A Prospective, Randomized, Staggered-onset, Double blinded, Sham-controlled Study to Evaluate Peripheral Vibrotactile Coordinated Reset Stimulation for Parkinson's Disease

Stanford Neurosurgery

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Investigator's Agreement

By signing below I confirm that I have read this protocol and agree that it contains all necessary details for conducting this study. I will conduct the study according to the procedures described in this protocol.

_____ _____
Principal Investigator's Signature Date

_____
Principal Investigator's Name

_____ _____
Principal Investigator's Signature Date

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Our study to evaluate peripheral vibrotactile coordinated reset stimulation for Parkinson's disease seeks to explore the safety and efficacy of an experimental non-invasive method to aid in the symptoms of Parkinson's disease. The purpose of the study is to verify the safety and tolerability of non-painful sensory (tactile) vibratory stimulation delivered to the fingertips of patients with Parkinson's disease.

BACKGROUND

Parkinson's disease

Every year over 50,000 people in the US are diagnosed with Parkinson's disease (PD) and about half a million people have the disease. Because the rate of PD increases in older adults, the burden will increase unless prevention and treatment improve. Current treatments for Parkinson's disease include both medications and surgical measures. Levodopa is still the mainstay of drug therapy in the form of carbidopa/levodopa (Sinemet, Rytary, Duodopa). Additional drugs are available that complement levodopa therapy, including dopamine agonists such as ropinirole (Requip) and pramipexole (Mirapex), COMT inhibitors such as entacapone (Comtan) and tolcapone (Tasmar), anticholinergics such as trihexyphenidyl (Artane) and benztropine mesylate (Cogentin), MAO inhibitors such as selegiline and amantadine (Symmetrel). Despite the use of these drugs singularly or as combination therapy, none significantly slow the underlying neurodegeneration and many can include intolerable side effects, especially when taken at higher doses as the disease progresses.

Patients with symptoms who become refractory to medication therapy can undergo Deep Brain Stimulation (DBS) surgery. DBS improves symptoms of PD by electrically stimulating brain cells in movement control areas of the brain through chronically implanted electrodes connected to a subcutaneous pulse generator typically placed below the clavicle. However, there are risks associated with this type of operation including risk of stroke, infection, seizure, hemorrhage or others we may not anticipate. Needless to say, less than 10% of surgical candidates for DBS with PD actually undergo the surgery, emphasizing the need for less invasive options.

(https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=109)

In a previous first in man study five subjects with idiopathic Parkinson's disease were treated with vibrotactile CR stimulation during three consecutive days for 4 h per day (Syrkin-Nikolau et al., 2018) This study demonstrated tolerability as well as feasibility of our method, and revealed a significant improvement of gait and bradykinesia, persisting for at least one month after three days of vibrotactile coordinate reset (CR) stimulation.

Based on this study, we propose to deliver vibrotactile CR stimulation during a longer treatment period, in order to assess durability and efficacy vs. a sham vibrotactile approach. This study is designed to best assess vibrotactile CR stimulation compared to sham as an alternative to best medical therapy for Parkinson's disease. With our

project, we are hoping to establish a simple, non-invasive treatment that will provide ongoing relief with minimal side effects or inconvenience to the patient.

Sham control

Parkinson's patients are particularly vulnerable to the placebo effect. The best method of reducing placebo effects in a placebo effect prone population is to blind the participants. In order to do this, sham participants will receive a non-stimulation (0 amplitude) chip that is inserted into the vibrotactile device. All participants will be told that they will receive 1 of two chips, 1 is regular vibrotactile reset and the other (sham) is called Stochastic resonance vibrotactile coordinated reset. The patient will learn that Stochastic resonance treatment is most effective when the patients vibratory stimulus threshold (i.e the minimum perception thresholds) is set as 90% . This means that the patient should not feel the vibrations on their fingers if they receive vibratory stochastic resonance. We will take vibrotactile threshold measurements from patients to make this story convincing and to add another dependent measure. If placed into the sham condition, the patient will receive no stimulation, however they will be convinced that they are receiving stimulation

Vibrotactile CR stimulation therapy system is a commercially available (though not yet FDA-approved), non-invasive, battery-operated mobile device. The device consists of a handheld component with vibro-tactile stimulators (tactors) and is fitted and programmed by a qualified healthcare professional familiar with Parkinson's disease treatment (e.g., physicians, advanced practice providers, nurses and/or their clinical research assistants).

Several brain diseases are characterized by abnormal neuronal synchronization. CR stimulation was developed to specifically counteract neuronal synchronization (Tass 2003). CR stimulation is a spatio-temporally patterned desynchronizing stimulation technique. According to computational studies CR stimulation induces a reduction of the rate of coincidences and, mediated by synaptic plasticity, an unlearning of abnormal synaptic connectivity (Tass & Majtanik 2006). A sustained desynchronization is achieved by shifting the neuronal system from a pathological to a physiological attractor (Tass & Majtanik 2006). It was shown computationally that CR is effective regardless of whether it is delivered directly to neuronal somata or indirectly via excitatory or inhibitory synapses (Popovych & Tass 2012). Accordingly, it was hypothesized that CR stimulation can be realized using both invasive and non-invasive stimulation modalities (Popovych & Tass 2012).

In accordance with theoretical predictions, electrical deep brain CR stimulation has pronounced therapeutic after-effects in Parkinsonian monkeys (Tass et al., 2012a) as well as cumulative and lasting therapeutic and desynchronizing after-effects in Parkinsonian patients (Adamchic et al., 2014a).

In patients with tinnitus, acoustic CR stimulation leads to a significant clinical improvement (Tass et al., 2012b) as well as a decrease of pathological neuronal synchrony in a tinnitus-related network of auditory and non-auditory brain areas (Tass et

al., 2012b; Adamchic et al., 2014b(along with a normalization of tinnitus characteristic abnormal interactions between different brain areas (Silchenko et al., 2013; Adamchic et al., 2014c).

The somatosensory neuronal response to vibratory stimuli [Weiss et al., 2009] provides a dynamic stimulus response characteristics required to robustly deliver CR stimulation [Tass 2017]. As abnormal neuronal synchrony appears to play a major role in Parkinson's disease [Hammond et al., 2007], desynchronization of abnormal synchrony represents a possible target for intervention in Parkinson's patients. It was therefore hypothesized that vibratory CR stimulation might cause a desynchronization of abnormal neuronal synchrony in Parkinson's disease patients and, in turn, induce a decrease of abnormal synaptic connectivity, ultimately giving rise to a sustained relief of symptoms [Tass 2017]. In a first-in-human study in five subjects with idiopathic Parkinson's disease tolerability and feasibility of vibrotactile CR stimulation therapy was demonstrated [Syrkin-Nikolau et al., 2018]. Subjects received 2x2-hour vibrotactile CR stimulation per day during three consecutive days. The CR treatment caused significant effects on gait and bradykinesia, as shown by off medication kinematic assessments during the three treatment days as well as at a one-week and a four-week follow up visit [Syrkin-Nikolau et al., 2018].

Primary Hypothesis

Vibrotactile CR stimulation is not expected to cause discomfort or pain in patients as confirmed in a prior study with Parkinson's disease (IRB# 45096; Syrkin-Nikolau et al., 2018). It is expected to lead to a decrease in severity of motor symptoms from baseline to 6 months, as measured by the Movement Disorders Society's Unified Parkinson's Disease Rating scale (MDS-UPDRS) part III and patient motor diaries to capture mean time when patients' medications have worn off and are not controlling symptoms (OFF time), time when patients' medications are working effectively to control symptoms (ON time), ON time with troublesome dyskinesia, and sleep time – all factors which can be affected by Parkinson's disease. As secondary endpoints, we expect this may result in the patient's ability to reduce reliance upon dopaminergic medications, therefore we will measure changes in levodopa dose equivalency. Additionally, we will assess for improvement in non-motor symptoms of Parkinson's disease, ability to perform activities of daily living and reduction in dyskinesia, which will be measured by the Movement Disorders Society's Unified Parkinson's Disease Rating scale (MDS-UPDRS), parts 1, 2 and 4 and the Schwab and England Activities of Daily Living score. We expect patient quality of life will increase after stimulation, which will be measured by the Parkinson's Disease Questionnaire-39 (PDQ-39) scale. To get a general sense of symptom change, we will assess the patient and clinician Global Rating of Change (GRC) scale and the Patient Global Impression of Change. We will also asses speech using comprehensive speech evaluations. We predict that this decrease in symptoms will be apparent within 1 month of vibrotactile stimulation and that this treatment will be durable as assessed up to 1-months post-stimulation.

Relevance

If the results of this study suggest that vibrotactile CR stimulation is safe and effective for the treatment of Parkinson's disease, this non-invasive treatment approach would have a substantial impact on Parkinson's disease.

Patient Population

Patients presenting Parkinson's disease as identified by Stanford physicians in clinic, will be eligible for participation in this study. Patients will be screened and selected from the population of people with Parkinson's disease who are routinely seen in the Stanford Neuroscience Clinic. It should be emphasized that patients will be allowed to continue any oral medications once stimulation is initiated for their Parkinson's disease symptoms. The doctor and/or research coordinator may introduce the study to potential candidates in-person at Stanford's Neuroscience Clinic, and the research coordinator can also contact potential candidates by the phone after the doctor's referral.

Study Sites

The Stanford University Medical Center will be the Coordinating Center for this study. Stanford's Neuroscience Outpatient Clinic will be used for study visits and assessments.

Inclusion Criteria

1) Age 18 and older
2) Diagnosis of idiopathic Parkinson's disease.
3) Levodopa responsiveness as defined by at least a 30% reduction in MDS-UPDRS motor subscale (excluding tremor scores) in the ON vs OFF medication state.
4) Willing to participate in the vibrotactile stimulation sessions for 2 consecutive days initially and willing to return for follow-up visits
5) Able to provide informed consent.
6) Appropriate social support

Exclusion Criteria

1) Hoehn and Yahr stage greater than 3 in the on medication state
2) Presence of other forms of non-idiopathic parkinsonism, including but not limited to atypical parkinsonism, medication induced parkinsonism, vascular Parkinsonism
3) Any illness that in the investigator's opinion precludes participation in the study
4) Subjects unable to communicate with the investigator and staff

Study Procedures

Once the participant has given informed consent and after baseline screening, the participant will be enrolled in the study and will come to Stanford for 4 visits, each visit being 2 consecutive days. Participants will undergo a series of motor evaluations, speech assessments and EEGs. Participants will be enrolled in the study for 7 months. They will receive treatment for 6 months and no treatment for 1 month. Patients will return for follow up visits every 3 months up until the 6 month follow up. After the 6

month follow up the patient will go off stimulation for 1 month and return for the 7 month follow up to asses long term effects. Data will be accessed only by Stanford researchers on-site

PD-related brain oscillations will also be assessed by high density (256-channel; Geodesic EEG system, EGI Electrical Geodesics, Inc. EEG recordings. Acute effects of stimulation as well as acute after-effects of stimulation on the power of cortical currents in different brain areas as well as on phase amplitude coupling between different brain oscillations will be studied with methods as in [I. Adamchic, B. Langguth, C. Hauptmann, P.A. Tass: Abnormal brain activity and cross-frequency coupling in the tinnitus network. Frontiers in Neuroscience 8 (2014) 284; I. Adamchic, T. Toth, C. Hauptmann, H. Meister, M. Walger, B. Langguth, I. Klingmann, P.A. Tass: Auditory coordinated reset stimulation has a specific desynchronizing effect on tinnitus related oscillatory brain activity. Neuroimage: Clinical 15 (2017) 541-558]. EEG is expected to also provide further objective parameters. Moreover, EEG markers may enable predictions of long-term stimulation effects by correlating acute electrophysiological effects and after-effects with long-term clinical (and electrophysiological) effects of stimulation. We anticipate to correlate changes of neural synchrony in different brain areas with different changes of motor, cognitive, somatosensory, and visual symptoms. Particular stimulation parameters may differentially affect different symptoms. Because of this, there may be changes of the finger representation in the somatosensory cortex over time.

Thus, future optimization may be possible by individually calibrating (personalizing) stimulation based on biomarkers. This will be the subject of a future study, but we will leverage the opportunity the proposed study provides to collect this electrographic data. We anticipate that vibrotactile CR counteracts PD-related patterns of EEG power (i.e. synchrony) and effective connectivity.

After being trained on how to use the device and administer the traditional physical exams and assessments by the study investigators, the PI's clinical staff will apply the device therapy, monitor the participant through the sessions to ensure patient comfort and proper device function, and perform the assessments instructed. Dr. Tass will lead the training of all key personnel on the use of the E-3 vibrotactile stimulator and the protocol will be discussed during an in-service for all research personnel involved in the study to ensure that everyone understands the protocol prior to participating in any research activity. A patent for vibrotactile CR stimulation is filed and owned by Stanford University. Inventor is Peter Tass who will provide as needed consultation to this study at no fee. Stanford Office of Technology and Licensing is actively setting up an industrial collaboration for this treatment of Parkinson's disease.

The vibrotactile stimulator will be attached gently to the fingers (thumb excluded) bilaterally using a glove with an elastic band a Velcro strip or a similar method. When the stimulation is activated, the stimulators will apply gentle vibration to the different fingers sequentially. (**Figure 1)**

Figure 1: *Vibro-Tactile System integrated into glove*

Approximately one week later (Day 7 – this will be an optional visit for as needed training) and four weeks later (Day 28), the participant will return for follow-up physical examinations and assessments only, again occurring at the Stanford Outpatient Neuroscience clinic. These visits will last approximately two hours.

Statistical Analysis

Our primary hypothesis is that vibrotactile CR stimulation (i) will improve the outcome measured as On-time at least by 30% compared to the baseline after three months of usage. We also expect that (ii) the relative increase in On-time in the intervention arm (using vibrotactile CR stimulation) will be at least 20% compared to the control arm (Sham) after three months of usage. In order to test these hypotheses, we will perform Welch's t-test (paired t-test for the first hypothesis and unpaired two-sample t-test for the second hypothesis). Our power analysis shows that the sample size of 10 patients for each arm will provide 85% - 98% of power for detecting statistically significant difference based on the mean On Time of 7.3 at baseline and SD of 2-2.5 that were obtained from our preliminary study.

Based on this power analysis, we are planning to enroll a minimum of 60 patients. 30 patients will be randomized to receive the real stimulation initially. The remaining 30 will be randomized to receive sham stimulation, using dedicated sham stimulation pattern***.***

Protocol summary

Day 0: *Baseline testing (screening):*

- Patient medical history
- General physical exam
- Neurological exam
- Concomitant and PD medications (Levodopa equivalents in mg)
- OFF MDS-UPDRS, part III 12 hour washout of short-acting and 24 hour washout of long acting levodopa containing medications)
- ON MDS-UPDRS, part III (1-2 hours after taking levodopa)
- MOCA and SCOPA
- Clinically trained staff (MD, PA, or RN) will review the consent form in detail with the participant and answer any questions about the study. After consent, the participant will be enrolled in the study and randomized to CR or sham.

- Blinding form – patient
- Blinding form – assessing clinician (MD, PA, RN)

Surveys to be completed after accepted into study and prior to the 1st day of enrollment. Survey will be completed on medication and sent via email

1. *MDS-UPDRS, Parts I-II, and IV*
2. *Parkinson's Disease Questionnaire-39 (PDQ-39) scale*
3. *Schwab and England Activities of daily living score*
5. *Beck depression and Anxiety inventory*

Day 1: 1-2 weeks after baseline screening

- Off Medication UPDRS
- Randomization to CR vs Sham vibrotactile stimulation
- Vibrotactile threshold measurements
- EEG recordings to assess PD-related brain oscillation
- Smell Test
- Comprehensive speech evaluation

Day 2

- Off medication UPDRS
- In-clinic, wearable accelerometer/gyroscope (Kinesia One; ambulatory parkinsons disease monitoring (APDM)) to capture tremor and gait
- •Patient does stimulation for 2 x2 hours with a break in between
- •Repeat UPDRS part III to asses acute CR treatment
- •Repeat In-clinic, wearable accelerometer/gyroscope (Kinesia One; APDM) to capture tremor and gait

Weekly Phone Call to assess AE's, review diary and change in medications

Month 1- month 6 (daily, at home):

- 2hr vibrotactile stimulation (CR vs sham), Session 1 morning
- 2hr vibrotactile stimulation (CR vs sham), Session 2 late afternoon
- Hauser diary to capture OFF time, ON time, ON time with troublesome dyskinesia, sleep time

Patients will return **at 3, 6 and 7 months** and will follow the same procedures as enrollment day 1 and 2

After the 6 month follow up, the patient will receive no stimulation for 1 month to asses long term effects and return at 7 months for a follow up assessment.

Typical tactile stimulation parameters are cyclic with cycle period between 200ms and 1000ms. During each stimulation cycle, each tactor delivers vibratory stimulation once, with vibration pulse length of up to 250 ms per pulse (1 for each finger). Typical cumulative stimulation duration is between 1 and 4, typically 2 hours per day.

Vibro-tactile coordinated reset (CR) neuromodulation therapy system is a commercially available, non-invasive, battery-operated mobile device. The device consists of a handheld component with vibro-tactile stimulators (tactors) and is fitted and programmed by a qualified healthcare professional familiar with treatment of Parkinson's disease (e.g., neurologists and/or their clinical research assistants).

The healthcare professional sets the individual stimulation parameters via a PC application called 'neuro player' and programs the patient device directly via USB connection or via an SD card, which is thereafter plugged into the patient device. The patient device is wired to the vibro-tactile stimulators or controllers that can be hung around the neck of the patients, which allows free movement of the patient. The stimulating tactors (**Figures 2 and 3**) are implemented inside a glove and are flexibly and individually attached to the fingertips (**Figure 4**) via elastic Velcro bands (**Figure 1**).

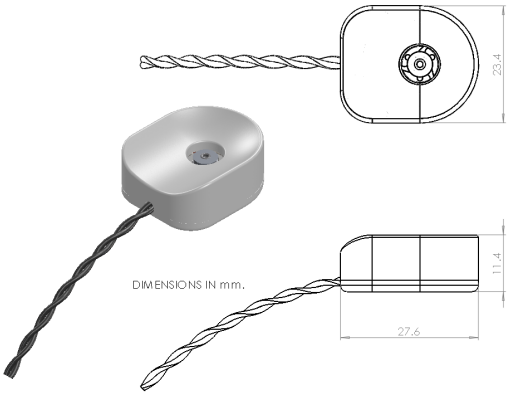
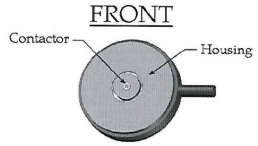


Figure 2: Fingertip Stimulator



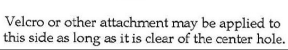
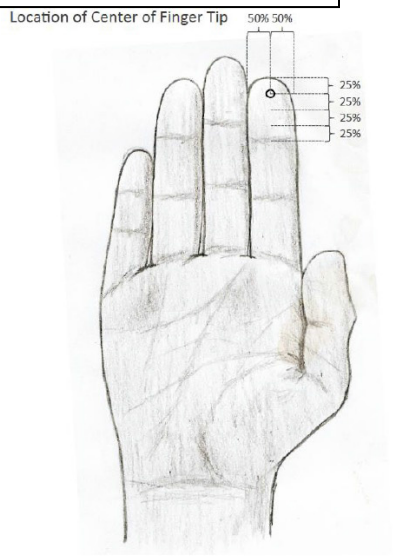


Figure 3: Individual Tactor

Figure 4: Fingertip definition



A display presents information about battery status and progress of the schedule therapy application. Via a push button, the device and the therapy it delivers can be turned on or off.

Risks

The same tactile stimulator system has been studied in a pilot and published in 2018 (Syrkin-Nikolau et al., 2018; Stanford IRB-approved study, IRB# 45096). —at the time not yet integrated into a glove—was already IRB approved and successfully used in epilepsy patients under the supervision of Prof. Robert Fisher in the research study at Stanford University performed under protocol #31684. Preliminary testing by the researchers has not indicated any discomfort or worsening of symptoms. Therefore, Neurotherapies Reset has determined that the vibro-tactile CR therapy does not pose a significant risk to the human subjects; the vibro-tactile CR device, therefore, has been classified as a non-significant risk (NSR) device. However, given that the device is not yet FDA approved, and has not been tested under this exact protocol before, there is a possibility the stimulation could be uncomfortable or even painful for some patients, could worsen one's symptoms or could have other unexpected effects including psychological complications. See the Withdrawal section below for no-go criteria. If there is any discomfort, the researchers can shut off tactile stimulation at any time.

Benefits

The patient's Parkinson's disease symptoms may be reduced, and quality of life may be increased, as a result of the vibratory stimulation, either for a transient period of time such as a few hours post-stimulation, or possibly even for several weeks to months. Ultimately, this pilot study could provide evidence that vibro-tactile stimulation is a safe and effective method to treat symptoms of Parkinson's disease, which would provide a much-needed alternative to medication, surgery and other invasive procedures in the future.

Withdrawal

Each Subject, the Sponsor or its designee and the Investigator reserve the right at any time to terminate a Subject's participation in the clinical investigation.
Possible reasons for withdrawal from the study:

1. Subject voluntarily withdraws consent
2. Subject develops an Adverse Event (AE) that would not allow him or her to continue in the study
3. Subject has an AE which in the opinion of the Investigator warrants withdrawal from the study. Such an AE would include anything unexpected that requires hospitalization. The Sponsor or its designee must be notified within 2 business days
4. A decision is made by the Subject and/or Investigator that the Subject should be withdrawn from the study

Alternative to Participation

There are several alternatives to participation that each potential study candidate should discuss with their physician. The alternatives include not participating and seeking no other treatment, or not participating and seeking a variety of combinations of the following, standard-practice treatments: oral medications for central pain, invasive surgical therapies, and adjunctive therapies. Additionally, however, candidates should understand that choosing to participate is not mutually exclusive with receiving any other treatments.

Data collection, transfer and storage

Clinical data: We will complete a log that documents all patients who are treated with vibro-tactile stimulation. For patients who are considered but not enrolled in this trial, the reason for exclusion will be recorded. The data collection process will entail site staff completing case report forms (CRFs) for the initial capture of research data during participant encounters and the data will be entered into a secure database. Clinical data obtained on the case report forms will include patient demographics, previous medical conditions, Concomitant and PD medications (Levodopa equivalents in mg), MDS-UPDRS, Parts I-II, Off MDS-UPDRS, part III 12 hour washout of short-acting and 24 hour washout of long acting levodopa containing medications), On MDS-UPDRS, part III (1-2 hour after levodopa medication), MDS-UPDRS, part IV, Collect data from electronic motor diary – wearable (accelerometer/gyroscope) to capture off time, on time, on time with troublesome dyskinesia, sleep time, PDQ-39, Schwab and England Activities of daily living score, Patient and clinician Global Impression of change scale and speech assessments.
All data will be accessed only by Stanford researchers on-site.

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