Investigating Central Neurophysiologic Correlates of Non-Motor Symptoms of Parkinson's Disease

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NIH-FDA Phase 2 and 3 IND/IDE Clinical Trial Protocol Template

INVESTIGATING CENTRAL NEUROPHYSIOLOGIC CORRELATES OF NON-MOTOR SYMPTOMS OF PARKINSON'S DISEASE

Short Title: Parkinson's disease TMS+EEG study

Protocol Number: 23-0751

Principal Investigator: Miriam Sklerov, MD MS

Sponsor: N/A

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Version Number: 2.1.0

3 December 2021

Summary of Changes from Previous Version: N/A

Affected Section(s)	Summary of Revisions Made	Rationale
Justification for dose	Allowing for fewer repetitions of stimulation trains	This will improve tolerability and participant retention

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and
clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

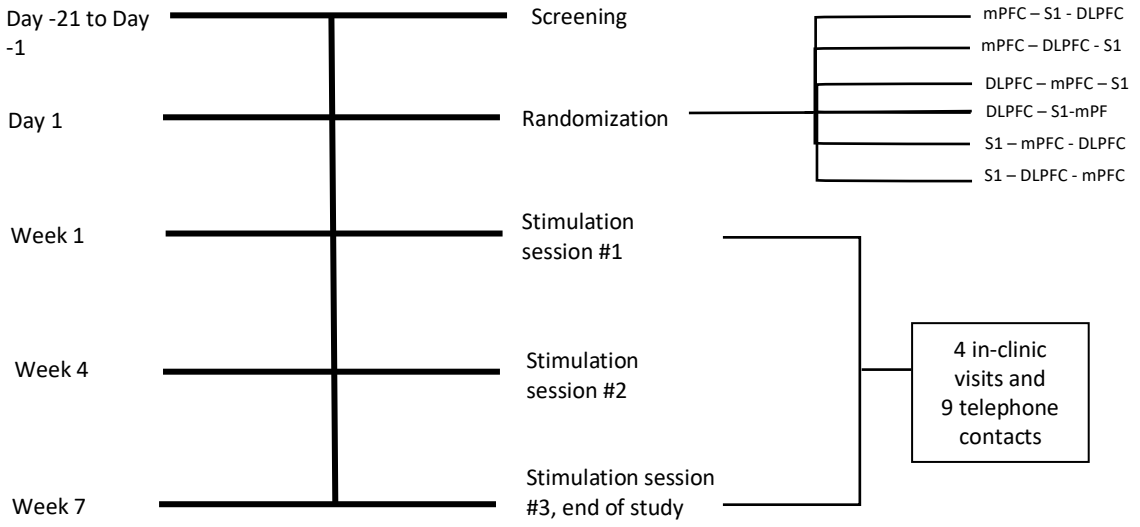
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**Investigating Central Neurophysiologic Correlates of Non-motor Symptoms of Parkinson's Disease**
Study Description:	This is a randomized, single-blinded, triple crossover study with 3 one-day iTBS, separated by a wash-out period of 3 weeks[1], sufficient for physiologic effects of one session of iTBS to return to baseline. Participants will undergo accelerated iTBS to 3 brain regions: medial prefrontal cortex (mPFC) (experimental site), dorsolateral prefrontal cortex (DLPFC) (alternative experimental site), or primary sensory cortex (S1) (control site). Participants will complete symptom questionnaires, neurologic examination and cognitive assessments, and orthostatic vital signs recording before and after each brain stimulation session.
Objectives:	
	Primary Objective: Aim 1: To determine whether iTBS to the medial prefrontal cortex (mPFC) produces more robust changes in frontal midline theta (FMT) EEG power in people with Parkinson's disease compared with stimulation at the dorsolateral prefrontal cortex (DLPFC) or the primary sensory cortex (S1). Aim 2: A. To evaluate FMT power correlations with burden of autonomic symptoms in Parkinson's

	disease. B. To evaluate FMT power correlations with burden of depression symptoms in Parkinson's disease Exploratory Objectives: Aim 3: To evaluate the effect of iTBS on autonomic symptoms one day after, and 4 days after stimulation. Aim 4: To evaluate the effect of iTBS on depression symptoms one day after, and 4 days after stimulation. Aim 5: To create a database of EEG and TMS data in people with PD for the purpose of future research into novel neurostimulation therapies for PD NMS
Outcome measures:	Primary Outcome Measures: Aim 1: Degree of change of frontal midline theta power on EEG after brain stimulation. Aim 2: Degree of association between autonomic symptoms and frontal midline theta EEG power; Degree of association between depression symptoms and frontal midline theta EEG power. Exploratory Outcome measures: Aim 3: Change in SCOPA-AUT and OHQ from before to after iTBS; Aim 4: Change in BDI-II from before to after iTBS
Study Population:	Study population will be men and women of all demographic groups with Parkinson's disease age 50-90 years who do not have a diagnosis of severe dementia who reside in North Carolina.
Phase:	N/A (pilot study)
Description of Sites/Facilities Enrolling Participants:	UNC Medical Center will be the only participating site.
Description of Study Intervention:	Participants will undergo three sessions of intermittent theta-burst stimulation (iTBS), an FDA-approved therapy for treatment of depression, while at rest. Stimulation will be delivered to the medial prefrontal cortex, dorsolateral prefrontal cortex, and the primary sensory cortex (one site per stimulation session). Electroencephalography will be collected immediately before and after stimulation, and questionnaires and clinical evaluations will be completed before and after stimulation sessions.
Study Duration:	Three years
Participant Duration:	The total number of contacts per subject, including in-person, telephone, email, and mailings will range from 4-15. Duration of each contact will range from 10 minutes – 2.5 hours. Total duration of an individual subject's participation is expected to be 5-6 hours for informed consent, initial clinical evaluation and screening, questionnaires, and EEG/TMS visit.

1.2 SCHEMA


Day -21 to Day -1
Screening
Day 1
Randomization
mPFC – S1 - DLPFC
mPFC – DLPFC - S1
DLPFC – mPFC – S1
DLPFC – S1-mPF
S1 – mPFC - DLPFC
S1 – DLPFC - mPFC
Week 1
Stimulation session #1
Week 4
Stimulation session #2
Week 7
Stimulation session #3, end of study
4 in-clinic visits and 9 telephone contacts

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Screening Day -7 to -1**	**Visit 1, Week 1**	Telephone visit, Week 1+1 day	Telephone visit, Week 1+4 days	**Study Visit 2 Week 4**	Telephone visit, Week 4+1 day	Telephone visit, Week 4+4 days	**Study Visit 3 Week 7**	Telephone visit, Week 7+1 day	Telephone visit, Week 7+4 days
Informed consent	X									
Demographics	X									
Medical history	X									
Randomization	X									
iTBS + EEG		X			X			X		
Concomitant medication review	X	X			X			X		
MDS-UPDRS	X	X			X			X		
Montreal Cognitive Assessment	X									
Orthostatic Vital signs	X	X			X			X		
Adverse event review and evaluation		X	X	X	X	X	X	X	X	X
Freezing of Gait questionnaire	X	X			X			X		
Epworth Sleepiness Scale	X									
REM sleep disorder questionnaire	X									
OHQ and SCOPA-AUT		X	X	X	X	X	X	X	X	X
Beck Depression Inventory - II		X	X	X	X	X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Parkinson's disease (PD) is the second most common neurodegenerative disease in the US. Autonomic dysfunction (AuD) and depression are common non-motor symptoms of PD which are strongly predictive of poor disease outcomes, and lack effective treatments. Non-invasive brain stimulation, such as transcranial magnetic stimulation (TMS), is a safe, effective, FDA-approved treatment for major depression disorder and psychotic disorders, and is undergoing study for treatment of motor symptoms

in PD. Intermittent theta-burst stimulation (iTBS) is a TMS paradigm that has been found to be as effective in fewer treatments than traditional TMS paradigms, and is FDA approved to treat major depression disorder. Few studies have investigated the use of any neurostimulation tool to treat non-motor symptoms of PD. The overarching objective of this study is to determine the feasibility of using transcranial magnetic stimulation to treat AuD and depression in PD. Based on preliminary evidence implicating brain structures (the medial prefrontal cortex and the anterior cingulate gyrus) in both AuD and depression in PD, the central hypothesis in this study is that the medial prefrontal cortex is a major driver of AuD and depression in PD, and an effective brain stimulation target.

2.2 BACKGROUND

Parkinson's disease (PD) is a common, progressive neurodegenerative disease characterized by a combination of motor and non-motor symptoms that is made debilitating by both motor and non-motor symptoms. The prevalence of PD in North Carolina (NC) is about 400 cases per 100,000 among Medicare beneficiaries [1]. Non-motor symptoms (NMS) of PD are common and associated with significant morbidity and mortality[2]. Autonomic nervous system dysfunction, which causes symptoms such as orthostatic hypotension (OH), constipation and gastroparesis, urinary retention or incontinence, and sexual dysfunction, affects more than half of PD patients [2-4], and is strongly predictive of poorer quality of life and overall prognosis [5, 6]. Similarly, refractory depression in PD is a common and disabling NMS[3]. Unfortunately, both of these NMS have limited treatment options.

Both invasive (Deep brain stimulation, DBS) and more recently non-invasive (transcranial magnetic stimulation, TMS) neurostimulation are used for the clinical and/or experimental treatment of motor symptoms but have yet to be thoroughly investigated in the context of NMS in PD. The development of brain stimulation treatments requires an understanding of structural and functional brain networks[4–6]. The feasibility of such rational design of brain stimulation is made possible with the growing understanding of brain network dysfunction in PD[7,8]

The hypothalamus (HTH), anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), and insula play key roles in the central autonomic network (CAN), by modulating autonomic function[9], and in the limbic network where they regulate emotion. Pathology is found in these areas in PD[10]. Functional and structural brain MRI studies in PD consistently implicate the CAN, including the mPFC, as a substrate in AuD[11–14]. Other key nodes of both autonomic and depression networks, such as the dorsolateral prefrontal cortex (DLPFC), remain spared by PD pathology[10]. MRI abnormalities in the ACC and mPFC in PD depression mirror findings in PD AuD[15–19].

Our group used resting state functional MRI (rs-fMRI) to study brain correlates of autonomic symptoms in PD[11]. In a publicly-available database of *early* PD, we found reductions in hypothalamic functional connectivity in PD with high burden of autonomic symptoms[11]. Our preliminary brain MRI data in people with PD points to central dysregulation in PD autonomic dysfunction, particularly implicating the HTH, ACC, and mPFC (**Fig. 1**, Appendix). Interestingly, these regions of the CAN are also important nodes of the limbic network, implicated in the regulation of mood and emotion[20].

Electroencephalography (EEG) provides high temporal resolution for the measurement of brain network dynamics and their modulation by non-invasive brain stimulation[21–23]. EEG correlates of autonomic function in the neurologically healthy localize to frontal midline areas and associate with theta oscillations (4-8 Hz)[24–28]. The majority of these studies are primarily focused on heart rate variability (HRV) responses,

thought to represent sympathetic and parasympathetic autonomic nervous system function, though this is agreed to be an indirect measure and remains controversial[29]. There are no studies investigating EEG correlates of AuD in PD to our knowledge. *I hypothesize that altered frontal midline theta (FMT) oscillations are a marker of AuD and thus a target for non-invasive brain stimulation*.

TMS is a form of non-invasive neurostimulation used to modulate brain networks. TMS, effective when applied to the dorsolateral prefrontal cortex (DLPFC) or mPFC[30], is FDA approved for the treatment of major depressive disorder (MDD). Theta-burst TMS (TBS) was recently developed for treatment of neurologic and psychiatric symptoms. TBS has equivalent if not longer-lasting effects compared with traditional repetitive TMS (rTMS)[31,32]. Continuous TBS is thought to have inhibitory effects while intermittent TBS (iTBS) has excitatory effects[33]. In MDD, iTBS is equivalent or more effective compared with rTMS and has recently been FDA approved[34,35].

Studies of effects of TMS on autonomic function exhibit mixed results[36]. Four studies, including only one study in PD, found that DLPFC stimulation has a positive effect on autonomic function or symptoms[37–40]. There has been one study investigating the effect of iTBS on autonomic function[41]. In this study, iTBS was applied to the DLPFC in subjects with MDD while concordant HRV was assessed. Intriguingly, this study reported significant heart rate decelerations in the iTBS groups compared to sham (placebo) stimulation, indicating autonomic nervous system engagement. Interestingly, there are no published reports of TMS targeted to CAN structures to probe autonomic function. Taken together, the literature suggests iTBS applied to CAN network nodes, particularly the mPFC which is implicated in PD pathology as well as depression and AuD, may improve AuD by restoring FMT oscillations and top-down control of the CAN.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Psychological risk

Breach of confidentiality: While there is the potential for breach of confidentiality, all study personnel will minimize this risk to study subjects. All data will be de-identified before analysis, and any treatment outcome data will be treated with strict confidentiality. Electronic data will be stored on password-protected servers within the UNC School of Medicine and any hard-copy data will be stored in locked cabinets in locked offices in the UNC Department of Neurology.

Risk of embarrassment: There is a risk of distress or embarrassment for the participant if they have difficulty performing well on cognitive and physical tests. The research team will take extra care to perform these evaluations in a judgement-free manner, and provide appropriate encouragement to the participant, as is routinely done in a clinical setting. Additionally, we will request that the participant be alone in the examining room with the examiner, without care partner or other persons in the room, while performing these examinations, unless otherwise preferred by the participant, to help minimize this risk.

Physical risk:

Risk of injury and discomfort: Transcranial magnetic stimulation (TMS) is FDA approved for treatment of many neuropsychiatric symptoms in the USA. TMS is not related to electroconvulsive therapy, which applies many orders of magnitude higher stimulation electrical current. The level of electrical stimulation produced by TMS is within the range of activity that is endogenous to the brain. Furthermore, the intensity of stimulation is calibrated to the sensitivity of the individual participant such that the level of stimulation is matched to the naturally occurring brain activity in that individual. In order to monitor side effects, participants will be asked to complete an adverse effects from stimulation questionnaire after each stimulation session. Research personnel supervising the stimulation sessions will also check with the participant periodically during the stimulation session to ensure the participant is comfortable. If any side effects occur that are rated by the participant as stronger than "moderate", or the participant reports severe discomfort during stimulation, the stimulation session will be terminated immediately.

There is a very low theoretical likelihood that stimulation of neuronal circuits can lead to epileptic discharges. To minimize this risk, we will exclude potential participants with personal history of epilepsy or risk factors for epilepsy. If abnormalities on EEG or a seizure is witnessed during the course of the study, a referral will be made to the UNC Department of Neurology for follow up, and/or the participant's treating neurologist will be notified. In the unlikely event that a seizure with loss of consciousness is witnessed during the course of the study, the participant will be instructed not to operate a motor vehicle until cleared by the Department of Motor Vehicles (DMV).

One of the scales that will be administered assess symptoms of depression (BDI-II questionnaire). Upon receiving this questionnaire, the research coordinator will check the scoring for this assessment. If the patient scored in the "severe" range (>28 points), the PI will be notified, and appropriate immediate referrals for care will be made per the patient's preference. The participant's treating neurologist or primary care physician will be immediately notified via a phone call. 911 will be called in the event that a participant is threatening to hurt themselves or others.

Hearing loss is a potential risk of TMS. This is a rare and moderate to severe risk. To protect against hearing loss, ear plugs are worn by the participant and by the technical operator during stimulation sessions.

There have been rare reports of mood episode switches in people with Bipolar disorder after iTBS (from depressed mood to mania or hypomania). This is a rare but potentially severe.

Other potential risks associated with participation in this study include:

- Scalp irritation irritation due to application of the electroencephalogram electrodes to the scalp. This is infrequent and mild.
- Headache and dizziness are rare and mild
- Muscle tightness and twitching during stimulation are very common and mild

2.3.2 KNOWN POTENTIAL BENEFITS

The primary potential benefit for research subjects in this study is the benefit of adding to medical knowledge. There is a potential benefit for symptoms of depression as well.

3 OBJECTIVES ANDOUTCOME MEASURES

OBJECTIVES	Outcome Measures
Primary	
Aim 1: To determine whether iTBS to the medial prefrontal cortex (mPFC) produces more robust changes in frontal midline theta (FMT) EEG power in people with Parkinson's disease compared with stimulation at the dorsolateral prefrontal cortex (DLPFC) or the primary sensory cortex (S1). Aim 2: A. To evaluate FMT power correlations with burden of autonomic symptoms at baseline before stimulation in Parkinson's disease. B. To evaluate FMT power correlations with burden of depression symptoms at baseline before stimulation in Parkinson's disease	Aim 1: Degree of change of frontal midline theta power on EEG after brain stimulation. Aim 2: Degree of association between autonomic symptoms and frontal midline theta EEG power; Degree of association between depression symptoms and frontal midline theta EEG power.
Exploratory	
Aim 3: To evaluate the effect of iTBS on autonomic symptoms one day after, and 4 days after stimulation. Aim 4: To evaluate the effect of iTBS on depression symptoms one day after, and 4 days after stimulation. Aim 5: To create a database of EEG and TMS data in people with PD for	1. Change in SCOPA-AUT and OHQ from before to after iTBS; 2. Change in BDI-II from before to after iTBS

OBJECTIVES	Outcome Measures
the purpose of future research into novel neurostimulation therapies for PD NMS	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, triple crossover (three stimulation sites which will be done at separate study visits), single-blinded study design. The difference in stimulation site precludes double-blinding as the study personnel will be aware of the difference in location while running the experiment.

Aim 1: To determine whether iTBS to the medial prefrontal cortex (mPFC) produces more robust changes in frontal midline theta (FMT) EEG power in people with Parkinson's disease compared with stimulation at the dorsolateral prefrontal cortex (DLPFC) or the primary sensory cortex (S1).
Hypothesis:

H_0: Mean change in Frontal midline theta power on electroencephalogram after iTBS to the medial prefrontal cortex will be equal to FMT changes after dorsolateral prefrontal cortex stimulation and stimulation of S1.

H_1: Mean change in Frontal midline theta power on electroencephalogram after iTBS to the medial prefrontal cortex will be greater than FMT changes after dorsolateral prefrontal cortex stimulation and stimulation of S1.

Aim 2A: To identify associations between symptoms of autonomic dysfunction at baseline before stimulation and frontal midline theta band frequency on electroencephalogram.

H_0: There is zero correlation between severity of autonomic dysfunction symptoms at baseline before stimulation with frontal midline theta power at baseline on electroencephalogram.

H_1: There is a negative correlation between severity of autonomic dysfunction symptoms at baseline before stimulation with frontal midline theta power at baseline on electroencephalogram.

Aim 2B: To identify associations between symptoms of depression at baseline before stimulation and frontal midline theta band frequency on electroencephalogram.
Hypothesis:

H_0: There is no correlation between severity of depression symptoms at baseline before stimulation with frontal midline theta power on electroencephalogram at baseline.

H_1: There is negative correlation between depression symptoms at baseline before stimulation with frontal midline theta power on electroencephalogram at baseline.

Exploratory objectives
Aim 3: To evaluate the effect of iTBS on autonomic symptoms one day after, and 4 days after stimulation.
Hypothesis:

H_0: Change in SCOPA-AUT and OHQ will be zero one day after stimulation and 4 days after stimulation compared to pre-stimulation.

H_1: Change in SCOPA-AUT and OHQ will be less than zero one day after stimulation and 4 days after stimulation.

Aim 4: To evaluate the effect of iTBS on depression symptoms one day after, and 4 days after stimulation.
Hypothesis:

H_0: Change in BDI-II will be zero one day after stimulation and 4 days after stimulation compared to pre-stimulation.

H_1: Change in BDI-II will be less than zero one day after stimulation and 4 days after stimulation.

Aim 5: To create a database of EEG and TMS data in people with PD for the purpose of future research into novel neurostimulation therapies for PD NMS.
Hypothesis: We will maintain a de-identified database of EEG, clinical, and demographic data from people with PD undergoing iTBS.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The stimulation locations in the current study design were chosen due to prior data implicating the medial prefrontal cortex and dorsolateral prefrontal cortex in both autonomic and affective disorders. Primary sensory cortex was chosen as a control site due to it's limited involvement in Parkinson's disease pathology, autonomic function, and depression. We chose a control stimulation location rather than sham stimulation because participants will be able to feel the difference between real and sham stimulation in this crossover design. A triple crossover design was chosen to maximize study recruitment and minimize subject variability between stimulation arms.

4.3 JUSTIFICATION FOR DOSE

Transcranial magnetic stimulation (TMS) is a safe, non-invasive tool routinely used in clinical care which applies magnetic fields to the brain using coils placed on the scalp. During the first stimulation session in the study, participants will receive a motor thresholding procedure in which electrodes are attached to

the first dorsal interosseous muscle of the right hand, or another muscle on the hand or arm that is accessible to be targeted by TMS to the motor cortex. The contralateral motor cortex will be targeted by single pulses of TMS with increased stimulator output until a motor evoked potential (MEP), defined as a near-instantaneous increase in muscle activity greater than 200 microvolts, is generated. Next, the intensity of single pulse TMS will be lowered until a MEP is generated on five out of 10 pulses. This is defined as the individual's motor threshold. If MEP determination of motor threshold is not possible, the researcher will use visible twitches as a proxy for MEP. Participants will receive iTBS at 80% of their motor threshold.

Subjects will undergo iTBS to the mPFC, left DLPFC, and left primary sensory area in a triple cross-over study design. I will use a MagVenture MagPro X100 TMS device with active cooling coil. Stimulation location will be determined using established scalp coordinates for each stimulation location with the "10-20" international coordinate system [42–45]. For the mPFC, stimulation will be done between the Fpz and Cz EEG electrode location. For left DLPFC, stimulation will be done at the F3 location using the Beam-F3 technique[46,47]. For the primary sensory cortex, stimulation will be done 1.5cm posterior to the motor hotspot and at vertex position used for intensity calibration. Accelerated iTBS will be performed in the reclined position to reduce symptoms of orthostatic hypotension, with subjects awake and at rest. Subjects will receive bursts of 3 pulses at 50 Hz repeated at 200-msec intervals (5Hz) for two seconds[48,49]. The two-second trains will be repeated 20 times every 10 seconds (3:30 total stimulation time), and followed by a rest period. This sequence may be repeated up to 4 times. Behavioral effects of stimulation last at least 36 hours after one stimulation session with this protocol[1].

A high-density EEG net (128 electrodes including electrooculography electrodes; MagStim EGI, Inc.) and two submental electromyography (EMG) electrodes will be applied. Continuous qEEG recording will be performed for 8 minutes while the participant is asked to keep their eyes open and focused on a crosshairs. Sampling rate during the continuous recording will be 1 kHz with Cz as the reference and a channel between Cz and Pz as ground, using an EGI system with SDK AmpServer Pro (Geodesic, Eugene, Oregon). Collecting EEG with TMS does not pose any additional risk over TMS on its own. EEG electrodes are placed on the scalp to record electrical brain activity. EEG does not involve brain stimulation and is used purely as a neuroimaging tool, posing minimal risk.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Men and women between 50 and 90 years of age, without a diagnosis of severe dementia
2. Carry a diagnosis of idiopathic Parkinson's disease based on the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria
3. Have had symptoms of Parkinson's disease for at least 3 years
4. Hospital's study-specific informed consent must be obtained
5. Must have capacity to provide informed consent in English
6. For female participants, confirmation that they have not had a menstrual period in over 12 months, or that they will use an effective form of contraception during the study

5.2 EXCLUSION CRITERIA

1. Inability to provide informed consent.
2. Severe dementia
3. History of epilepsy or brain surgery
4. Severe tremor or dyskinesia that would interfere with EEG as determined by the PI
5. Parkinson's patients with clinically significant medical or neurological conditions which may be an alternative cause of orthostatic hypotension, such as neuropathy, renal failure, heart failure, cardiac arrhythmias, severe diabetes, or spinal cord injuries
6. We will exclude patients who are treated with medications which can significantly lower blood pressure or heart rate, such as antihypertensive medications, diuretics, and alpha-blocking medications
7. Presence of other known central nervous system disease that may interfere with performance or interpretation of EEG or TMS
8. Presence of any implanted metal devices including, but not limited to, pacemakers, deep brain stimulators, vagal nerve stimulators, bladder stimulators, or cochlear implants.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of availability for study visits or a concomitant medication that is subsequently stopped may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment: Our sample for this study is 48 participants with Parkinson's disease age 50-90 years (See Sample Size Calculation). To recruit 48 participants, we will need to pre-screen 400 potential participants, and screen 90 potential participants, according to our experience in recruiting people with Parkinson's disease at our center. Participants will be recruited from among patients who are seen in neurology clinics at UNC for evaluation and treatment of idiopathic Parkinson's disease. A member of the research team will review data available in Epic for eligibility and recruitment, and flag patients who may qualify for the study. The treating neurologist will also be asked to consider potential participants' eligibility and ability to provide informed consent. Once potential participants have been identified, they will be asked in person, over telephone, and/or emailed by our research team to assess their interest in the study, and provide information about the research study. If the potential participant indicates they are interested, the study coordinator or research assistant will set up a time for the potential participant to have a screening research visit.

Retention: Retention strategies will include incentive payment upon completion of all study arms. Additionally, the research staff will call the participant at least 2 days prior to each study visit to remind them of the upcoming visit.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INVESTIGATIONAL PRODUCT

We will use the MagPro X100 system (MagVenture Inc., Alpharetta, GA, USA) for transcranial magnetic stimulation. The MagPro X100 is an advanced, high performance magnetic stimulator designed for research use. It is a high-quality product that allows a wide range of stimulation paramaters. This stimulator allows selection of different waveforms, current direction, stimulation rates. It is easily connectable to external equipment via programmable input and output triggers. The system operates via a built-in computer, and is controllable from an external device.

6.1.1.1 SAFETY FEATURES

In the USA, federal law regulates the sale of Medical Devices through the US Food and Drug Administration (FDA). Devices which are permitted to be marketed for their intended use must have either a 510(k) or PMA clearance.

MagPro stimulators R20, R30, R30 with MagOption, X100, and X100 with MagOption are all FDA 510(k) cleared (k160280, K061645, K091940, and k150641).

k150641: The intended use is treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.

k160280, K061645, K091940: The intended use is for stimulation of peripheral nerves for diagnostic purposes. The use of devices for other than their FDA cleared intended use is considered as investigational. Such use is only permited if the Investigational Device Exemption (IDE) guidelines have been followed.

All investigational devices must be labeled in accordance with the labeling provisions of the IDE regulation (§ 812.5) and must bear a label with this statement: "CAUTION Investigational Device. Limited by Federal (or United States) law to investigational use."

6.1.1.2 PREPARATION AND ADMINISTRATION OF STUDY INVESTIGATIONAL PRODUCT

After participants have completed questionnaires and EEG, they will be comfortably seated. The researcher will be thoroughly trained in the safe use of TMS. All researchers administering TMS have written and digital documentation of training. Researchers will be present at all times during stimulation. To monitor side effects of stimulation, a questionnaire will be administered after each stimulation session.

6.1.2 STUDY INTERVENTION DESCRIPTION

Screening: Participants will be recruited from among patients who are seen in neurology clinics at UNC for evaluation and treatment of idiopathic Parkinson's disease. A member of the research team will review data available in Epic for eligibility and recruitment, and flag patients who may qualify for the study. The treating neurologist will also be asked to consider potential participants' eligibility. Once potential participants have been identified, they will be asked in person, over telephone, and/or emailed by our research team to assess their interest in the study, and provide information about the research study. If the potential participant indicates they are interested, the study coordinator or research assistant will set up a time for the potential participant to have a screening research visit. Screening visits may be scheduled in the UNC Neurology clinic, or at the Frohlich laboratory, depending on convenience for the participant. At the screening visit, the study team member conducting the visit will clearly state that agreement or refusal to participate will in no way influence the patient's care. If the patient does not want to participate, this will be documented in the patient's chart, and the patient will not be contacted in the future about this study. If the patient is interested in participating in the study, the study inclusion and exclusion criteria will be reviewed again with the patient at the study visit. The study will be explained in detail to the potential participant, all questions will be answered to the potential participant's satisfaction, and the study coordinator, research assistant, PI, or co-I will obtain informed consent in person.

Once consent is obtained, the participant will be assigned an anonymous research ID number. Only the study team members will have access to data linking the participant's research data and any PHI. Demographic data will be obtained, including age, sex, concurrent medications, and disease duration. A trained research team member will administer a brief cognitive test (the Montreal Cognitive Assessment or MoCA)[50], the Movement Disorders Society Unified Parkinson's Rating Scale (MDS-UPDRS)[51], and will obtain orthostatic vital signs.

Stimulation study visits

Clinical Evaluations: The SCOPA-AUT[52], a validated questionnaire for autonomic symptoms in PD, and the Orthostatic Hypotension Questionnaire (OHQ)[53], a validated questionnaire for symptoms of orthostatic

intolerance, will be administered before, and then by telephone one day after, and four days after each stimulation session. The Beck Depression inventory II (BDI-II)[54], recommended for screening and assessment of depression severity in PD[55], will be administered before, and then by telephone one day after, and four days after each stimulation. A trained research team member will administer the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS)[51], a validated rating scale of PD symptom severity, at baseline. Participants will have orthostatic blood pressure measurement with a standard sphingomanometer cuff before and after each stimulation session. All evaluations will be done with subjects in the "on" medication state with regards to dopaminergic medication dosing. Quantitative EEG (qEEG) recordings will be done before and immediately after each stimulation session. ***EEG:*** A high-density EEG net (128 electrodes including electrooculography electrodes; MagStim EGI, Inc.) and two submental electromyography (EMG) electrodes will be applied. Continuous qEEG recording will be performed for 8 minutes while the participant is asked to keep their eyes open and focused on a crosshairs. Sampling rate during the continuous recording will be 1 kHz with Cz as the reference and a channel between Cz and Pz as ground, using an EGI system with SDK AmpServer Pro (Geodesic, Eugene, Oregon). ***Intermittent theta-burst stimulation:*** Subjects will undergo iTBS to the mPFC, left DLPFC, and left primary sensory area in a triple cross-over study design. I will use a MagVenture MagPro X100 TMS device with active cooling coil. Stimulation location will be determined using established scalp coordinates for each stimulation location with the "10-20" international coordinate system [42–45]. For the mPFC, stimulation will be done at the Fp1 EEG electrode location, which can be calculated as along the midline of the scalp and 10% of the distance from nasion to inion. For left DLPFC, stimulation will be done at the F3 location using the Beam-F3 technique[46,47]. For the primary sensory cortex, stimulation will be done 1.5cm posterior to the motor hotspot used for intensity calibration. Stimulation will be delivered at 80% active motor threshold. Accelerated iTBS will be performed in the reclined position to reduce symptoms of orthostatic hypotension, with subjects awake and at rest. Subjects will receive bursts of 3 pulses at 50 Hz repeated at 200-msec intervals (5Hz) for two seconds[48,49]. The two-second trains will be repeated 20 times every 10 seconds (4 minutes total stimulation time), and followed by a 20 minute rest period. This sequence will be repeated 4 times. Behavioral effects of stimulation last at least 36 hours after one stimulation session with this protocol[1]**.** TMS is FDA-approved for the treatment of symptoms of depression, and is a widely-used safe clinical tool.

6.1.3 DOSING AND ADMINISTRATION

During the first stimulation session in the study, participants will receive a motor thresholding procedure in which electrodes are attached to the first dorsal interosseous muscle of the right hand, or another muscle on the hand or arm that is accessible to be targeted by TMS to the motor cortex. The contralateral motor cortex will be targeted by single pulses of TMS with increased stimulator output until a motor evoked potential (MEP), defined as a near-instantaneous increase in muscle activity greater than 200 microvolts, is generated. Next, the intensity of single pulse TMS will be lowered until a MEP is generated on five out of 10 pulses. This is defined as the individual's motor threshold. If MEP determination of motor threshold is not possible, the researcher will use visible twitches as a proxy for MEP. Participants will receive iTBS at 80% of their motor threshold.

Subjects will undergo iTBS to the mPFC, left DLPFC, and left primary sensory area in a triple cross-over study design. I will use a MagVenture MagPro X100 TMS device with active cooling coil. Stimulation

location will be determined using established scalp coordinates for each stimulation location with the "10-20" international coordinate system [42–45]. For the mPFC, stimulation will be done at the Fp1 EEG electrode location, which can be calculated as along the midline of the scalp and 10% of the distance from nasion to inion. For left DLPFC, stimulation will be done at the F3 location using the Beam-F3 technique[46,47]. For the primary sensory cortex, stimulation will be done 1.5cm posterior to the motor hotspot used for intensity calibration. Accelerated iTBS will be performed in the reclined position to reduce symptoms of orthostatic hypotension, with subjects awake and at rest. Subjects will receive bursts of 3 pulses at 50 Hz repeated at 200-msec intervals (5Hz) for two seconds[48,49]. The two-second trains will be repeated 20 times every 10 seconds (4 minutes total stimulation time), and followed by a 20 minute rest period. This sequence will be repeated 4 times. Behavioral effects of stimulation last at least 36 hours after one stimulation session with this protocol[1]**.**

A high-density EEG net (128 electrodes including electrooculography electrodes; MagStim EGI, Inc.) and two submental electromyography (EMG) electrodes will be applied. Continuous qEEG recording will be performed for 8 minutes while the participant is asked to keep their eyes open and focused on a crosshairs. Sampling rate during the continuous recording will be 1 kHz with Cz as the reference and a channel between Cz and Pz as ground, using an EGI system with SDK AmpServer Pro (Geodesic, Eugene, Oregon). Collecting EEG with TMS does not pose any additional risk over TMS on its own. EEG electrodes are placed on the scalp to record electrical brain activity. EEG does not involve brain stimulation and is used purely as a neuroimaging tool, posing minimal risk.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

To control for bias, we have decided on a prospective, controlled, triple crossover (three stimulation locations at separate study visits) study design. Participants will be blinded as to stimulation location, and each participant will experience stimulation at all locations. Each participant will have all rating scales performed by the same rater. Potential confounding factors, such as age, disease duration, cognitive function, and overall disease severity will be evaluated and controlled for, as indicated, in the final statistical models.

Stimulation order will be randomized and counter-balanced. Participants are assigned a study ID number and randomized upon signing the informed consent form. Subject ID will be entered into the randomization algorithm by the research assistant. A randomization table will be generated by a computerized script that randomizes and counterbalances by ID, generating an Excel spreadsheet. We will perform complete counterbalancing, there are 6 potential sequences (mPFC-DLPFC-S1, mPFC-S1-DLPFC, DLPFC-mPFC-S1, DLPFC-S1-mPFC, S1-mPFC-DLPFC, S1-DLPFC-mPFC) and a plan for 48 participants. Every effort will be made to completely counterbalance our sample. Thus effects of stimulation order will be minimized.

Treatment Assignment Procedures: Participants will receive stimulation to the medial prefrontal cortex, the dorsolateral prefrontal cortex, and the primary sensory cortex. The order of stimulation will be randomized and counterbalanced. Randomization will be performed using a script that generates a

spreadsheet. Randomization will be done after the screening visit is completed, before initiation of stimulation sessions.

6.3 STUDY INTERVENTION COMPLIANCE

Compliance is determined by completion of all three stimulation sessions.

6.4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. Information about concomitant medications will be collected in pre-screening procedures, at the screening visit, and at each stimulation visit. Excluded medications include antihypertensive medications, diuretics, and alpha-blocking medications.

6.4.1 RESCUE MEDICINE

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from stimulation does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- All remaining study questionnaires

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

- There are factors that, in the opinion of the PI, would place the participant at increased physical or psychological risk, or preclude the participant's compliance or completion of the study

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Safety data will be collected on any participant that is discontinued due to an AE or SAE. Every effort will be made to complete protocol-specific follow up procedures if possible. If voluntary withdrawal occurs, the participant will be asked to continue scheduled evaluations and complete an end-of-study evaluation. Medical and psychological follow up will be coordinated by the research team as described in this protocol. The researcher will make a note to file for all withdrawals.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within two weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 SELF-COMPLETED QUESTIONNAIRES

Participants will fill out the following questionnaires:

- Scales for Outcomes in Parkinson's – autonomic (SCOPA-AUT) – Autonomic self-completed symptom questionnaire, contains 21 questions plus 2 questions that are specific for men and 2 specific for women; therefore ever participant will answer 23 questions[52]. Each item score range is 0-3 for severity of symptoms. Score range is 0-69 points, where higher points

indicates higher burden of symptoms. This will be completed prior to each stimulation session in person, and over telephone one day after and 4 days after stimulation

- Orthostatic Hypotension Questionnaire (OHQ)[53] - a validated questionnaire for symptoms of orthostatic intolerance, contains 10 questions. Each question is scored out of 10 possible points. Score range is 0-100, where higher points indicates higher burden of symptoms. This will be completed prior to each stimulation session in person, and over telephone one day after and 4 days after stimulation
- Beck Depression inventory II (BDI-II)[54] - recommended tool for screening and assessment of depression severity in PD[55]. Consists of 21 questions, each question ranges in score from 0-3 points. Score range is 0-63, where higher points indicates higher burden of symptoms. This will be completed prior to each stimulation session in person, and over telephone one day after and 4 days after stimulation
- MDS - Unified Parkinson's disease Rating Scale (MDS-UPDRS) parts 1b and 2 – Validated clinical tool, it is a rating scale for disease severity in Parkinson's disease. Part 1b is the Non-Motor Aspects of Experiences of Daily Living, and consists of 7 questions, each worth 0-4 points. Score range is 0-28 points. Part 2 is the patient ADL questionnaire and contains 13 questions[51], each worth 0-4 points. Score range is 0- 52 points, This will be completed at the screening visit only.
- Freezing of Gait questionnaire– Assesses symptoms of freezing of gait in Parkinson disease. Continains 6 questions, each scored 0-4[56]. Score range is 0-24, with higher score meaning higher burden of symptoms. This will be completed at the screening visit only
- Epworth sleepiness scale – Assesses symptoms of fatigue and sleepiness. Contains 8 questions, each scored 0-4.[57] Score range is 0-24, with higher score meaning higher burden of symptoms. This will be completed at the screening visit only.
- REM sleep disorder screening questionnaire – Screening questions about symptoms of REM sleep behavior disorder. This questionnaire contains 10 questions, one question has 4 parts[58]. Each question and question part is scored 0-1. Score range is 0-13, with higher score indicating higher burden of symptoms. This will be completed at the screening visit only

8.1.2 OBJECTIVE EVALUATIONS

Participants will undergo the following disease rating scales and cognitive examination evaluations prior to stimulation:

- The MDS UPDRS part Ia - this is a questionnaire, administered by the investigator, and consists of 6 question, each scored 0-4 points. Score range is 0-24. It takes 10 minutes to administer[51]. This will be completed at the screening visit
- MDS UPDRS part III – this is the neurological examination portion of the MDS UPDRS, and takes about 10 minutes to complete[51]. Each question is scored 0-4. Score range is 0-132, with higher score indicating higher burden of motor symptoms. This will be completed at the screening visit
- The MDS UPDRS part IV – this is the dyskinesia rating portion. It consists of 6 questions, each scored from 0-4 points and takes 10 minutes to complete[51]. Score range is 0-24. This will be completed at the screening visit.

- MoCA – Montreal Cognitive Assessment. This is a neurocognitive screening tool, and takes about 15 minutes to administer[50]. The visiospatial/executive function portion consists of three questions with a score range of 0-5; the naming portion consists of three questions with a score range of 0-3; the attention portion consists of 4 questions with a score range of 0-6; the abstraction portion has 2 questions and has a score range of 0-2; The delayed recall is one question and is scored 0-5 points; and orientation is 6 questions with a score range of 0-6 points. The total score range is 0-30, where lower score indicates higher burden of symptoms. This will be completed at the screening visit.
- Participants will undergo EEG before and immediately after brain stimulation. A high-density EEG net (128 electrodes including electrooculography electrodes; MagStim EGI, Inc.) and two submental electromyography (EMG) electrodes will be applied. Continuous EEG recording will be performed for 8 minutes while the participant is asked to keep their eyes open and focused on a crosshairs. Sampling rate during the continuous recording will be 1 kHz with Cz as the reference and a channel between Cz and Pz as ground, using an EGI system with SDK AmpServer Pro (Geodesic, Eugene, Oregon). EEG frequency will be reported in Hz. The primary outcome measure, FMT power, will be reported in μ.
- iTBS: Subjects will undergo iTBS to the mPFC, left DLPFC, and left S1 in a triple cross-over study design. The MagVenture MagPro X100 TMS device with active cooling coil will be used. Stimulation location will be determined using established scalp coordinates for each stimulation location with the "10-20" international coordinate system [42–45]. For the mPFC, stimulation will be done at the Fp1 EEG electrode location, which can be calculated as along the midline of the scalp and 10% of the distance from nasion to inion. For left DLPFC, stimulation will be done at the F3 location using the Beam-F3 technique[46,47]. For the primary sensory cortex, stimulation will be done at the motor hotspot used for intensity calibration. Stimulation will be delivered at 80% active motor threshold. Accelerated iTBS will be performed in the reclining position to reduce symptoms of orthostatic hypotension, with subjects awake and at rest. Subjects will receive bursts of 3 pulses at 50 Hz repeated at 200-msec intervals (5Hz) for two seconds[48,49]. The two-second trains will be repeated 20 times every 10 seconds (4 minutes total stimulation time), and followed by a 20 minute rest period. This sequence will be repeated 4 times. Behavioral effects of stimulation last at least 36 hours after one stimulation session with this protocol[1].

8.2 SAFETY AND OTHER ASSESSMENTS

Pre-screening for the study will involve review of the medical chart for the presence of exclusionary criteria, particularly medical conditions and medications, which may put the participant at risk during the study. These criteria will also be reviewed with the participant at the screening visit and at each stimulation session prior to stimulation. Screening will be performed within 21 days of initial study stimulation visit.

Safety will be monitored throughout the study. A stimulation adverse effects questionnaire will be used based on common side effects experienced with TMS. This questionnaire will be administered at the end of each stimulation session. Additionally, participants will be continually asked about their comfort level during stimulation sessions. If a participant reports greater than moderate level of discomfort during stimulation, the stimulation will be immediately discontinued.

The PI will monitor the study for any adverse and serious adverse events. All serious adverse events will be reported to the IRB. Should there be a serious adverse event that occurs that increases the risks to the participants, the study will be stopped and an investigation will be conducted and a findings report generated before the study is resumed. At the time of enrollment, we will ensure we have an active and accurate phone number on file to contact the subject.

Medical follow-up
In the event that a subject is found during the course of the study to need medical or psychological follow-up related to their study involvement, the following procedures will be followed to address their issues.

Medical: For urgent issues, we will direct subjects to the nearest emergency room versus urgent care center for evaluation, based off of the described difficulties and symptoms. For nonurgent (subacute, chronic) issues related to neurologic condition, a follow-up appointment within our department will be scheduled for within 72 hours of the communication. If the issue is unrelated to their movement disorder but also nonurgent, we will communicate with the subject's primary care physician and, when appropriate, disclose necessary information regarding the study protocol should it be relevant to the complaints at hand.
Psychological: for urgent issues, we will direct subjects to the nearest crisis unit if necessary (including but not limited to suicidal ideations or intentions, severe and rapid depression/anxiety). For nonurgent (subacute/chronic) issues, will supply patient with local mental health care specialists near them as well as contact information for those within the university system to obtain the next available appointment.

The burden of cost of all medical care for conditions which arise in the course of participation in the study will on the subject. In case symptoms occur outside of business hours, the subjects will be provided the telephone number of the hospital page operator and the operator will be asked to page the PI directly. For non-urgent issues, the subjects will be asked to call Dr. Sklerov's office number or the research assistant's phone number which are listed on the consent form of which the subject will receive a copy. For urgent or emergent issues, the subjects will be instructed to present to their nearest emergency room.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment,

they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits, during study telephone calls, and interviews of a study participant presenting for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All AEs will be captured and recorded at each stimulation visit in person, and one day after, and four days after each stimulation visit over telephone. The AE report form will be completed by the researcher, and will include details about the stimulation, what is known about previous reported side effects, if the AE occurred in temporal relation to the stimulation, whether the AE improves or completely resolves once stimulation is ceased, whether the AE is worsening of a baseline symptom, and whether the AE is related to concurrent medication or medical condition. This form will be presented to the PI who will review and sign the form. Completed forms will be placed in the participant's file in the study binder. AEs will also be documented in the AE log, which will also document the date, severity, relationship to treatment (as determined by the PI), actions taken, and outcome. Medical conditions and symptoms present prior to start of stimulation on the day of the visit will not be considered an AE.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study team is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and the reviewing IRB within 10 working days after they first

receive notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 10 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 30 days of the investigator becoming aware of the problem.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

Statistical planning and analysis will be done by the PI Dr. Sklerov in collaboration with Dr. Flavio Frohlich and consultation with biostatistician Dr. Hongtu Zhu.

9.1 STATISTICAL HYPOTHESES

Aim 1

H_0: Mean change in Frontal midline theta power on electroencephalogram after iTBS to the medial prefrontal cortex will be equal to FMT changes after dorsolateral prefrontal cortex stimulation and stimulation of S1.

H_1: Mean change in Frontal midline theta power on electroencephalogram after iTBS to the medial prefrontal cortex will be greater than FMT changes after dorsolateral prefrontal cortex stimulation and stimulation of S1.

Primary Outcome Measure: The primary objective will test the degree of change in frontal midline theta (FMT) power (μ)before and after iTBS at each stimulation location. The primary outcome measure will be FMT power. *Aim 2a Hypothesis:*

H_0: There is zero correlation between severity of autonomic dysfunction symptoms at baseline before stimulation with frontal midline theta power at baseline on electroencephalogram.

H_1: There is a negative correlation between severity of autonomic dysfunction symptoms at baseline before stimulation with frontal midline theta power at baseline on electroencephalogram.

Aim 2b Hypothesis:

H_0: There is no correlation between severity of depression symptoms at baseline before stimulation with frontal midline theta power on electroencephalogram at baseline.

H_1: There is negative correlation between depression symptoms at baseline before stimulation with frontal midline theta power on electroencephalogram at baseline.

- Primary Outcome Measures: We will test associations between autonomic symptoms, depression symptoms, and FMT power at baseline before stimulation, where the FMT power (μ) will be the primary outcome measure.

Exploratory objectives
Aim 3 Hypothesis:

H_0: Change in SCOPA-AUT and OHQ will be zero one day after stimulation and 4 days after stimulation compared to pre-stimulation.

H_1: Change in SCOPA-AUT and OHQ will be less than zero one day after stimulation and 4 days after stimulation.

- Primary Outcome Measures: Change in SCOPA-AUT and OHQ from before to one day and 4 days after stimulation

Aim 4 Hypothesis:

H_0: Change in BDI-II will be zero one day after stimulation and 4 days after stimulation compared to pre-stimulation.

H_1: Change in BDI-II will be less than zero one day after stimulation and 4 days after stimulation.

- Primary Outcome Measure: Change in BDI-II before to one day and 4 days after stimulation

Aim 5 is to maintain a de-identified database of EEG, clinical, and demographic data from people with PD undergoing iTBS.

9.2 SAMPLE SIZE DETERMINATION

Aim 1: There is no preliminary data for effect size estimation using the paradigm and patient population suggested in this study. The primary outcome measure in aim 1 is change in FTM.

H_0: Mean change in Frontal midline theta power on electroencephalogram after iTBS to the medial prefrontal cortex will be equal to FMT changes after dorsolateral prefrontal cortex stimulation and stimulation of S1.

H_1: Mean change in Frontal midline theta power on electroencephalogram after iTBS to the medial prefrontal cortex will be greater than FMT changes after dorsolateral prefrontal cortex stimulation and stimulation of S1.

I expect a medium effect size of $f^2 \geq 0.15$. With significance level set at α = 0.05, using linear multiple regression modeling in G*Power software, with 3 predictors, an N of 45 subjects yields power of 0.82 for this crossover design. In a published study examining theta power using EEG plus iTBS at the dorsolateral prefrontal cortex in healthy adults, they found significant changes in theta power after iTBS with an N of 10 subjects[59]. Therefore we propose 48 subjects for this current study, which should sufficiently power our study for the primary outcome measures.

Aim 2: Though there is no preliminary data for theta band power correlates of depression or autonomic symptoms in Parkinson's disease, there are studies that have looked at EEG spectral power correlations of cognitive symptoms in PD. In one study that contained sufficient published data to calculate power, they found a correlation between EEG spectral power and executive dysfunction in PD with an OR of 0.130 (95% CI [0.02-0.83])[60]. The primary outcome measure in Aim 2a and Aim 2b is FTM. I used G*Power software to calculate sample size for a linear regression model with a significance level set at α = 0.05 and Power = 0.80, which yielded a necessary sample size of 22 subjects. 45 subjects yields a power of 0.98 (95% confidence interval [0.24 – 0.99]). We will propose to recruit 48 subjects to ensure that our study is sufficiently powered.

Aim 2a:

H_0: There is zero correlation between severity of autonomic dysfunction symptoms at baseline before stimulation with frontal midline theta power at baseline on electroencephalogram.

H_1: There is a negative correlation between severity of autonomic dysfunction symptoms at baseline before stimulation with frontal midline theta power at baseline on electroencephalogram.

Aim 2b:

H_0: There is no correlation between severity of depression symptoms at baseline before stimulation with frontal midline theta power on electroencephalogram at baseline.

H_1: There is negative correlation between depression symptoms at baseline before stimulation with frontal midline theta power on electroencephalogram at baseline.

Exploratory objectives: There are no controlled studies using TMS or iTBS to treat autonomic symptoms. I used a meta-analysis of iTBS used to treat depression to estimate effect size[61]. They found a Hegdal g of 1.0 (95% CI [0.3-1.7])for improvement in depression symptoms after iTBS. The primary outcome measure in Aim 3 is change in SCOPA-AUT and OHQ, and the primary outcome measure in Aim 4 is change in BDI-II after stimulation. Using G*Power software to calculate sample size for a multiple linear regression with 2 predictors, with α = 0.05 and N=45, which yields a power of 0.95 (95% CI [0.26-1.00]). We propose to recruit 48 subjects.

Aim 3:

H_0: Change in SCOPA-AUT and OHQ will be zero one day after stimulation and 4 days after stimulation compared to pre-stimulation.

H_1: Change in SCOPA-AUT and OHQ will be less than zero one day after stimulation and 4 days after stimulation.

Aim 4:

H_0: Change in BDI-II will be zero one day after stimulation and 4 days after stimulation compared to pre-stimulation.

H_1: Change in BDI-II will be less than zero one day after stimulation and 4 days after stimulation.

Therefore, we propose 48 subjects for this current study which should anticipate adequate levels of power for hypothesis testing of parameters defined based on the primary outcome variables. To recruit 48 participants, based on our recruitment for prior studies with similar patient population at UNC, we anticipate pre-screening 400 potential participants' charts. We anticipate then screening 90 potential participants to find 48 participants who fulfill inclusion and exclusion criteria and who are interested in participating in the study, and are reasonably expected to be able to complete the study protocol.

9.3 POPULATIONS FOR ANALYSES

We will use a modified Intention-to-Treat Analysis Dataset (e.g. participants who at least started the stimulation, whether or not they were able to complete the stimulation session, and/or sufficient follow-up outcome data).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

All data are double entered by independent keyboard operators, compared to identify discrepancies, then reconciled with the data manager. All datasets are backed up daily. Linear mixed models with repeated measures across different regions or over time will be the primary analytic tool for testing our *a priori* hypotheses. To model correlation among repeated measures, we will primarily consider either random intercept or AR(1). We will use the likelihood ratio test (or Wald test) statistic to test

the hypotheses. We will appropriately handle missing data (e.g., missing responses and/or covariates) by using imputation or other methods. To identify significant component terms in each of the models, we will examine the parameter estimates, 95% confidence intervals, and p-values of the component terms in an analysis of fixed effects for the final mixed models. Before undertaking statistical modeling, we will perform descriptive analyses and examine the distributions of all measures. Appropriate transformations or nonparametric statistical tests will be considered if necessary. *All* statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CIs) and/or standard errors (SEs) to convey levels of precision / imprecision. Following is a detailed plan for testing each hypothesis and the power assessment when feasible.

Descriptive statistics: Categorical data (sex) will be presented as percentages. Continuous data (age, disease duration, scores on SCOPA-AUT, OHQ, BDI-II, MDS-UPDRS all parts, freezing of gait questionnaire, Epworth Sleepiness scale, REM sleep behavior disorder questionnaire, and MoCA, will be presented as means with standard deviation and range.

Primary analysis, Aim 1: To test the degree of change in the power of FMT before and after iTBS at each location, we will use linear mixed models with FMT being the dependent variable. We will primarily include stimulation location (mPFC, DLPFC, S1), time (before, after stimulation), and the interaction term Location*time in the model.
Primary Analysis, Aim 2: 1. To test associations of autonomic symptoms in PD subjects with FMT, we will use linear regression modeling. The dependent variable will be FMT, whereas primary covariates will be SCOPA-AUT, OHQ score, and magnitude of systolic blood pressure reduction during orthostatic blood pressure measurement. We will further use linear regression models to examine the associations between depression symptoms in PD subjects and FMT, using linear regression modeling. Exploratory Analyses: 1. We will use linear mixed modesl to examine the effect of iTBS on autonomic symptoms one day after, and 4 days after stimulation. SCOPA-AUT and OHQ will be the dependent variable in the ANOVA analysis. The factors will be stimulation location (mPFC, DLPFC, S1) by time (before and after). 2. Similarly, we will use linear mixed models to evaluate the effect of iTBS on depression symptoms one day after, and 4 days after stimulation. BDI-II will be the dependent variable, whereas the primary factors will be stimulation location (mPFC, DLPFC, S1) by time (before and after). In all statistical models, Some key confounding factors (age, disease duration) will be controlled in both linear mixed effects and regression models. Post-hoc analysis will be performed using Tukey's method to control for multiple comparisons.

9.4.2 ANALYSIS OF THE PRIMARY OUTCOMES

See above 9.4.1

9.4.3 ANALYSIS OF THE EXPLORATORY OUTCOMES

See above 9.4.1

9.4.4 SAFETY ANALYSES

Safety outcome will be the adverse effects questionnaire filled out at the end of each stimulation session (mean, median, and range), and the presence of AEs, SAEs, and UAEs which are deemed to be related to stimulation. AEs, SAEs, and UAEs reporting will be done at each stimulation visit, as well as 1 day and 4 days after each visit over telephone. Each AE will be counted only once per participant. AEs will be reported as start date, stop date, severity, relationship to stimulation, expectedness, outcome, and duration. Adverse events leading to premature discontinuation from the study, and serious treatment-emergent AEs, will be presented in a table.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics reported will include age, sex, and disease disease duration, as well as scores on scales: MoCA, MDS-UPDRS sub-scores, SCOPA-AUT, OHQ, BDI-II, Epworth Sleepiness Scale, Freezing of Gait Questionnaire, REM sleep behavior disorder questionnaire, and orthostatic blood pressure reduction.

9.4.6 PLANNED INTERIM ANALYSES

Interval safety assessments will be done quarterly, or more frequently if a SAE arises. During these assessments, all AEs and SAEs will be reviewed by the study team and advisors. Changes to the protocol will be considered if needed improve safety. All study data will be checked for completeness and quality in real-time by study personnel, and at least quarterly, to ensure sound data collection.

9.4.7 SUB-GROUP ANALYSES

Associations between the covariates of gender, age, and disease duration with the dependent and independent variables will be evaluated. Covariates will be accounted for in ANCOVA or linear regression models, respectively.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and the IRB. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or Food and Drug Administration (FDA).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data,

and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI.

All research activities will be conducted in as private a setting as possible.

This is a single site, investigator-initiated clinical trial, so there is no site monitoring plan in place. The latest version of the IRB approved protocol for this clinical trial will be followed. This responsibility is on the PI and researchers in the study. If there is a deviation from the protocol, the deviation from protocol log will be filled out, and deviations will be sent to the IRB every 8 weeks if necessary.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

Electronic research data will be stored on password-protected servers within the UNC School of Medicine, and on the lab SharePoint, a HIPAA-secure cloud application approved by the UNC School of Medicine. Any hard-copy data will be stored in locked cabinets in locked offices in the UNC Department of Neurology. This data will be de-identified, and will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored as described above. Permission to transmit data to researchers outside of the current study will be included in the informed consent.

10.1.5 ETHICAL STANDARD

The PI will ensure that study procedures are conducted in full conformity with the principles set forth in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

10.1.6 KEY ROLES AND STUDY GOVERNANCE

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Dr. Flavio Frohlich (Associate Professor, Department of Psychiatry, UNC School of Medicine) and Dr. David Rubinow (Professor, Chair Emeritus, Department of Psychiatry, UNC School of Medicine) will serve as senior advisors on this protocol. They will work with the PI to review AEs, SAEs, and UAEs, and to revise the study protocol or determine termination of the study as indicated.

10.1.7 SAFETY OVERSIGHT

Safety oversight will be under the direction of the PI, in conjunction with the advisors. The PI will review AEs in real time and make decisions regarding a participant's continuation of the clinical trial. AEs will be assessed at each stimulation visit, as well as one day after and four days after each stimulation session over telephone.

10.1.8 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

This is a single site, investigator-initiated clinical trial, so there is no site monitoring plan in place. The latest version of the IRB approved protocol for this clinical trial will be followed. This responsibility is on the PI and researchers in the study. If there is a deviation from the protocol, the deviation from protocol log will be filled out, and deviations will be sent to the IRB every 8 weeks if necessary.

Informed consent forms and HIPAA forms will be reviewed regularly to ensure that they are filled out appropriately and consent form process was properly followed.

Documentation of Adverse events (AE) and Serios Adverse Events (SAE) will be kept in the study binder for each participant, which is found in room 2135 of the UNC Physicians Office Building. It is the responsibility of the research staff to report all adverse events to the PI in a timely manner. All AEs and SAEs will be discussed with the PI.

10.1.9 QUALITY ASSURANCE AND QUALITY CONTROL

The study personnel will perform quality management of study conduct and study data, documentation and completion at least on a quarterly basis for the duration of the study period. Any missing data or data anomalies will be reviewed with the PI for clarification/resolution.

The study will provide direct access to all trial related source data/documents, and reports for the purpose of inspection by local and regulatory authorities.

10.1.10 DATA HANDLING AND RECORD KEEPING

10.1.10.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study personnel under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

All questionnaires will be in paper format and will be collected by the study coordinator in person at the study visit or via mail as described above. In order to maintain privacy and confidentiality regarding subject participation, there will be no more than one printed copy of a spreadsheet with subject ID numbers linked to their identifiers, which will only consist of name, medical record number, study ID number, age, and date of birth. This spreadsheet will be kept in the office of study personnel, within a locked cabinet with multiple layers of physical security to enter this office including necessary UNC employee badge access. An electronic copy of this form will be stored in a HIPAA compliant fashion, as detailed below**.** Once the study has ended, only codes shall remain, and the aforementioned spreadsheet shall be destroyed in a HIPAA-compliant fashion. This will not directly affect any UNC medical records.

Consent forms will be scanned and loaded into Epic, and a copy will be saved for our records on the UNC School of Medicine Neurology secure server, which is HIPAA compliant and password-secured. The original hard copy will be stored in a locked office, inside a locked office cabinet, located in the Physician's office building. The participants will receive a copy of the signed consent form for their own personal records.

All clinical data and logs of collected data will be recorded on paper forms and then transferred to computerized data forms. Paper forms will be stored in double-locked storage. All computerized records will be password protected and HIPAA compliant. Electronic study data will be stored as Excel spreadsheets and kept on School of Medicine (SOM) IT secure network, and on a cloud-based UNC SOM approved HIPAA-compliant server. Study data may also be stored in the UNC REDCap system. This is a secure, password-protected, HIPAA compliant web application developed by the NIH that is widely used in clinical research. A data dictionary will be created by the study coordinator and the PI. Data accuracy and completion will be monitored periodically by the PI using SAS software to look for missing data points and out of range values. Confidentiality will be maintained by storing all collected study information labeled with only the anonymous study identification numbers. Electronic data will be stored using only study identification numbers in password protected databases and encrypted endpoints. The linked identified data will be stored separately from the deidentified research data on the SOM IT secure network. No individual identifying information will be included in any clinical reports or sample logs in this study.

Stored data will include all data collected during the course of the study, and data obtained from the participants' clinical chart including autonomic testing parameters, clinical scales, questionnaires, co-

morbid medical conditions, date of PD diagnosis, age, concomitant medications, prior surgeries. The PI, co-Is, and research assistant will be in charge of data management.

10.1.10.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 5 years have elapsed since the formal discontinuation of the study intervention, as recommended by the UNC School of Medicine.

10.1.11 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the IRB. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.12 PUBLICATION AND DATA SHARING POLICY

We plan submit the data obtained from this study for publication in a peer reviewed journal in a timely manner once recruitment and data analysis are complete.

10.1.13 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership and institutional regulatory boards have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ADL	Activities of Daily Living
AE	Adverse Event
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
AuD	Autonomic dysfunction
BDI-II	Beck depression inventory - II
CAN	Central autonomic network
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
Cz	Central midline sagittal plane electrode location on electroencephalography
DBS	Deep Brain Stimulation
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DLPFC	Dorsolateral prefrontal cortex
DMV	Department of Motor Vehicles
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EEG	Electroencephalogram
EMG	Electromyogram
F3	Left frontal electrode location at position 3 on electroencephalography
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
FMT	Frontal Midline Theta
Fp1	Left anterior pre-frontal electrode location on electroencephalography
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
HTH	Hypothalamus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
iTBS	Intermittent Theta-Burst Stimulation
ITT	Intention-To-Treat

LSMEANS	Least-squares Means
MDD	Major Depression Disorder
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Motor evoked potential
MOCA	Montreal Cognitive Assessment
MOP	Manual of Procedures
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
MSDS	Material Safety Data Sheet
NC	North Carolina
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NMS	Non-motor symptoms
OH	Orthostatic Hypotension
OHQ	Orthostatic Hypotension Questionnaire
OHRP	Office for Human Research Protections
PD	Parkinson's disease
PHI	Protected Health Information
PI	Principal Investigator
PPMI	Parkinson's Progression Markers Initiative
QA	Quality Assurance
QC	Quality Control
qEEG	Quantitative electroencephalogram
REM	Rapid eye movement
rs-fMRI	Resting State functional MRI
S1	Primary sensory cortex
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCOPA-AUT	SCales for Outcomes in PArkinson's - Autonomic
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TMS	Transcranial Magnetic Stimuylation
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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