in any analyses or publication. The master list containing the link between the data and the identity is kept on a computer that is double password protected. All health information, as well as study data, gathered at the time of the study, are kept in locked files, accessible only to study personnel. We adhere to all HIPAA privacy rules that affect research protocols.

e. Financial risks to the participants.

There are minimal financial risks to the participant. The risks include lost time from work and travel expenses.

9. Benefits

a. Description of the probable benefits for the participant and for society.

- i. Individual participant.

There are no direct benefits to participants.

- ii. Society

This study will help provide a better understanding of the role of the cerebellum in Parkinson's disease. In the future, this research may aid in the development of treatment for people with PD.

10. Payment and Remuneration

- a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

The subjects will be paid \$25.00 for the initial screening session and \$50.00 for each of the six subsequent sessions. They will also have free valet parking for each visit. There is no penalty for not completing a session.

11. Costs

- a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There is no cost to the subjects for participating in the study.