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Computational Modeling of 60 Hz Subthalamic Nucleus Deep Brain Stimulation for Gait Disorder in Parkinson's Disease

Informed Consent Document

23April2021

Northwell Health

Campus: North Shore University Hospital

Consent for Participation in a Research Study

Study Title: Computational modeling of 60Hz STN DBS for gait disorder in Parkinson's disease

Principal Investigator: Ritesh Ramdhani, MD

Sponsor: National Institutes of Health (NIH)

About this research
You are being asked to participate in a research study.

This consent form will give you information about the study to help you decide whether you want to participate. Please read this form, and ask any questions you have, before agreeing to be in the study.

Important Information
This information gives you an overview of the research. More information about these topics may be found in the pages that follow.

Why am I being asked to provide my consent?	This is a research study, which is different than personal medical care. Scientists do research to answer important questions which might help change or improve the way we do things in the future.
Do I have to join this research study?	No. Taking part in this research study is voluntary. You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled.
Why is this research study being done?	The goal of this research is to further our understanding and application of low frequency subthalamic deep brain stimulation in Parkinson's patients with gait disorder.
What will happen to me during the study?	Investigators will collect demographic information, medical history, DBS surgical history, and medication information from you, and if necessary, by reviewing your medical records. This study will be conducted in two phases: <u>Phase I:</u> An evaluation of your walking and limb movements using wearable sensor devices will occur after overnight withdrawal of your Parkinson's medications and one hour after administration of levodopa. If you currently have a deep brain stimulator (DBS), it will be turned off for these assessments. <u>Phase II:</u> Your DBS will be reprogrammed in both high and low frequencies. Evaluation of your gait and limb movements will be conducted as in Phase I in both the unmedicated and medicated states for the different stimulation settings. At the end of the study assessments, you will return to your initial programming settings and resume your medication regimen as per your standard of care.

How long will I participate?	This study will take place in 2 to 3 Study Visits: Chronic DBS Patients: Study Visits will range from 1-4 weeks Preoperative DBS patients: Study Visits will range from 12-15 weeks
Will taking part expose me to risks?	Your Parkinson's medications will be withdrawn the night before the study visit(s). Withdrawal of Parkinson's medications will increase your motor symptoms (e.g., muscle stiffness, tremor, slowness, and/or walking problems), which can put you at risk of falling. During the study, you will be administered levodopa in the form of carbidopa/levodopa 25-100 tablet(s). Oral levodopa can cause side effects such as nausea, lightheadedness, fatigue, and low blood pressure. During the study, your DBS will be adjusted, which can cause possible transient sensory and motor symptoms (e.g., tingling, pulling sensations)
Are there any benefits to participation?	This research may not benefit you directly, but you will have the opportunity to have your motor symptoms comprehensively assessed with wearable sensors. Furthermore, information we learn about this disease or condition may help patients in the future.
What are my alternatives to participation?	If you do not join this study, you have other choices for management. Talk to your doctor about your choices. Your other choices may include: • Standard management, including routine tests, medical therapies and follow-up • Another research study if you meet study qualifications • No treatment Your doctor can also tell you the important risks and benefits associated with the alternative treatment.

Please review the rest of this document for details about these topics and additional things you should know before making a decision about whether to participate in this research.

Introduction
You are being asked to join a research study. The purpose of a research study is to answer specific questions, sometimes about the safety of a drug or device and how well it works. Being in a research study is different from being a patient. When you are a patient, you and your doctor have freedom in making decisions about your healthcare. When you are in a research study, the researcher will follow the rules of the research study as closely as possible, while monitoring your health.

You do not have to be in this study to receive medical care. You should ask questions before you decide if you want to participate. You can also ask questions at any time during the study.

Why is this research study being done?
The purpose of this research study is to further our understanding and application of low frequency deep brain stimulation in Parkinson's patients with gait disorder.

Why is this research?
This is a research study because the investigators are trying to determine whether there is benefit to certain gait problems in Parkinson's patients with DBS who are switched from high frequency to low

frequency settings. In addition, the investigators seek to determine the effects of both levodopa and low frequency DBS on gait.

You are being asked to participate in this study because you have been diagnosed with Parkinson's disease and either (1) have chronic bilateral deep brain stimulators implanted into the brain target called the subthalamic nucleus (STN-DBS) or (2) will be undergoing STN-DBS implantation.

How many people will take part in this study?
This research study plans to enroll 30 participants.

How long will you be in this study?
This study will be conducted in two phases: Phase I is expected to last 2-3 hours. If you currently have DBS, you will continue on to Phase II during the same study visit. If you are unable to complete Phase II, you may complete it during another 1-2 study visits within 4 weeks. If you are under the clinical care of the PI (Dr. Ramdhani) you may have the option to complete part of the study during a routine clinical visit. The study coordinator can evaluate whether this is a convenient option for you and explain how this may change the order of testing and/or the timeline.

If you are in the DBS preoperative stage, Phase II will take place 12-15 weeks from the date of your standard of care initial programming visit.

What will happen in this research study?
Study investigators will collect demographic data, medical history, DBS surgical history, and medication history from you and if necessary, by reviewing your medical records.

The study is conducted in 2 phases as described below:

Phase I

- You will be instructed to take your last dose of anti-parkinsonian medication(s) the night before or approximately 12hrs prior to the study visit. If you have DBS, your stimulator will be turned off for approximately 50 minutes prior to starting the assessments.
- You will then be outfitted with small full body sensor devices and will be guided by the research coordinator to conduct several walking tasks.
- After the walking assessment, the presence of hand tremors and speed of your limb movements will then be evaluated using small sensors affixed to your finger and ankle. You will be asked to follow tasks displayed on a tablet device in order to conduct these evaluations.
- A movement disorders specialist will then conduct the Movement Disorders Society-Unified Parkinson's Disease Rating Scale—specific limb and gait movements will be scored by clinical observation.
- Afterwards, you will be instructed to take carbidopa/levodopa 25/100mg at a dose that is approximately 1.5times your typical dose of your anti-parkinsonian medication. (You will not take more than 3 tabs of carbidopa/levodopa 25/100).
- When you are receiving the best benefit from the administered levodopa or 60 minutes after carbidopa/levodopa is given, you will then repeat the same sensor-based movement assessments. We will also conduct a brief (10 min) evaluation of your thinking and memory by asking a series of oral questions.
- If the effects of the carbidopa/levodopa begin to wear off before the study assessments have been completed, additional carbidopa/levodopa will be administered up to 1.5 times your typical dose of antiparkinsonian medication.

Phase II

- You will be instructed to take your last dose of anti-parkinsonian medication(s) the night before or approximately 12hrs prior to the study visit.
- Your weight will be taken.
- Reprogramming of your DBS in low and high frequency settings will be done by Dr. Ritesh Ramdhani for each of the 4 contact pairs for the 2 electrodes. The amplitude will be slowly raised until sustained sensory or motor side effects are produced in high frequency. The amplitude below the side effect threshold will be used for testing of each contact pair.
- Movement assessments akin to Phase I will be conducted for each contact pair in both high and low frequencies
- Assessment of the MDS-Unified Parkinson's Disease Rating Scale for each contact pair condition will also be conducted by a movement specialist through clinical observation.
- You will then be instructed to take carbidopa/levodopa 25/100mg at a dose that is approximately 1.5 times your typical dose of anti-parkinsonian medication. (You will not take more than 3 tabs of carbidopa/levodopa 25/100).
- When you are receiving the best benefit from the administered levodopa or 60 minutes after levodopa is given, you will then repeat the same sensor-based assessments for each contact pairs at both low and high frequencies.
- If the effects of the carbidopa/levodopa begin to wear off before the study assessments have been completed, additional carbidopa/levodopa will be administered up to 1.5 times your typical dose of antiparkinsonian medication.

If you already have STN-DBS, you will continue on to Phase II during the same study visit. If you are in the DBS preoperative stage, Phase II will be conducted 12-15 weeks after your initial programming.

Your programming settings will only change during the study visit. At the end of each study visit, you will return to your initial programming settings and resume your home medication regimen.

Washout Period
During this study, the medications you normally use for your Parkinson's disease will be withdrawn overnight. You will receive no medication. As a result, you will have an increase in symptoms including stiffness, tremor, slowness, shuffling and/or freezing episodes.

Drugs and Devices
Drug: Carbidopa/Levodopa 25-100 (Sinemet) is a tablet that is administered orally and approved for the treatment of Parkinson's disease.

Device: Deep brain stimulation (DBS) is FDA-approved for the treatment of Parkinson's disease with subthalamic nucleus (STN) being the commonest brain target implanted. Only patients who will be undergoing bilateral STN-DBS implantation as part of their standard of care or who already have bilateral STN-DBS will be eligible to participate. STN-DBS implantation will not be provided as a part of this study.

COVID-19 Prescreening and Testing
During the COVID-19 pandemic, several safety measures will be implemented to protect you and the study team. We will conduct a telephone preappointment screening within one week of the first scheduled study visit. Prescreening will include a list of standard questions related to COVID-19 to determine if you have any possible symptoms of COVID-19 or possible exposure. If you report

symptoms of or possible exposure to COVID-19, the first study visit may be postponed for 14 days. Once your prescreening is negative for COVID-19, you will be required to undergo COVID-19 testing approximately 72 hrs prior to the first study visit. Testing involves inserting a 6-inch long swab (like a long Q-tip) into the cavity between the nose and the mouth for 15 seconds and rotating it several times. The swabbing is then repeated on the other side of the nose to make sure enough material is collected. The swab is then inserted into a container and sent to a lab for testing. You will be informed of your test results and whether or not the study visit is confirmed or needs to be rescheduled. Repeat prescreening and COVID-19 testing may be required if your initial test result comes back positive for COVID-19. Preappointment screening will take place within 48 hrs of each subsequent study visit. Depending on the results of your screening, the study visit may be postponed or repeat COVID-19 testing may be required. Repeat COVID-19 testing may also be required if your study visits are scheduled over an extended period of time (more than 14 days). COVID-19 testing will be performed at a Northwell facility – a list of locations will be provided by the study coordinator. The cost of each COVID-19 test will be paid for by study funds. Please note if you are fully vaccinated against COVID-19, you will not need to undergo COVID-19 testing unless you report possible symptoms of the virus during one of the preappointment screenings. Proof of vaccination may be requested.

What are the risks of the research study? What could go wrong?
Anytime Parkinson's medications are withdrawn for 12hrs, you will experience increased motor symptoms including shuffling or freezing of gait if already present, which can place you at risk of falling.

The risks of administration of carbidopa/levodopa 25/100mg includes nausea, lightheadedness, and lowered blood pressure.

During the DBS adjustments, transient stimulation induced sensory (e.g., paresthesia) or motor symptoms (e.g. muscle contractions or pulling sensations) may occur as amplitudes are incrementally raised for each electrode contact during Phase II.

There is a small risk of loss of private information; however, there are procedures in place to minimize this risk.

The COVID-19 test can be uncomfortable and may induce tearing, coughing, and sneezing during the procedure.

Unknown Side Effects
As with any changes to DBS settings, there might be side effects that are unknown at this time. You will be closely watched for side effects. You should report any unusual events to the study staff.

What are the benefits of this research study?
This research may not benefit you directly, but you will have the opportunity to have your gait comprehensively assessed. Furthermore, information we learn about this disease or condition may help patients in the future.

Will I receive my results?
We may learn things about you from the study activities which could be important to your health or to your treatment; however, we will not share this information with you.

Drug Availability after Completion of Study

After study completion, participants will resume their home medication regimen (including their anti-Parkinson's drugs) as per their standard of care.

If you do not want to take part in this research study, what are your other choices?
If you do not join this study, you have other choices for treatment. Talk to your doctor about your choices. Your other choices may include:

- Another research treatment
- Standard treatment
- No treatment
- Comfort care
- Treatment provided on this study

Are there any costs for being in this research study?
You will not have any added costs from being in this study.

Will you receive any payments for participating in this research study?
You will be compensated $50 per visit for your time for being in this study. If you do not complete the entire study, you will be paid for the number of visits that you have completed. Payment can be made at the end of each study visit or as a lump sum once your participation is complete. Upon request, transportation can be provided or the cost of which reimbursed. Receipts may be required and costs must be within reason. The study coordinator can review these options with you in advance of participation.

If the total payment you receive from Northwell Health, during this year, is equal to $600 or more, the payment is required to be reported to the IRS. Although this study does not pay $600, if you participate in other Northwell Health studies, it is possible your payment could end up totaling $600. If this occurs, the payment you receive on this study will be reported to the IRS. In this case, you will be issued a 1099 form and be required to provide your social security number at that time for reporting purposes. You will also be responsible for reporting this income while filing your tax return.

What happens if you are injured while participating in this study?
If you are hurt from being in the study, you will receive medical care and treatment as needed from Northwell Health. However, you will be responsible for the costs of such medical treatment, directly or through your medical insurance or other forms of medical coverage. No money will be given to you.

What are your rights as a research participant?
Your participation in this project is voluntary. The quality of your medical care will be the same, whether you join, refuse to join, or decide to leave the study.

If you do not join the study, you will not be penalized or lose benefits to which you are entitled. If you join the study, you may withdraw at any time without prejudice to your future care at Northwell Health. Follow-up examinations may be needed to assure your well-being.

Could you be taken off the study before it is over?
It is also possible that your participation in this study may end without your consent. This decision may be made by a researcher, study sponsor or the Institutional Review Board (IRB-the committee that oversees research at this institution).

Reasons for withdrawal may include:

- failure to follow instructions,
- failure to show up for study visits,

- it is not in your best interest to continue on this study, or
- the study is stopped.

If you withdraw from this study or if you are withdrawn from the study, any data (or samples) already collected will continue to be used. However, no new data will be collected.

What happens if new information is learned?
You will be told of any new findings that may change your decision to continue to participate. Your consent to continue to take part in this study may be obtained again.

What will happen with the information we collect as part of this research study?
Any study information about you will be kept private and will only be given out with your permission. If the results of this study are published, your name will not be used. Your research records will be private to the extent allowed by law. In order to make sure the research is done properly, the Human Research Protection Program (the group of people that oversees research at this institution) may need access to information about your participation in this study.

What information will be collected and used for this study?
If you agree to be in this study, we will collect health information that identifies you. We may collect the results of tests, questionnaires and interviews. We may also collect information from your medical record. We will only collect information that is needed for the research. This information has been described in this consent form. If you sign this consent form, you are giving us permission to collect, use and share your health information. This permission is called authorization. If you do not want to provide authorization, then you cannot participate in this research study.

Who else will see your information?
Study records that identify you will be kept private. You will not be identified in study records or publications disclosed outside Northwell Health, except as detailed below.

The following reviewers may access your study and medical records to make sure that this study is being done properly:

- Representatives from Federal and state government oversight agencies, such as the Department of Health and Human Services and the Food and Drug Administration.
- Representatives from Northwell Health's Human Research Protection Program (a group of people that oversee research at this institution)
- Representatives from the National Institutes of Health (NIH).

Data collected as part of this research study will be shared with our collaborators at the University of Tennessee, Knoxville. To protect your privacy, this data will be deidentified, meaning it will be stripped of all identifying information such as your name, date of birth, and address, prior to transfer.

We will do our best to protect the privacy of your records but it is possible that once information is shared with people listed on this form, it may be released to others. If this happens, your information may no longer be protected by the federal law.

In the future, we may publish results of this study in scientific journals and may present it at scientific meetings. If we do we will not identify you.

If the researchers learn about potential serious harm to you or someone else or other public health concerns, it will be shared with the appropriate authorities.

Will you be able to access your records?
If your research records are used for decisions related to your clinical care, then you have the right to review this information and request changes. This is limited to information about your treatment, and does not include information related to procedures or tests that are for research purposes only. You may access this information only after the study analysis is complete. You have the right to know who has and who will see your records. To request this information, please call the Human Research Protection Program at **(516) 465-1910**.

How long will your health information be kept?
There is no limit on the length of time we will keep your information for this research because it may be analyzed for many years. We will keep it as long as it is useful, unless you decide you no longer want to take part or we close the study. You are allowing access to this information indefinitely.

Can you change your mind?
If you change your mind about being in the study, you may withdraw at any time. If you want us to stop collecting your health information, you need to send a letter to the researcher at the following address:

Dr. Ritesh Ramdhani
Northwell Health – Neuroscience Institute
611 Northern Boulevard
Great Neck, NY 11021

Your letter needs to say that you have changed your mind and do not want the researcher to collect and share your health information. You may also need to leave the research study if we cannot collect any more health information. We may still use the information we have already collected. We need to know what happens to everyone who starts a research study, not just those people who stay in it.

Will information about this study be available to the public?
A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

Certificate of Confidentiality
To help us protect your privacy, this research is covered by a Certificate of Confidentiality from the US Department of Health and Human Services (DHHS). The Certificate of Confidentiality means that researchers cannot be forced to identify you, even under a court subpoena. The Certificate does not mean the Secretary of DHHS approves or disapproves of the project. It adds special protection for the research information about you. You should know, however, that researchers may provide information to appropriate individuals or agencies if harm to you, harm to others or child abuse becomes a concern. A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. However, if an insurer, employer or other person learns about your participation and gets your consent to receive research information, then the researchers will have to provide your information.

Will my information be used for research in the future?
Information collected from you for this research may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify you will be removed before any information or specimens are shared. Since identifying information will be removed, there will

not be an additional consent for future research. By consenting to participate in this study you are agreeing to allow your de-identified data to be used by future researchers without additional consent.

Does the investigator of this study receive money if you take part?
The investigators on this study receive money to conduct the study, but do not financially benefit from your participation. The money they receive is to pay them back for the costs of conducting the research study. Funding for this research study is provided by the National Institutes of Health (NIH). If your doctor is an investigator for this study, s/he is interested in both your healthcare and the conduct of this research. You do not have to take part in a research study conducted by your doctor.

Who can answer your questions about this study?
If you have any questions about the study, you may call Dr. Ramdhani at **(516) 325-7000**. If you have questions about side effects or injury caused by research you should call Dr. Ramdhani at **(516) 325-7000**. If you need emergency care, dial 911 or go to the nearest Emergency Room. If you have questions about your rights as a research participant, or concerns about being in the study, or would like to offer input, you may contact the Office of the Institutional Review Board (the committee that oversees research at this institution) at **(516) 465-1910**. A signed copy of this consent form will be given to you.

[Signature Page Follows]

Summation/Signature
You have read the above description of the research study. You have been told of the risks and benefits involved and all your questions have been answered to your satisfaction. A member of the research team will answer any future questions you may have. You voluntarily agree to join this study and know that you can withdraw from the study at any time without penalty. By signing this form, you have not given up any of your legal rights.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____
Signature of Witness Date

_____
Printed Name of Witness
(Note: A witness can be a member of the research team, but cannot be the same person signing consent as the investigator)

Investigator's Statement
In addition to advising the above participant of other forms of treatment and therapy which are appropriate, I have offered an opportunity for further explanation of the risks and discomforts which are, or may be associated with this study and to answer any further questions relating to it.

_____ _____
Investigator's signature **Date**

_____
Investigator's printed name