

**EFFECTS OF REDUCED DEEP BRAIN STIMULATION FREQUENCIES
IN PARKINSON'S DISEASE**

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DEDICATION

This Scholarly Project thesis is dedicated to my family and friends who have provided me unconditional support throughout my life and education.

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is widely used and proven to be highly effective in helping alleviate symptoms of Parkinson's disease (PD). Nevertheless, although high-frequency DBS (>120 Hz) is initially effective in improving patients' motor symptoms (mainly bradykinesia and tremors), many patients still develop gait disturbances, such as freezing of gait (FOG). Recent studies have reported that stimulation of the STN with low frequencies produce positive effects on gait disorders and reduces the number of FOG events. As research is being done to investigate how reduced DBS frequencies will affect gait and balance control, it is also important to understand what effects reduced DBS stimulation will have on their PD symptoms. The aim of this study was to investigate the effects that reduced DBS frequencies have on the severity of PD patients' symptoms. The effects were studied in twelve PD patients (receiving DBS treatment) after reducing their DBS frequency. The varied DBS frequencies included: their clinically determined stimulation setting (CDS), a low stimulation setting (30 Hz), and an intermediate stimulation frequency (80 Hz). Symptom severity was measured using the Unified Parkinson's Disease Rating Scale (UPDRS-III), and the Hoehn-Yahr (HY) stage score. The results were supportive of what we expected; that as DBS frequencies are decreased from the patients' clinically determined setting, the clinical symptoms worsened. This is an important observation which will allow the appropriate clinical decisions be made as we continue to investigate the effects of reduced frequency DBS on gait and posture control.

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INTRODUCTION

Background: Parkinson's disease (PD) is a progressive disorder that produces variable degrees of motor and non-motor symptoms. The gradual progression of the disease is the result of idiopathic loss of dopamine-generating cells in the midbrain, specifically the substantia nigra.^[18] The symptoms of PD vary over the course of the disease.^[11] In the early stages of the disease, the four cardinal features are generally evident and include a resting tremor, rigidity (joint stiffness), bradykinesia (slowness of movement), and postural instability. In later disease states, advanced PD patients develop cognitive and behavioral problems, as well as dementia.^[11] The manifestation and progression of symptoms in patients with advancing PD have significant deleterious implications on the affected individual's quality of life.^[23] In PD patients, there is an up to a nine fold increase in falls, leading to fractures that can cause significant disability, dependence and increased morbidity.^[26]

No cure exists for PD; treatment options currently include medication, surgery, and rehabilitation. Among the surgical options, deep brain stimulation (DBS) of the subthalamic nucleus (STN) has proven to be an effective therapeutic option.^[3] When complemented with pharmacological treatments (mainly levodopa and dopamine agonists), DBS has also proven viable for treating the primary symptoms associated with advanced PD.^[21] Although patient outcomes can vary following DBS implantation, remarkable improvements in motor symptoms generally result.^[1] For example, STN DBS can help relieve many of the cardinal/segmental symptoms of PD. Such improvements include relief of tremors, rigidity, and bradykinesia.^[1] Nevertheless, treatment and management of PD through STN DBS presents unique challenges discussed in the following section.

Significance and Rationale for Research Question: STN-DBS is considered to be one of the most effective treatments in advanced PD. Typically, high frequency stimulation (>130 Hz) is the stimulator setting commonly used, and has provided benefit in treating the cardinal symptoms of PD. However, HFS has not shown to be as effective in the treatment of axial predominant symptoms, such as: gait disturbances including FOG, postural instabilities, and

negative effects on speech.^[27] Over the long term, axial symptoms have shown to worsen in 60% to 80% of patients despite being treated with STN-DBS.^[28]

Currently there is little long-term data on the management of gait disorders and freezing of gait (FOG). A lack of understanding of the mechanism(s) of action in DBS has also resulted in disagreement regarding the proper treatment of PD.^[7] Additionally, despite showing marked initial improvement in cardinal symptoms while receiving DBS treatment, many patients still develop gait disturbances.^[21]

Gait disturbances and increased occurrence of FOG episodes are common and disabling, symptoms of advanced PD.^[5] These symptoms have been shown to negatively affect mental health, quality of life, and daily function. For example, patients experiencing increased occurrences of FOG episodes will oftentimes have a fear of falling, leading to immobility, social isolation, reduced fitness, and increased likelihood of developing osteoporosis.^[11, 12, 17]

Although high-frequency DBS is very effective in improving bradykinesia and tremors, its efficacy in improving gait disorders has been disappointing and remains controversial.^[7]

Recent studies have reported that stimulation of STN with low frequencies produces positive effects on gait disorders and reduces the number of freezing episodes.^[21] Beta-range local field potentials (LFPs) have been associated with clinical symptoms of PD. Decreases in beta-range oscillations have also been associated with improvement of Parkinson symptoms during high-frequency stimulation (>120 Hz). When lower frequencies are used, reduced stimulation frequency of 80 Hz may improve bradykinesia^[1, 21] whereas continuous stimulation at 60 Hz may improve FOG.^[15] These observations suggest that the frequency of stimulation may be a critical determinant of the effects of DBS on gait.

Based on this information, this study sought to investigate the effects of reduced DBS frequencies on the severity of clinical symptoms, gait and balance control seen in PD patients. Although data was collected for gait and balance control evaluation, this thesis will focus on determining the effects that reduced DBS frequencies had on the severity of clinical symptoms.

Research Questions: Specifically, this study examined and evaluated the effects of deep brain stimulation at various frequencies, such as clinically determined stimulation settings—low stimulation frequency (30 Hz) and intermediate stimulation frequency (80 Hz)—on the patients’ clinical symptoms, gait and balance control. The first research question listed below is this thesis’ primary question. Data was collected to address the second and third questions regarding how DBS affects gait and balance control in PD patients, and will be the focus of our future investigations.

1. Does deep brain stimulation at reduced frequencies such as 80 Hz and 30 Hz affect clinical symptoms in people with Parkinson’s disease?

The severity of PD symptoms was evaluated clinically using the Unified Parkinson’s Disease Severity Scale (UPDRS-III), and the Hoehn-Yahr (HY) stage score. This hypothesis is the focus of this thesis, however, the alternative hypotheses described below are mentioned for completeness and will likely be the focus of future investigations.

2. Does deep brain stimulation at reduced frequencies such as 80 Hz and 30 Hz improve gait performance in people with PD?

The gait parameters obtained during DBS frequencies of 80 Hz and 30 Hz can be compared to those obtained during subjects’ clinically determined DBS settings. Increases in step length, gait speed, arm swing, and bilateral coordination and/or decreases in double support duration, asymmetry, and variability in stride time intervals may indicate that the benefits are due to the reduced stimulation frequency.

3. Does deep brain stimulation at lower frequencies improve balance control in people with PD?

Posture control may be evaluated in terms of the Barrow Neurological Institute balance scale and sway measures during quiet standing. These measures include sway area, sway excursions, and root mean square distance of sway and accuracy, time taken, path length and movement velocity during posture shift tasks. Improvements in posture control may be indicated by increases in movement velocity and decreases in BNI balance scale score and sway measures.

Goals of the Study: The goal of this study is to investigate the effects of reduced deep brain stimulation frequencies on clinical symptoms in people with Parkinson's disease. Additionally, this study provides research in an area of clinical neurology that is not well understood.

MATERIALS AND METHODS

Sample Size: There are only a few studies that investigated the effects of low frequency deep brain stimulation of STN in people with Parkinson's disease. These studies included 8-10 subjects and reported some statistically significant changes in some of the measures. Unfortunately, they did not provide the data necessary to perform sample size calculations. Based on this, we chose a sample size of 12 subjects to account for any differences in severity of PD symptoms between different frequencies of stimulation.

Selection Criteria: Subject population consisted of PD patients receiving STN DBS treatment at the Muhammad Ali Parkinson Center/Barrow Neurological Institute. Selection criteria included patients (a) whose diagnoses of PD were in accordance with the UK Brain Bank criteria, (b) 30–80 years of age, (c) with an Hoehn-Yahr (HY) score between 2 and 3.5 (on a scale of 0 to 5) during med-off/DBS-on condition, (d) were able to walk without assistance, (e) were at least three months postimplantation, and (f) had stable stimulator settings and an antiparkinsonian medication regime (in the judgment of the treating clinician) for at least two weeks before their baseline visit date. A candidate with a recent history of unstable heart and lung disease; evidence of pregnancy; an untreated chemical addiction or abuse; an uncontrolled psychiatric illness; major neurological (e.g., stroke), musculoskeletal (e.g., rheumatoid arthritis), or metabolic (e.g., diabetes) problems; and cognitive impairment (score of less than 25 for the mini-mental state examination) were excluded.

IRB and Security of Research Records: The Human Subjects Institutional Review Board at St. Joseph's Hospital and Medical Center approved all study-related procedures and informed consent was obtained from subjects prior to initiating the study (see appendix for informed consent form).

Although absolute confidentiality cannot be guaranteed, strict security protocols were, and remain, in place to ensure subjects' research records are kept private. When possible, all information included in subjects' research records that could be used to directly identify them were coded by the research team prior to disclosure to the persons or parties listed above. The

investigator maintained the key that links the code to subjects, and only he had access to the key. However, coding is not possible in some cases. For example, representative regulatory authorities, or the IRB, may require subjects' name or date of birth. In this situation it would not be possible to withhold this identifying information. The results of this research study may be published in scientific journals and/or may be presented at scientific meetings, but subjects' identity will not be revealed.

Experimental Evaluation: Gait, posture, and severity of PD symptoms were evaluated during the following medication-off conditions with varying DBS frequencies, being: 1) DBS at clinically determined settings (CDS, 2) DBS with the frequency reduced to about 80 Hz (intermediate frequency–INT condition), and 3) DBS further reduced to about 30 Hz (low frequency–LOW condition). Note: Subjects discontinued antiparkinsonian medications at least 12 hours before participating in clinical evaluations.

To avoid bias, the sequences of testing conditions (CDS, INT, and LOW) were randomized, and both the patients and clinical assessor were blinded to the manipulated frequency conditions. A physician, qualified research team personnel or technician made the appropriate DBS setting adjustments before performing the evaluations (the clinical and quantitative assessments). For any manipulation in the above-mentioned DBS settings, a minimum time period of 30 minutes was allowed for the stimulation change to take effect. It is known that the therapeutic effects of STN DBS do not instantaneously respond to reductions in frequency but rather decay gradually.^[3]

Experiment Overview: The following conditions were randomized and double blinded:

1. **CDS condition**—Med-off and DBS-on
2. **INT condition**—Med-off and DBS-on intermediate frequency (80 Hz)
3. **LOW condition**—Med-off and DBS-on reduced frequency (30 Hz)

Note: After data collection (described below) during the above conditions, the subjects were asked to take their usual dosage of antiparkinsonian medications before leaving the clinic.

Evaluation Using Clinical Scores: In addition to quantitative evaluation of gait and posture control (described below), the severity of PD symptoms were evaluated clinically using part three (motor part) of the Unified Parkinson's Disease Rating Scale (UPDRS-III), the Barrow Neurological Institute (BNI) balance scale, and the Hoehn-Yahr (HY) stage score. These clinical scores are used to evaluate the severity of disability, and any changes following DBS alterations would suggest effects of a reduced stimulation frequency. The recently developed BNI scale focuses on the specific impairments of PD that have been shown to be related to falls, such as turning,^[4,13,24] standing on one foot,^[10,16] and tandem walking.^[2,6]

The UPDRS is a commonly used scale in the clinical study of Parkinson's disease. The motor exam portion (UPDRS-III) of the UPDRS was used to scale the severity of symptoms seen in the subjects at the three varied DBS frequency settings. The scale ranges from 0-4 depending on the clinical severity of the symptoms. The following items were scored by an experienced clinician for each DBS condition, and can be seen below.

Figure 1: Part III (Motor Part) of the Unified Parkinson’s Disease Rating Scale (UPDRS-III).

Motor Exam	Score (0-4)
3.1 Speech	
3.2 Facial expression	
3.3 Rigidity	
a. Neck	
b. R-UE	
c. L-UE	
d. R-LE	
e. L-LE	
3.4 Finger tapping	
a. Right hand	
b. Left hand	
3.5 Hand movements	
a. Right hand	
b. Left hand	
3.6 Pronation-Supination of hand movements	
a. Right hand	
b. Left hand	
3.7 Toe tapping	
a. Right foot	
b. Left foot	
3.8 Leg agility	
a. Right leg	
b. Left leg	
3.9 Arising from chair	
3.10 Gait	
3.11 Freezing of gait	
3.12 Postural Stability	
3.13 Body bradykinesia	
3.15 Postural tremor of hands	
a. Right hand	
b. Left hand	
3.16 Kinetic tremor of hands	
a. Right hand	
b. Left hand	
3.17 Rest tremor amplitude	
a. R-UE	
b. L-UE	
c. R-LE	
d. L-LE	
e. Lip/Jaw	
3.18 Constance of rest tremor	
Total Score	

Note: Additional experimentation and data collection was performed to evaluate changes in gait and posture control at the various DBS frequency settings. The methods used to collect the gait and posture control data are described below, however, the data and interpretation of this thesis will focus on the changes observed in clinical scores (as described above) with various DBS frequencies.

Evaluation of Gait: Gait was evaluated quantitatively using three trials of Timed-Up and Go (TUG) test and one trial of a six-minute walking test. With respect to TUG, which is strongly correlated to functional mobility,^[20] the following task will be performed: get up from a chair, stand up, walk seven meters, turn around, walk back, and sit down. A lightweight sensor-based wearable gait system (APDM Mobility)^[14] was used for gait measurements. The lightweight sensors were secured using a Velcro strap on the subjects' left and right wrists, left and right ankles, trunk, and lumbar region of the back. The system measured stride-by-stride, stride length, stride time, swing time, single and double support duration, walking velocity, cadence, range of swing of legs and arms, time taken to go from sitting to standing and vice versa, time taken for turning, and the number of steps to make a turn. Subjects were closely monitored and supported in the event of freezing, loss of balance, or falls.

Evaluation of Posture Control: Posture control was assessed using center-of-pressure (COP)-based sway measures in trials of quiet standing (three 1-minute trials) and during postural shift tasks (three untimed trials). During quiet standing, subjects stood with their feet hip-width apart with each foot positioned side-by-side on a force platform (Bertec). For posture-shift tasks, visual feedback of COP allowed subjects to observe their weight distribution in the form of a red dot. The subjects were asked to move the red dot, i.e., their center of pressure (by shifting their weight) into the target circle and hold it within the target for two seconds. Targets were presented in a center-out and back-to-center sequence (the five outer targets require shifts to left, right, front, and frontal diagonals). If the target is not acquired within ten seconds, the target disappeared and the next target was presented. The magnitude of the posture shift and the size of the target was individualized for each subject as 30% and 10%

respectively, of their limits of stability (estimated as the anterior shift of the subject's navel during an 8° rotation about the ankle).^[8]

RESULTS

Assumptions: Inferential analysis involved a repeated measures analysis of variance (ANOVA) design. Assumptions for the repeated measures ANOVA are outliers, normality of the sampling distribution, and sphericity.

Outliers in a dataset have the potential to distort results of an inferential analysis. A check of box plots for the Parkinson's disease symptom variables used during inferential analysis was performed to visually inspect for outliers. Many outliers were found for the symptom variables. However, all outliers were within the acceptable range of possible scores for each of the symptoms. Since all outliers were within the acceptable score ranges, it was determined that all records would be retained for analysis and that the outlier assumption was not violated.

Normality for the data distribution of Parkinson's disease symptom variables of the participants over each of the three DBS conditions was investigated with SPSS Explore. A visual check of histograms indicated non-normality. However, further inspection showed that the means, medians, and 5% trimmed means for each of the variables were close in value. The ANOVA analyses used for inference in this study are robust to deviations from normality, providing the assumption for sphericity was met. The sphericity assumption was met for most of the ANOVA tests. And when sphericity was not met, a corrected test-statistics value was used for determination of significance. Therefore, it was decided that any deviations from normality were not adversely impacting the analyses, and the ANOVA tests were used on all of the variables during inferential analysis.

Sphericity was checked for all individual analyses. For variables that violated the assumption of sphericity, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. Statistics for the sphericity assumption and corrections to the findings if needed are presented with the results of each ANOVA analysis.

Hypothesis Testing: A series of repeated measures ANOVA analyses were conducted to explore the impact of deep brain stimulation frequencies on different Parkinson's disease symptoms. Each analysis included one repeated measures (within-groups) independent variable of Condition, with three levels of: (a) Condition 1 – Clinically Determined Setting (CDS); (b) Condition 2 – Intermediate Frequency (80 Hz); and (c) Condition 3 – Low Frequency (30 Hz). A total of 35 ANOVAs were performed and included tests for 33 Parkinson's disease symptoms, a total motor exam score for each of the three conditions, and a Hoehn and Yahr Staging score for each of the three conditions. Results are presented according to each symptom or outcome tested. Table 1 presents a summary of the ANOVA findings.

Speech (3.1): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of speech. Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.44, p = .803$. Therefore, the assumption of sphericity was assumed for the dependent variable of Speech. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's speech, $F(2, 24) = 0.27, p = .613$.

Facial Expression (3.2): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of facial expression. Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 3.38, p = .184$. Therefore, the assumption of sphericity was assumed for the dependent variable of Facial Expression. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's facial expression, $F(2, 22) = 0.23, p = .797$.

Rigidity in the Neck (3.3): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of rigidity in the neck. ANOVAs were also performed for the four areas in the neck: right upper extremity, left upper extremity, right lower extremity, and left lower extremity. Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.85, p = .653$. Therefore, the assumption of sphericity was assumed for the dependent variable of Rigidity in the Neck.

Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's rigidity in the neck, $F(2, 24) = 1.54, p = .234$.

Right Upper Extremity (3.3a): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 2.45, p = .294$. Therefore, the assumption of sphericity was assumed for the dependent variable of Rigidity in the Neck – Right Upper Extremity. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's rigidity in the upper right extremity of the neck, $F(2, 24) = 0.83, p = .450$.

Left Upper Extremity (3.3b): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 1.13, p = .570$. Therefore, the assumption of sphericity was assumed for the dependent variable of Rigidity in the Neck – Left Upper Extremity. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's rigidity in the upper left extremity of the neck, $F(2, 24) = 3.88, p = .035$. However, a comparison of the means in post hoc analysis showed no significant differences.

Right Lower Extremity (3.3c): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.22, p = .896$. Therefore, the assumption of sphericity was assumed for the dependent variable of Rigidity in the Neck – Right Lower Extremity. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's rigidity in the lower right extremity of the neck, $F(2, 24) = 4.88, p = .017$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Rigidity in the Neck – Right Lower Extremity at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 1.04, SE = 0.12$) than Condition 3 ($M = 1.54, SE = 0.14$).

Left Lower Extremity (3.3d): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.86, p = .652$. Therefore, the assumption of sphericity was assumed for the dependent variable of Rigidity in the Neck – Left Lower Extremity. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's rigidity in the lower left extremity of the neck, $F(2, 24) = 5.62, p = .010$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Rigidity in the Neck – Left Lower Extremity at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 0.58, SE = 0.17$) than Condition 3 ($M = 1.04, SE = 0.17$).

Finger Tapping (3.4): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of finger tapping.

Right Hand (3.4a): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 1.63, p = .443$. Therefore, the assumption of sphericity was assumed for the dependent variable of Finger Tapping – Right Hand. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on finger tapping in a participant's right hand, $F(2, 24) = 0.18, p = .839$.

Left Hand (3.4b): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 1.89, p = .388$. Therefore, the assumption of sphericity was assumed for the dependent variable of Finger Tapping – Left Hand. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on finger tapping in a participant's left hand, $F(2, 24) = 4.32, p = .025$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Finger Tapping – Left Hand at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 1.27, SE = 0.20$) than Condition 3 ($M = 1.81, SE = 0.19$).

Hand Movements (3.5): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of hand movements.

Right Hand (3.5a): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 4.47, p = .107$. Therefore, the assumption of sphericity was assumed for the dependent variable of Hand Movements – Right Hand. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on hand movements in a participant's right hand, $F(2, 24) = 9.24, p = .001$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Hand Movements – Right Hand at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 1.39, SE = 0.20$) than Condition 2 ($M = 1.81, SE = 0.22$) and Condition 3 ($M = 1.96, SE = 0.23$).

Left Hand (3.5b): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 1.16, p = .561$. Therefore, the assumption of sphericity was considered not violated for the dependent variable of Hand Movements – Left Hand. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on hand movements in a participant's left hand, $F(2, 24) = 6.81, p = .005$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Hand Movements – Left Hand at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal

means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 1.31, SE = 0.22$) than Condition 3 ($M = 1.92, SE = 0.17$).

Pronation Supination of Hand Movements (3.6): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of pronation supination of hand movements.

Right Hand (3.6a): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.82, p = .663$. Therefore, the assumption of sphericity was assumed for the dependent variable of Pronation Supination of Hand Movements – Right Hand. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on pronation supination of hand movements in a participant's right hand, $F(2, 24) = 15.08, p < .0005$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Pronation Supination of Hand Movements – Right Hand at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 1.46, SE = 0.21$) than Condition 2 ($M = 1.92, SE = 0.16$) and Condition 3 ($M = 2.27, SE = 0.18$).

Left Hand (3.6b): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.36, p = .835$. Therefore, the assumption of sphericity was considered not violated for the dependent variable of Pronation Supination of Hand Movements – Left Hand. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on pronation supination of hand movements in a participant's left hand, $F(2, 24) = 8.85, p = .001$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Pronation Supination of Hand Movements – Left Hand at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated

that Condition 1 had significantly lower mean values ($M = 1.39$, $SE = 0.22$) than Condition 3 ($M = 2.19$, $SE = 0.17$).

Toe Tapping (3.7): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of toe tapping.

Right Foot (3.7a): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.01$, $p = .997$. Therefore, the assumption of sphericity was assumed for the dependent variable of Toe Tapping – Right Foot. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on toe tapping in a participant's right foot, $F(2, 24) = 2.70$, $p = .088$.

Left Foot (3.7b): Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 7.55$, $p = .023$. Degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.67$). Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on toe tapping in a participant's left foot, $F(2, 24) = 0.88$, $p = .394$.

Leg Agility (3.8): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of leg agility.

Right Leg (3.8a): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 1.68$, $p = .431$. Therefore, the assumption of sphericity was assumed for the dependent variable of Leg Agility – Right Leg. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on leg agility in a participant's right leg, $F(2, 24) = 2.90$, $p = .075$.

Left Leg (3.8b): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 3.41$, $p = .181$. Therefore, the assumption of sphericity was assumed for the dependent variable of Leg Agility – Left Leg. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on leg agility in a participant's left leg, $F(2, 24) = 7.10$, $p = .004$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Leg Agility – Left Leg at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 1.04, SE = 0.21$) than Condition 2 ($M = 1.58, SE = 0.14$) and Condition 3 ($M = 1.85, SE = 0.24$).

Arising from a Chair (3.9): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of arising from a chair. Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.63, p = .731$. Therefore, the assumption of sphericity was assumed for the dependent variable of Arising from a Chair. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's arising from a chair, $F(2, 24) = 1.21, p = .315$.

Gait (3.10): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of gait. Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.56, p = .757$. Therefore, the assumption of sphericity was assumed for the dependent variable of Gait. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's gait, $F(2, 24) = 4.17, p = .028$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Gait at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 2 had significantly lower mean values ($M = 1.12, SE = 0.20$) than Condition 3 ($M = 1.19, SE = 0.16$).

Freezing of Gait (3.11): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of freezing of gait. Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 8.02, p = .018$. Degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon=0.66$). Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's freezing of gait, $F(2, 24) = 0.41, p = .587$.

Postural Stability (3.12): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of postural stability. Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 0.85, p = .655$. Therefore, the assumption of sphericity was assumed for the dependent variable of Postural Stability. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's postural stability, $F(2, 24) = 1.46, p = .037$. However, a comparison of the means in post hoc analysis showed no significant differences.

Posture (3.13): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of posture. Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 5.20, p = .074$. Therefore, the assumption of sphericity was assumed for the dependent variable of Gait. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's gait, $F(2, 24) = 1.90, p = .171$.

Body Bradykinesia (3.14): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of body bradykinesia. Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 8.88, p = .012$. Degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon=0.63$). Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's body bradykinesia, $F(2, 22) = 3.34, p = .082$.

Postural Tremor of Hands (3.15): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of postural tremor of hands.

Right Hand (3.15a): Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 15.48, p < .0005$. Degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon=0.56$). Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on postural tremors in a participant's right hand, $F(2, 22) = 5.42, p = .035$. However, a comparison of the means in post hoc analysis showed no significant differences.

Left Hand (3.15b): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 2.16, p = .340$. Therefore, the assumption of sphericity was considered not violated for the dependent variable of Postural Hand Tremors – Left Hand. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on postural tremors in a participant's left hand, $F(2, 24) = 3.06, p = .065$.

Kinetic Tremor of Hands (3.16): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of kinetic tremor of hands.

Right Hand (3.16a): Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 1.25, p = .535$. Therefore, the assumption of sphericity was considered not violated for the dependent variable of Kinetic Hand Tremors – Right Hand. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on kinetic tremors in a participant's right hand, $F(2, 24) = 3.50, p = .046$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Kinetic Hand Tremors – Right Hand at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 0.27$, $SE = 0.15$) than Condition 3 ($M = 0.69$, $SE = 0.20$).

Left Hand (3.16b): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 1.05$, $p = .592$. Therefore, the assumption of sphericity was considered not violated for the dependent variable of Kinetic Hand Tremors – Left Hand. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on kinetic tremors in a participant's left hand, $F(2, 24) = 1.70$, $p = .205$.

Rest Tremor Amplitude (3.17): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of rest tremor amplitude. ANOVAs were performed for the five areas of: right upper extremity, left upper extremity, right lower extremity, left lower extremity, and lip/jaw.

Right Upper Extremity (3.17a): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 3.99$, $p = .136$. Therefore, the assumption of sphericity was assumed for the dependent variable of Rest Tremor Amplitude – Right Upper Extremity. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's rest tremor amplitude in the upper right extremity, $F(2, 24) = 4.27$, $p = .026$. However, a comparison of the means in post hoc analysis showed no significant differences.

Left Upper Extremity (3.17b): Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 10.63$, $p = .005$. Degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.62$). Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's rest tremor amplitude in the upper left extremity, $F(2, 24) = 1.14$, $p = .317$.

Right Lower Extremity (3.17c): Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 3.52, p = .172$. Therefore, the assumption of sphericity was assumed for the dependent variable of Rest Tremor Amplitude – Right Lower Extremity. Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's rest tremor amplitude in the lower right extremity, $F(2, 24) = 2.54, p = .100$.

Left Lower Extremity (3.17d): Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 9.80, p = .007$. Degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon=0.63$). Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's rest tremor amplitude in the lower left extremity, $F(2, 24) = 0.87, p = .392$.

Lip/Jaw (3.17e): Mauchly's test of sphericity could not be computed because Conditions 1 and 2 had lip/jaw measurements of zero for all participants, and only one participant had a measurement other than zero for Condition 3 (record #7, value = 1.5). Since there was no variability between the DBS conditions (Conditions 1 and 2 were constant and Condition 3 was almost constant), sphericity could not be determined. However, to maintain a conservative interpretation of results, the Greenhouse-Geisser estimate of sphericity was used to correct the degrees of freedom for the analysis ($\epsilon=0.50$). Tests of within-subjects effects indicated that there was not a significant within-subjects effect of the three DBS frequencies on a participant's rest tremor amplitude in the lip/jaw, $F(2, 24) = 1.00, p = .337$.

Constancy of Rest Tremor (3.18): A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the Parkinson's disease symptom of constancy of rest tremor. Mauchly's test of sphericity indicated that the assumption of sphericity was not violated, $\chi^2(2) = 2.97, p = .227$. Therefore, the assumption of sphericity was assumed for the dependent variable of Constancy of Rest Tremor. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's constancy of rest tremor, $F(2, 20) = 4.62, p = .022$. However, a comparison of the means in post hoc analysis showed no significant differences.

Total Clinical Score: A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the participants' total clinical scores. Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 6.67, p = .036$. Degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon=0.69$). Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's total clinical score, $F(2, 24) = 13.00, p = .001$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Total Clinical Score at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 30.89, SE = 1.85$) than Condition 2 ($M = 37.12, SE = 3.22$) and Condition 3 ($M = 43.31, SE = 3.92$).

Hoehn and Young Staging: A repeated measures ANOVA was conducted to explore the impact of deep brain stimulation frequencies on the participants' Hoehn and Young staging scores. Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 1.01, p = .603$. Therefore, the assumption of sphericity was assumed for the dependent variable of Hoehn and Young Staging score. Tests of within-subjects effects indicated that there was a significant within-subjects effect of the three DBS frequencies on a participant's Hoehn and Young staging score, $F(2, 24) = 4.09, p = .030$.

Post hoc analysis was performed utilizing three separate independent samples t-tests with standardized dependent variable of Hoehn and Young Staging score at the three DBS frequencies (clinically determined setting, 80 Hz, and 30 Hz). A comparison of the estimated marginal means for the three deep brain stimulation (DBS) conditions indicated that Condition 1 had significantly lower mean values ($M = 2.31, SE = 0.15$) than Condition 3 ($M = 2.69, SE = 0.13$).

TABLE 1:

Effects of Deep Brain Stimulation (DBS) Conditions on Parkinson's Disease Symptoms Parameters

Symptom	CDS			ANOVA	
	Condition	INT Condition	LOW Condition	F	Sig.
Speech	1.58±0.25	1.58±0.23(1.000)	1.50±0.18(1.000)	0.20	.822
Facial expression	1.75±0.19	1.81±0.17(1.000)	1.83±0.17(1.000)	0.23	.797
Rigidity					
Neck	1.50±0.22	1.65±0.22(.793)	1.78±0.26(.393)	1.54	.234
R-UE	1.69±0.13	1.69±0.24(1.000)	1.92±0.25(1.000)	0.83	.450
L-UE	0.85±0.16	1.08±0.27(.640)	1.35±0.25(.092)	3.88	.035
R-LE	1.04±0.12	1.15±0.20(1.000)	1.54±0.14(.049)	4.88	.017
L-LE	0.58±0.17	0.73±0.20(1.000)	1.04±0.17(.023)	5.62	.010
Finger tapping					
Right hand	1.69±0.18	1.77±0.17(1.000)	1.65±0.24(.023)	0.18	.839
Left hand	1.27±0.20	1.58±0.23(.539)	1.81±0.19(.014)	4.32	.025
Hand movements				11.7	
Right hand	1.39±0.20	1.81±0.22(.002)	1.96±0.23(.015)	4	.001
Left hand	1.31±0.22	1.65±0.22(.097)	1.92±0.17(.021)	6.81	.005
Pronation-supination of hand movements				15.0	
Right hand	1.46±0.21	1.92±0.16(.013)	2.27±0.18(.001)	8	<.001
Left hand	1.39±0.22	1.81±0.12(.128)	2.19±0.17(.007)	8.85	.001
Toe tapping					
Right foot	1.54±0.13	1.81±0.17(.510)	1.96±0.13(.128)	2.70	.088
Left foot	1.77±0.20	1.81±0.23(1.000)	2.00±0.20(.820)	0.88	.394
Leg agility					
Right leg	1.42±0.16	1.65±0.13(.640)	1.85±0.14(.177)	2.90	.075
Left leg	1.04±0.21	1.58±0.14(.047)	1.85±0.24(.033)	7.10	.004
Arising from chair	0.27±0.12	0.50±0.18(.640)	0.46±0.18(.719)	1.21	.315
Gait	1.19±0.16	1.12±0.20(1.000)	1.58±0.15(.194)	4.17	.028
Freezing of gait	0.31±0.18	0.23±0.19(1.000)	0.39±0.21(1.000)	0.41	.587
Postural stability	0.81±0.32	0.89±0.29(1.000)	1.42±0.27(.107)	3.80	.037
Posture	1.58±0.22	1.73±0.23(.496)	1.73±0.23(.496)	1.90	.171

TABLE 1 (cont'd)

Symptom	CDS			ANOVA	
	Condition	INT Condition	LOW Condition	F	Sig.
Body bradykinesia	1.88±0.13	1.96±0.23(1.000)	2.25±0.14(.036)	3.34	.082
Postural tremor of hands					
Right hand	0.17±0.11	0.54±0.23(.130)	0.63±0.27(.102)	5.42	.035
Left hand	0.15±0.10	0.42±0.16(.141)	0.27±0.12(.570)	3.06	.065
Kinetic tremor of hands					
Right hand	0.27±0.15	0.46±0.17(.626)	0.69±0.20(.043)	3.50	.014
Left hand	0.46±0.16	0.73±0.16(.393)	0.58±0.16(1.000)	1.70	.205
Rest tremor amplitude					
R-UE	0.27±0.20	0.42±0.29(.656)	0.77±0.31(.092)	4.27	.026
L-UE	0.04±0.04	0.19±0.13(.656)	0.39±0.23(.538)	1.14	.317
R-LE	0.08±0.08	0.27±0.18(.719)	0.54±0.29(.268)	2.54	.100
L-LE	0.08±0.08	0.15±0.15(1.000)	0.31±0.24(1.000)	0.87	.392
Lip/Jaw	---	---	0.12±0.12(1.000)	1.00	.337
Constancy of rest tremor	0.09±0.09	0.41±0.22(.396)	0.86±0.34(.098)	4.62	.022
Total Score	30.89±1.85	37.12±3.22(.011)	43.31±3.92(.006)	13.0	.001
Hoehn and Yahr Staging	2.31±0.15	2.46±0.17(1.000)	2.69±0.13(.034)	4.09	.030

Note. Entries are estimated marginal means ± standard error. Values in parentheses are *p*-values compared to CDS condition.

DISCUSSION

While deep brain stimulation of the subthalamic nucleus (STN) has proven to be an effective therapeutic option for PD patients' motor symptoms, many patients still develop gait disturbances.^[1,3,21] Recent studies have suggested that frequency of the stimulation may be a critical determinant of the effects DBS on gait. To the best of our knowledge, our ongoing research is novel in that it will be the first to look at the effects of differing STN DBS frequencies on gait and balance quantitatively. Although reduced DBS frequencies may hold promise in improving gait and balance control, it is important to understand if, and how severely, patients' clinical symptoms will be affected by the reduced frequency.

This study examined the effects of reduced DBS stimulation on the severity of PD symptoms. Clinical scales (UPDRS-III and H&Y stage score) were used to determine the severity of symptoms across the varied DBS frequencies. Significant changes were seen in the clinical values across differing DBS conditions. As demonstrated in Table 1, the majority of symptoms increased in severity as the DBS frequency was reduced, with several of them being found to be statistically significant changes (p -value <0.05). Most notably, the Total Clinical Score (i.e., the cumulative score of the severity of symptoms) increased as the DBS frequency was reduced. This finding was found to be significant, with a p -value of 0.001. Additionally, the Hoehn and Yahr Staging values increased with decreasing frequencies, with a p -value of 0.30.

These results are supportive of what we expected; that as you decrease the frequency of DBS from the patients' therapeutic setting, the clinical symptoms worsened (became more severe). However, this was an important observation to make so that appropriate clinical decisions can be made as we continue to investigate the effects of reduced frequency DBS on gait and posture control. It is likely that the potential improvements in gait and posture control at reduced DBS frequencies will have to be weighed against the increase in PD clinical severity.

FUTURE DIRECTIONS

One limitation of this study includes the sample size. Twelve subjects were studied, however, patient recruitment and data collection is ongoing. Moving forward, we will continue to investigate the effects that reduced frequency DBS has on clinical severity, as well as analyze the data collected in the same patient population studying its effects on gait and balance control. As the sample size increases, we can also begin to control for additional variables (i.e., sex and ethnicity) without losing statistical power.

CONCLUSION

This study sought to examine the effects of reduced DBS frequencies on the clinical symptoms seen in PD patients. The DBS frequencies were varied such as clinically prescribed stimulation settings, intermediate stimulation frequency (80 Hz), and low stimulation frequency (30 Hz). Our findings suggest that with decreased DBS frequencies, clinical symptom severity increases. This is not surprising, however, will be an important factor to consider if further research supports the hypothesis that reduced DBS frequencies will improve patients' gait and posture control.

Ultimately, this study provides data in an area of clinical neurology that is not well understood, in addition to facilitating the collection of data which will allow the study of effects of reduced DBS frequencies on gait and balance control. Further research is needed to provide a better understanding of the mechanisms of DBS could help guide the needed standardization of DBS electrical parameters,^[22] thereby improving effective DBS system tuning to reduce or even eliminate gait and balance impairments, which are difficult to treat.^[1]

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Appendix A:

Protocol ID:

Sponsor: St. Joseph's Hospital and Medical Center

Title: *Effects of reduced deep brain stimulation frequencies in Parkinson's disease*

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WHY AM I BEING ASKED TO PARTICIPATE IN THIS STUDY?

You have been identified as a possible candidate for participation in a research study called "Effects of reduced deep brain stimulation frequencies in Parkinson's disease"

Federal regulations state that no investigator may involve a human being as a subject in research unless the investigator has obtained the informed consent of the subject or the subject's legal representative. Informed consent contains three elements: information, understanding, and voluntariness. Adequate *information* is important to your decision to participate in research (or not). Prior to enrollment, you must *understand* the research, the nature of your participation, and the potential risks and benefits of the study. Finally, an agreement to participate in research is valid only if it is *voluntarily* given.

This document explains the purposes of the research, the procedures to be followed, and the potential risks and benefits of the study. You should read this document very carefully and ask as many questions as you need to understand what your involvement in the study means. You should not sign the document until you have been given sufficient time to thoughtfully consider your participation in the study. We encourage you to consider your participation in consultation with family and friends and, if you wish, your primary care physician.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 20 persons with Parkinson's disease with implanted deep brain stimulator (DBS) will enroll in this research study. It is only being done at St. Joseph's Hospital and Medical Center.

WHY IS THIS STUDY BEING DONE?

This research study is being done to investigate whether reducing the frequency of deep brain stimulation improves balance and walking in people with Parkinson's disease.

WHAT IS INVOLVED IN THIS STUDY?

If you choose to take part in this research study, you will be asked to complete as many of the following depending on your ability.

Screening/Clinical evaluation session: (~ 1 hour)

If you agree to take part in this study and sign this form, the following may be completed to find out if you are eligible for participation in this study:

- Review demographics (*e.g.*, age, sex, and race).
- Review medical history and past and current medicines.
- Evaluate thinking abilities
- Evaluate the extent of neurological disorder

If you are eligible to participate, you may be asked to complete the following evaluation.

Experimental evaluation session: (~ 3.5 hours)

During this session, data on your balance and walking patterns (explained below) will be collected during each of the following conditions: (a) DBS on with usual settings, (b) Reduced stimulation frequency of about 80 Hz, and (c) Reduced stimulation frequency of about 30 Hz. The sequence of conditions (b) and (c) will be selected in a random way. You will be asked not to take your usual Parkinson's disease medication for at least 12 hours before this evaluation session. There will be a waiting period of at least 30 minutes between each of the above mentioned DBS conditions for the changes in the DBS frequency to take effect.

You will need to remember to wear comfortable shorts or pants, a comfortable shirt and athletic shoes. You will also be photographed and videotaped during these tests.

In this session, you will be asked to:

- (1) complete a brief interview in which you will be asked questions about your medication and if anything out of the ordinary has occurred since your last visit;
- (2) listen to a brief introduction which will inform you about what is going to happen in the test; and
- (3) complete the procedures required for that test (which are described below).

For each of the tests listed below, you will be asked to wear lightweight sensors that will be strapped to your arms, legs, or torso. These sensors will be removed at the end of the respective tests. During some tests, you may be asked to use any one or more of the following: a harness system; parallel bars; belt around the waist (a research staff member will be holding it to prevent falls) - for your safety in case you lose your balance during the test. This visit will include the following procedures with rest periods.

1. The staff will help you put on the equipment that is required for the experiment and a brief warm-up session will help you get used to the experiment
2. You may be asked to stand on an equipment platform quietly (with and/or without closing your eyes) and also to perform swaying motions to assess balance control
3. You may be asked to walk for about 6 minutes. You may also be asked to perform a timed walking test for about three times: getting up from a chair, walk for about 7 meters, turn, walk back and sit on the chair. You may be asked to walk as mentioned above and at the same time counting down by number 9 or 7 and/or through narrow corridors or doorways.
4. Your movement related difficulties will be evaluated using a clinical examination.

You will be closely monitored by a research team member to hold you in case of any freeze or fall. The above mentioned assessments will be performed during each of the three different DBS frequency settings.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will be for two visits (screening and experimental evaluation). Maximum efforts will be made to conduct both the visits within a 2-week time period. You may stop taking part in this study at time.

WHAT ARE THE RISKS OF THIS STUDY?

The procedures involved in this research study may involve unexpected risks or discomforts that are impossible to predict. These unforeseen risks or discomforts may affect you during your participation in the study and/or at some point in the future.

You should inform the research team about anything unusual that is happening with your health, including any worsening of existing medical conditions.

The known risks of this study are listed below.

You may experience some minor discomfort during the experimental sessions from the lightweight sensors. If this happens, you should inform the research staff and the devices will be adjusted. If the discomfort persists, the experimental session will be stopped.

There is a risk of falling during standing and walking from altering the frequency of the deep brain stimulator. Precautions will be taken to avoid falls and to minimize the risk of injury if a fall occurs.

WHAT ARE THE REPRODUCTIVE RISKS?

You may not take part in this study if you are pregnant.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Knowledge gained from the study may help to develop novel DBS stimulation protocols to improve balance and walking in people with Parkinson's disease.

WHAT OTHER OPTIONS ARE THERE?

Not participating in the study.

HOW WILL I BE INFORMED OF ADDITIONAL INFORMATION OR NEW FINDINGS?

The research team will inform you of any significant new findings developed during the course of this study that may affect your continued willingness to take part in the study. This may include changes in the procedures, the potential risks or benefits, or alternatives to participation.

WHAT ABOUT CONFIDENTIALITY?

Representatives from St. Joseph's Hospital & Medical Center, and regulatory authorities in the United States (such as the U.S. Department of Health and Human Services [DHHS] and the U.S. Food and Drug Administration [FDA]) and other countries may inspect your research records to check the progress of this study or to analyze the study data. Additionally, the Institutional Review Board for Human Research (IRB) at St. Joseph's Hospital & Medical Center, a committee that oversees the conduct of this study, may inspect your research records.

Although absolute confidentiality cannot be guaranteed, strict security will be in place to ensure that your research records are kept private. When possible, all information included in your research records that could be used to directly identify you will be coded by the research team prior to disclosure to the persons or parties listed above. The investigator will maintain the key that links the code to you, and only he will have access to the key. However, coding is not possible in some cases. For example, representative regulatory authorities, or the IRB, may require your name or date of birth. In this situation it would not be possible to withhold this identifying information.

The results of this research study may be published in scientific journals and/or may be presented at scientific meetings, but your identity will not be revealed.

WHAT ARE THE COSTS?

You or your insurance will not be billed for charges related to research-related procedures.

IS THERE COMPENSATION FOR PARTICIPATING?

You will not be compensated (paid) for taking part in this study.

WHAT HAPPENS IF I AM INJURED WHILE PARTICIPATING IN THIS STUDY?

If you believe that you have suffered a research-related injury, notify Dr. Lieberman at (602) 406-6262 immediately. St. Joseph's Hospital & Medical Center will provide treatment (including first aid, emergency treatment, and follow-up care) as needed. All related charges will, however, be billed to you or your insurance.

Dr. Lieberman, or St. Joseph's Hospital & Medical Center will not provide compensation (such as lost wages, lost time, or discomfort) to subjects who are injured as a result of participation in this study. This, however, does not waive your rights in the event of negligence.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this research study is voluntary, and refusal to take part will involve no penalty or loss of benefits to which you are otherwise entitled. You may stop taking part in the study at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to stop taking part, you must immediately notify Dr. Lieberman of your decision in writing.

The investigator(s) or regulatory authorities may stop your participation in this study at any time without regard to your consent. Some reasons your participation may be stopped are:

- If you do not follow the instructions of the research team.
- The investigator decides it is in the best interest of your health and welfare.
- The study is stopped.

WHOM DO I CALL IF I HAVE QUESTIONS?

If you have any questions about this research study or your participation in it, please feel free to ask the questions now. If you think of questions later or have concerns about your participation, please call Dr. Lieberman at (602) 406-6262 or write to St. Joseph's Hospital & Medical Center, Barrow Neurology Clinics, 500 W. Thomas Rd., Ste. 720, Phoenix, AZ 85013.

If you have any questions about your rights as a research subject or about the Institutional Review Board for Human Research (IRB) at St. Joseph's Hospital & Medical Center which reviewed this Informed Consent/Authorization document for compliance with federal guidelines, please call the IRB at (602) 406-3195 or write to: IRB Coordinator, Department of Research Administration, St. Joseph's Hospital & Medical Center, 350 W. Thomas Rd., Phoenix, AZ 85013.

CONSENT FOR PHOTOGRAPHY AND VIDEOTAPE

With your permission we would like to photograph and/or videotape you during your participation in this research study and use these records with your face shown in research presentations as well as scientific and educational publications (including but not limited to newspapers, television and/or radio broadcasts, books, brochures, magazines, project-related web sites, and motion pictures). Your name or other direct identifiers (such as your medical record number) will not be used in these research presentations and publications. Only a unique code that is assigned to you by the research team will identify your records.

Your decision to be photographed and/or videotaped during your participation in this study is voluntary. Refusal to be photographed and/or videotaped will involve no penalty or loss of benefits to which you are otherwise entitled, and will not affect your participation in the study.

If you agree to be photographed and/or videotaped, you may change your mind at any time. Please simply inform the investigator of your decision.

STATEMENT OF CONSENT FOR PHOTOGRAPHY AND VIDEOTAPE

Please read each sentence below and initial the applicable section. If you have any questions, please talk to the research team.

_____ **Yes**, I agree to be photographed and/or videotaped during my participation in the study. I understand that my records may be used in research presentations as well as scientific and educational publications, including project-related web sites.

_____ **No**, I do *not* agree to be photographed and/or videotaped during my participation in the study.

STATEMENT OF CONSENT

You are voluntarily deciding whether or not to participate in the research study described in this consent form. Your signature below indicates that you have read and understand the information provided, and that you have decided to participate. You will receive a copy of the signed informed consent document.

Printed Name of Subject or Subject’s Legal Representative

Signature of Subject or Subject’s Legal Representative

Date / Time

If the subject’s legal representative signed above, please print the subject’s name below, explain the representative’s relationship to the subject, and include a description of the representative’s authority to act on behalf of the subject. Additionally, please provide the reason the subject lacks the capacity to provide informed consent.

Printed Name of Subject

If the subject or the subject’s legal representative is illiterate, an impartial party must witness the informed consent process and print and sign their name below.

Printed Name of Impartial Witness

Signature of Impartial Witness

Date / Time

The person obtaining informed consent must print and sign their name below.

Printed Name of Person Obtaining Informed Consent

Signature of Person Obtaining Informed Consent

Date / Time

INVESTIGATOR'S STATEMENT

I attest that I, or my representative, discussed this study with the above named participant or legal representative. This person had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participate in this study.

Signature of Investigator

Printed Name of Investigator

Date