

# **Effect of Transcranial Direct Current Stimulation on Proprioceptive and Vibratory Sensation: Potential Benefit for Patients with Peripheral Neuropathy.**

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# 1. INTRODUCTION

## 1.1. Indication

The purpose of this study is to assess effect of transcranial direct current stimulation (tDCS) on vibratory and proprioceptive sensation in patients with peripheral neuropathy.

## 1.2. Background and Rationale

Distal symmetric polyneuropathy (DSP) is a common disease and it can occur in up to 30% of those between ages 70 and 80 years, especially those with diabetes or other diseases that can cause neuropathy[1]. Older individuals even without diabetes or other coexisting disease have increased prevalence of PN that puts them at a significantly increased rate of falling and fall-related injury as compared to similarly aged populations without neuropathy[2-4]. Peripheral nerve dysfunction contributes to age related mobility loss and susceptibility to accidental falls due to several factors including impaired proprioception and muscle weakness[5]. Biomechanical gait analyses have shown that patients with PN walk at slower speeds, with shortened stride lengths and greater base widths, stride times and double support times than age-matched healthy controls[6, 7]. Falls among older adults place a significant cost on the US health care system, resulting in over 662,000 hospitalizations and a total cost of over \$30 billion annually[8]. In a prospective follow up study of 32 patients with peripheral nerve dysfunction, 20 had at least one fall over a period of one year. Fourteen of these patients suffered a fall related injury[9]. Ankle proprioception was reduced in all of the patients with fall. Proprioception is likely to be affected early in the disease process, because it is a complex system that requires integration of sensory input from many receptors

Somatosensory in conjunction with visual and vestibular systems convey information about limb and body movement, force, pressure, tension, and movement in space that is needed for motor control[10]. The somatosensory system is responsible for the neural representation of proprioception. Proprioception is usually defined as the ability of the central sensory processing system to identify the position of the body segments and movements in space based on the sensory signals received from sensory receptors[11]. Mechanoreceptors located in joint capsule, ligaments, menisci, musculotendinous unit, and in the skin are involved in sending the proprioceptive feedback signal to the central somatosensory processing areas. Individuals who are deprived from such signals temporarily or permanently due to damage to the sensory nerves show a significant disturbance in movement planning and execution despite having a fully functional motor pathway. Precise ankle proprioceptive thresholds allow earlier perception of a perturbation that is necessary for stabilization or swing limb positioning to prevent falls. Additionally, Standing balance control relies substantively on ankle proprioception. Disrupting proprioception during standing increases body sway that has become part of routine bedside neurologic examination of gait and balance. It has been estimated that ankle proprioception has between 60-70 % contributions to body sway when deprived from other source of sensory feedback such as visual signal[12-14].

Exploring the neural correlates of maintaining balance during upright stand and walking and role of ankle proprioception has been difficult due to the fact that functional imaging are mostly done

with subjects lying down and immobile. The first brain mapping of ankle proprioception-related neural differences in young and older adults was provided in 2011. In this study, stimulating key proprioceptors (i.e., muscle spindles) in the feet with tendon vibration was done during fMRI. In young and older individuals, muscle spindle related neural activity was identified in brain areas that included primary and secondary sensorimotor cortices, secondary associative areas, and basal ganglia[15]. Another fMRI study focused on finding areas in the brain that their activity during proprioceptive stimulation shows high correlation with performance of the subjects in a complex balance task. Areas that were found to have high correlation were right anterior insula, right inferior frontal gyrus (BA 44/45), orbital frontal cortex (BA 47), and the right basal ganglia (pallidum and putamen)[16]. It has been tried to examine the neural correlates of balance control using mental imagery of standing upright while lying supine in an fMRI scanner. Reported areas of activation from these studies include premotor cortex, pre-SMA, dorsolateral prefrontal areas, precuneus, inferior parietal lobe, insula, and cingulate, among others[17, 18].

Objective quantification of proprioception may improve early detection of proprioceptive loss and help quantify this loss with aging. Present methods of proprioception quantification predominantly involve measurement of kinesthesia (ability to detect movement) and joint position sense (JPS). A common measure of kinesthesia is the threshold for perception of slow passive movement. Determining the error associated with active or passive reproduction of a joint angle assesses JPS. The most common used measures are passive or active matching and minimum detectable change in position. For example, one method that has been used to measure the proprioception at the ankle is to place one foot on a footpad that is tilted using a torque machine with a fixed speed. Subjects are asked to report as soon as they feel any movement in their ankle and the direction of the move. The angle when the patient pushes the button is used as threshold of proprioception. The other way of measuring it has been putting the ankle in a range of angles and use the angle that the subjects can report the direction of movement correctly more than 75% of trials as the threshold. Matching technique is asking the patient to reproduce an angle in the joint, either on the same side or on the other side. All of these measures have their own downsides and studies have tried to validate them with controversial results. Overall, it appears that threshold reporting is more sensitive than matching techniques. Functional measures such as time to sway and times walk have also been used to evaluate the effect of treatments such as physical therapy and balance training[19-21].

Currently there is no cure for most of the cases of PN and management is mostly focused on rehabilitation programs. Dynamic balance training has shown to have a modest effect on functional stability in patients with diabetic neuropathy but there is no accepted guidelines regarding a rehabilitation regimen that improve balance and prevent falls in these patients. There is little evidence that proprioception can be improved by exercise or bracing. Biofeedback strategies have only just started to be investigated in patients with PN and the results have not been convincing. Providing proprioceptive signal has not received much attention in developing prosthetic limbs or brain-compute interface protocols until more recently. Few studies have used BCI protocols to provide a tactile signal to prosthetic hands to improve the grip accuracy, but this has not been implemented for gait or balance[8, 10, 22-24].

Transcranial direct current stimulation (tDCS) is a commonly used non-invasive form of brain stimulation for studying brain functions in health and disease[25, 26]. It involves attachment of surface electrodes to the head through which very small electric currents (1 or 2mA) are applied via a current regulated device that is powered by a 9 volt battery. The currents are so small that they do not produce any sensation. Importantly, when the electrode is placed over the cortex, the small currents appear to affect the excitability of the neural tissue. For example, after anodal tDCS over the motor cortex, the amplitude of the motor evoked action potential is increased[27]. That is, a given external input to the motor cortex produces a greater magnitude of muscle activity after application of tDCS. This suggests that anodal tDCS tends to increase the excitability of the cortical region that it is applied to, making it so that a given amount of ‘input drive’ will produce a greater amount of neural activation. In contrast, cathodal tDCS stimulation of the cortex reduces its excitability. Since a tDCS device is relatively small and elicits no acoustic noise and muscle twitching compared with other brain stimulation techniques, it is suitable for sham-controlled clinical studies.

Usefulness of tDCS in modulating sensory functions has been reported before. For example, it has been shown that anodal stimulation of S1 can increase somatosensory evoked potential (SEP) while cathodal stimulation will reduce it[28]. It has been shown that performance of healthy subjects as well as patients with multiple sclerosis (MS) in a tactile task can be enhanced by anodal stimulation of S1[29]. It has also been reported that stimulation of M1 cortex with tDCS can increase SEP. Stimulation of motor cortex has also been shown to enhance the thermal and mechanical sensation as tested by quantitative sensory testing[30]. Additionally a dual hemispheric protocol -during which S1 on one side is stimulated and on the other side is inhibited to block the interhemispheric inhibitory pathways- has been tested in healthy individuals and has been shown to improve performance in tactile spatial discrimination tasks[31]. Interestingly, the effects of tDCS on sensation can last for several minutes[32]. Effects of tDCS on gait and balance as well as improving tactile and proprioceptive sensation has been tested mostly in patients with stroke or spinal cord injury[33-37]. There is no experiment to our knowledge that has examined the effect of stimulating motor and sensory cortices on enhancing the proprioceptive signal in patients with PN. Enhancing this signal by stimulating cortical areas, theoretically can enhance the impaired proprioceptive signal from the ankle and potentially improve the balance problems caused by it. tDCS has been used before in patients with PN safely and with various degree of success for treatment of neuropathic pain, but no study has ever reported any measures of proprioception or balance[26].

In the current study, we plan to test the hypothesis that tDCS of somatosensory, motor or prefrontal cortices can enhance the proprioceptive feedback received from the ankle joints or other sensory feedback signals important for controlling balance and gait and improve these measures in patients with PN. We plan to recruit patients with PN and measure the proprioception sense of the ankle using joint position sense as well as functional measures such as timed walk and time to sway to compare in these subjects before the stimulation and after the real and sham stimulation.

## **2. STUDY OBJECTIVES AND ENDPOINTS**

### **2.1. Objectives**

#### **Primary Objective:**

To evaluate the effect of tDCS on proprioception, defined as the minimum detectable angle of dorsiflexion or plantar flexion at the ankle.

#### **Secondary Objectives:**

1. To evaluate the effect of tDCS on the proprioception threshold of the big toe.
2. To evaluate the effect of tDCS on vibratory sensation threshold;
3. To evaluate the effect of tDCS on time to sway when standing with feet together and eyes closed.
4. To evaluate the effect of tDCS on timed walk test;

### **2.2. Endpoints**

#### **Primary Endpoint**

Minimum detectable angle of dorsiflexion and plantar flexion of the ankle.

#### **Secondary Measures and Efficacy Endpoints**

1. Time to sway when standing with feet together and eyes closed;
2. Vibratory threshold as measured by Rydel Seiffer graduated tuning fork;
3. Distance walked in a timed walk test;

## **3. STUDY DESIGN**

This study will be performed in patients with peripheral neuropathy who are walking independently, but have complains of balance problems such as recent falls or difficulty walking and show reduced vibratory and proprioceptive sensation during routine neurologic examination. These patients will be tested for proprioceptive and vibratory threshold at the toes and ankles before, during and after receiving anodal tDCS over sensory and motor cortices, as well as sham stimulation. Patients will be blinded and won't know if they are receiving actual stimulation or sham stimulation. Subjects will be asked to participate in 2 sessions. In one of the sessions, decided randomly, the sham stimulation will be applied and during the other session the real tDCS stimulation will be applied. Similar sets of assessments will be performed before, during and after application of real or sham stimulations.

## **4. SUBJECT SELECTION**

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

### **4.1. Inclusion Criteria**

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study;
2. Subjects who are willing and able to comply with scheduled visits, and study procedures and are able to read and participate in all study assessments;
3. Subjects with axonal predominantly sensory large-fiber distal symmetric polyneuropathy confirmed with EMG/NCS.
4. Subjects who are walking independently without use of cane or walker.
5. Subjects with impaired proprioception and/or vibration at the toes/ankle on routine neurologic examination.
6. Age older than 18 years;

### **4.2. Exclusion Criteria**

Subjects presenting with any of the following will not be included in the study:

1. Subjects with weakness in ankle dorsiflexion or plantar flexion;
2. Subjects with other etiologies for gait and balance disorder such as cerebellar ataxia, history of stroke, spinal canal stenosis, untreated B12 deficiency;
3. Subjects who are not able to walk independently;
4. History of seizure or a family history of epilepsy;
5. Cardiac pacemakers; cochlear implants; implanted medication pump.
6. Metal implants in the head, except for dental fillings or implants.
7. Increased intracranial pressure;



8. Pregnancy;
9. History of head trauma;
10. Subjects who are taking neuroleptic medications.

## **5. STUDY PROCEDURE**

The tDCS portion of the experiment will begin with DC current (maximum of 2 mA) stimulation delivered through surface electrodes (TransQE from IOMED®, surface area: 25 cm<sup>2</sup>) using a Phoresor® II Auto (Model No. PM850, IOMED®, Salt Lake City, Utah 84120, USA). One electrode will be positioned above the left or right primary motor cortex, the other electrode over the forehead [27].

For sham stimulation the electrodes will be placed in the same way as for real tDCS in the absence of real stimulation, this means stimulation will be increased to a current strength near to perception threshold and will be decreased afterwards and set to 0 mA output for the period of 20 min. With this procedure participants are usually unable to differentiate between tDCS and sham stimulation [38].

## **6. ASSESSMENTS**

### **6.1. Clinical Assessment**

Patients will have a complete neurologic examination by the PI and their medical records will be reviewed including EMG/NCS. A documentation of the disease onset, potential cause, onset of balance problem, most recent fall, examination of muscle strength, reflexes and sensory exam will be done by the PI.

### **6.2. Outcome Assessments**

#### **6.2.1. Proprioception Measurement**

Both minimum detectable change in joint position and position matching techniques will be used.

For minimum detectable change in joint position of the ankle, subject's foot will be placed on a foot pad with adjustable angle. The starting angle will be parallel to the floor. The angle will be changed by 2 degrees in each step and subject will be asked to report as soon as they feel a movement in their ankle with their eyes closed. Direction of movement will be at both dorsiflexion and plantar flexion.

For the matching position of the ankle, the footpad will be positioned in various angles ranging from 5 degree to 45 degree and will be asked to try to match the ankle on the other side with their eyes closed. The angle on the other foot will be measured and recorded. For the same-

side matching, subjects will be asked to remember than angle and try to reproduce it after the ankle is returned to the neutral position.

For measuring proprioception at the big toe, the experimenter will move the toe with steps of 2 degrees at a time and will ask subject to report any change as soon as felt with their eyes closed.

### **6.2.2. Measurement of Vibratory Threshold**

Vibratory threshold is measured by a Rydel Seiffer graduated tuning fork. The two arms of this tuning fork bear calibrated weights at their extremities. A triangle and an arbitrary scale from 0 (minimum score) to 8 (maximum score) imprinted on the weights allow assessment of vibration thresh- old. Once the arms are swinging, the fork vibrates at 64 Hz and the triangles on the weights appear double. The intersection of these two virtual triangles moves from 0 to 8 in an exponential way with decreasing vibration amplitude of the arms. The vibration extinction threshold is considered as the nearest value to the apparent point of intersection of the virtual triangles when the subject indicates that vibration is no longer perceived.

### **6.2.3. Time to Sway**

With patient staying with their feet together, they will be asked to close their eyes. Time until the onset of a postural sway will be recorded.

### **6.2.4. Timed Walk Test**

Subjects will be asked to walk a marked, pre-defined 6-meter distance at a normal speed and the time required for time walk will be recorded.

## **6.3. Safety and Risk Assessments**

Weak direct currents can be applied non-invasively, transcranially and painlessly. Such application leads to transient changes in corticomotor excitability that is fully reversible.

There are no known risks of percutaneous, transcranial DC stimulation of the brain, other than mild local discomfort at the electrode sites (much less than TMS for example). In the current published studies on humans [27, 38-42], 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 changes in diffusion weighted or contrast-enhanced MRI and in EEG after exposure to tDCS.

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. A review paper discussed the safety of tDCS in human. tDCS applications over motor and non-cortical areas in healthy individuals, migraine patients, post-stroke patients, and tinnitus patients ,etc. revealed the most common adverse effect after tDCS was a mild tingling sensation, followed by fatigue, then a light itching sensation under the stimulation electrodes. Not as common, but mentioned, were headache, nausea, and insomnia. The review paper concluded that tDCS is associated with very minor adverse effects in healthy humans and patients with varying neurological disorders[43]. Even higher intensities of current has been used for tDCS safely without complications[44, 45].

## **7. ADVERSE EVENT REPORTING**

All serious adverse events will be reported to the IRB immediately by the PI.

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

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

Exceptional adverse events due to tDCS that will be reported immediately

- Skin burn
- Seizures

## **8. DATA ANALYSIS/STATISTICAL METHODS**

### **8.1. Sample Size Determination**

Based on the review of the literature, a sample size of 15-20 patients often time has been used to investigate the effect of tDCS. We plan to recruit 20 patients in this study.

### **8.2. Analysis of Primary and Secondary Endpoints**

A repeated measure ANOVA will be used to compare the outcome measures before the stimulation, after the real stimulation and after the Sham stimulation.

## **9. QUALITY CONTROL AND QUALITY ASSURANCE**

The study site may be subject to review by the Institutional Review Board (IRB). It is important that the investigator and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **10. DATA HANDLING AND RECORD KEEPING**

### **10.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The investigator has ultimate responsibility for the collection and reporting of all clinical and safety data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

### **10.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and adequate documentation of relevant correspondence (eg, letters, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

## **11. ETHICS**

### **11.1. Institutional Review Board (IRB)**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB. All correspondence with the IRB should be retained in the Investigator File.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB in writing immediately after the implementation.

### **11.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002),

Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

### 11.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system in order to de-identify the trial subject

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by the IRB before use.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

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