PROTOCOL

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Project Title: Cortical physiology as a therapeutic target in Parkinson's disease related dementia and cognitive dysfunction
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I. Hypotheses and Specific Aims:

Aim 1. Determine whether graph theory measures of intrinsic network functional connectivity are associated with cognitive dysfunction in PD.
Hypothesis 1: Increased randomness and decreased efficiency of cortical networks contribute to PD cognitive dysfunction and will be associated with neuropsychological measures.

Aim 2. Develop a novel state-defining biomarker for cognitive dysfunction in PD based on measures of intrinsic regional activity and network connectivity using a machine learning approach.
Hypothesis 2: Cognitive dysfunction in PD can be characterized through a unique combination of regional and network features as measured by MEG and optimized through machine learning.

Aim 3. Determine the effects of rTMS on intrinsic network functional connectivity and cognitive dysfunction in PD.
Hypothesis 3: High frequency bifrontal rTMS will increase the efficiency of cortical networks including frontal nodes and will be associated with improvements in neuropsychological measures.

Exploratory Aim. Investigate how MRI measures of white matter, GABA function and resting state networks relate to MEG measures of functional connectivity.

Hypothesis 4: MEG measures of intrinsic functional connectivity will correlate with MRI measures and be reflective of underlying structural (white matter) and neurotransmitter (GABA) integrity.

II. Background and Significance:

Parkinson's disease (PD) affects 1-2% of people over age 65, representing over 1 million Americans.[1] Although traditionally characterized by its motor symptoms, over the course of PD cognitive symptoms have a greater impact on patient suffering and caregiver burden.[2] Three-fourths of patients surviving 20 years or longer develop dementia making it the leading cause of nursing home placement.[3] Despite the high prevalence of cognitive dysfunction in PD, its pathophysiology is poorly understood and current treatments have minimal effects on symptoms or progression.[4] Moreover, standard medical and surgical PD treatments have no effect on cognition and may in fact worsen cognition.[5] *Better treatment strategies for PD-related cognitive dysfunction based on an improved knowledge of neurobiological mechanisms are clearly needed.*

Functional connections between cortical regions are important for normal cognition and memory[6, 7] and that alterations in functional cortical connectivity may contribute to cognitive dysfunction in PD.[8] In the past decade, modern network theory has emerged as a powerful tool to describe the organization of functional brain networks using the mathematics of graph theory.[9] Two fundamental measures are path length, defined as the average distance between any two nodes in a network and a measure of global efficiency and integration; and the clustering coefficient defined as the average number of mutually connected nodes surrounding each node and a measure of local efficiency and modularity. Figure 1 shows an optimal balance between global and local efficiency can be achieved through clustered modules connected through integrating links, a design termed small-world architecture.[10] It is well-established that healthy brain networks demonstrate small-world architecture.[11] Importantly, loss of small world features are associated with cognitive dysfunction in multiple sclerosis and Alzheimer's disease (AD).[12-14] Known features of PD neurophysiology relevant to network connectivity include reduced cortical inhibition[15], which may lead to disrupted modularity, and pathological subcortical oscillations[16], which may drive increased randomness. *Our pilot data and other studies[17] suggest that network architecture is abnormal in PD but its relationship to cognitive dysfunction has not been examined.*

Figure 1. Diagrams of random network (left: low path length and clustering), small-world network (middle: low path length, high clustering), and lattice network (right: high path length, high clustering).

Magnetoencephalography (MEG) measures cortical activity on a millisecond time scale and can provide highly informative data for graph theory analyses.[13, 14] Advantages of MEG versus fMRI include high temporal resolution, ability to separate oscillatory spectra and direct measurement of neuronal activity (vs. blood flow).[18] One of the strengths and challenges of MEG analysis is the high volume of potentially relevant data generated. Machine learning refers to automated algorithms designed to facilitate pattern recognition and classification and are particularly advantageous for large and complex data sets where traditional statistical approaches are rapidly overwhelmed.[19] Machine learning has been successfully applied to many complex biological data sets including genomics, proteomics, and neuroimaging.[20-22] Notably, machine-learning algorithms have been successfully applied to develop diagnostic AD biomarkers from MEG data.[23] Our group has further shown that machine-learning MEG biomarkers can also track AD progression over time.[24] *Machine-learning approaches to MEG data offers significant promise to develop biomarkers relevant to cognitive dysfunction in PD.*

Repetitive Transcanial Magnetic Stimulation (rTMS) modulates brain activity using repeated pulses from a magnetic coil over the scalp. rTMS may induce effects through changes in cortical excitability[25], neuroplasticity[26], gene expression[27], neurotrophic factors[28], and neurotransmitters including dopamine[29]. *Recent studies further show that rTMS can modulate focal oscillatory activity[30] and network connectivity[31, 32]*. Our Preliminary Data suggests that rTMS similarly affects network connectivity in PD. The therapeutic potential of rTMS is established in certain neuropsychiatric illnesses, including FDA approval for depression, with responses following a course of rTMS lasting over 6

months.[33] rTMS can also improve cognitive function in healthy older adults[34], AD[35] (with benefits lasting up to 4 months), and PD[36, 37]. Limitations of the prior PD studies include not specifically enrolling subjects with cognitive impairment, not controlling for depression, not assessing the durability of benefits and not tying rTMS effects to mechanisms. *In this proposal we address these limitations in a clinical and mechanistic trial of rTMS in PD patients with mild cognitive impairment (MCI).*

As patients will be required to obtain an anatomical MRI for TMS and MEG localization, we are adding an exploratory Aim to better understand the underpinnings of MEG findings. First, we would like to compare how MEG measures of resting state networks compare to fMRI resting state measures which have previously been reported as abnormal in PD (Gottlich et al., 2013). Second to see how structural connectivity, measured with diffusion tensor imaging (DTI) of white matter tracts, relates to MEG measures of functional connectivity. White matter has also recently shown to be altered in PD (Kim et al., 2013). Finally, oscillatory activity within the beta- and gamma-range, as measured non-invasively using EEG and MEG methods, has been associated with intrinsic glutamatergic and GABAergic activity in animal and computational models of the neocortex (Lally et al., 2014; Gaetz et al., 2011). We thus aim to characterize biochemical levels in the motor cortex of our population samples by using proton magnetic resonance spectroscopy (1H-MRS).

III. Preliminary Studies/Progress Report:

The grant associated with this proposal has just been funded by the NIH/NINDS. It builds on preliminary data from my CCTSI KL2 grant showing that MEG measures of cortical function differ between healthy controls and PD patients, correlate with cognitive function in PD patients without cognitive impairment, and are partially normalized by rTMS.

IV. Research Methods

A. Outcome Measure(s):

Neuropsychological and Neurological Testing: Our *primary cognitive outcome* will be the total score on the Mattis Dementia Rating Scale (MDRS)[99] which measures multiple cognitive domains and is validated in PD.[100] An important secondary question is whether connectivity in specific networks are associated with domain specific deficits. We will thus perform tests in the following domains: 1) Executive function (Trails B, Verbal Fluency, Stroop)[101]; 2) Memory (Hopkins Verbal Learning Test)[102]; 3) Language (Boston Naming Test)[103]; 4) Attention (Brief Test of Attention)[104]; and 5) Visuospatial (Judgement of Line Orientation)[105]. Finally, we will perform the Unified Parkinson's Disease Rating motor section[106] to use as a covariate in models for disease severity.

MRI:

MRI scans will be acquired using a G.E. 3.0 T Signa, whole body magnet with an Excite upgrade and 8-channel head coil using a 3-D, extended dynamic range, inversion recovery SPGR ASSET parallel imaging sequence with excellent gray/white contrast. The T1-weighted series will consist of .94 mm thick coronal images and can be acquired in 9 minutes. MRI images will be aligned with MEG using SPM8 software.[107]

The following additional sequences will be optional for participants and add approximately one hour to the MRI scan but do not add risk and the patient does not have to do anything except lie still.

Participants will be informed that these scans are not essential to the study and that we can stop scanning at any point should they become uncomfortable.

Diffusion tensor imaging (DTI) is a MRI scanning technique that enables one to assess the diffusion of water in brain tissue. The risks to subjects are identical to those in standard T1-weighted MRI scanning (i.e., no more than minimal risk). The purpose of DTI is to better quantify the white matter, or axon segments, of the brain.

1H-MRS can be used to quantify a range of brain metabolites, including n-acetylaspartate and glutamine/glutamate, markers of neuronal density and/or neuronal integrity. The MRS scan will allow us to crudely quantify neuronal integrity within the motor cortex. We will focus a single voxel of interest on the left prefrontal cortex because whole brain human MRS is prohibitively time-consuming and impractical. We will test the hypothesis that changes in connectivity are correlated to decreased levels of glutamate and GABA within the frontal cortex in persons with Parkinson's disease.

For purposes of comparison to MEG resting state, echo-planar imaging-gradient recalled echo (EPI-GRE) data normally acquired during functional MRI scanning (fMRI) will be acquired during the MRI session. Subjects will simply rest in the prone position with their eyes open for 2 minutes and closed for 2 minutes. The 10 minute baseline MRI scan will allow us to compare the generators of resting state MEG gamma-band to resting state activation in fMRI.

The total MRI procedure, if patients consent to the additional sequences, will last approximately 70 minutes and will begin with the anatomical portion. In case the study subjects feel any discomfort anytime after this first acquisition, they will be freed of terminating the additional scans without being disqualified from the study.

MEG Data Collection: Magnetic field data will be recorded using a whole head neuromagnetometer (4D Neuroimaging) with an array of 248 sensors at rest with eyes open for 2 minutes and closed for 2 minutes at a 678 Hz sampling rate. Data will be processed offline using a 0.1-100 Hz band pass filter. Data will be manually examined and five 6-second artifact free epochs for both eye-open and closed conditions will be selected for further analyses. Artifact correction if needed will be performed using independent components analysis.[108] Sensors will be realigned to a common sensor array to allow group level analysis in a shared brain space.[109]

MEG Data Processing: Following data acquisition, there are 4 major steps for graph theory analysis.[63] First, data will be transformed into the frequency domain using Morlet wavelets and parceled into six standard frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), low beta (12-20 Hz), high beta (20-30 Hz) and gamma (30-60 Hz).[110] Further analyses will be performed separately for each band. Second, the strength of functional connectivity must be calculated between all sensors. Granger causality will be used for this step, providing a directional weighted measure of connectivity suitable for graph theory.[111, 112] Third, functional connections between nodes will be used to create a network graph. This is matrix representing the directed weighted connection strengths between all sensors for each frequency band. Advantages of creating a weighted network graph include ensuring full connectedness and avoiding potentially arbitrary thresholds required for binary networks.[61] Finally, graph analyses can be performed on the network graph using the Matlab-based Brain Connectivity Toolbox[61] and custom Matlab code. Our *primary MEG outcome measure* will be network small-worldness, calculated as the ratio of the mean clustering coefficient to the mean path length normalized to a randomly connected network.[113] *Planned secondary MEG outcome measures* will include global efficiency (a measure of global integration related to path length), nodal efficiency (a measure of modularity)[60], and degree distribution (a measure of network resilience)[114].

B. Description of Population to be Enrolled:

We will enroll 25 PD subjects over the age of 40 without cognitive impairment diagnosed with probable PD using UK Brain Bank Criteria[38] and 55 PD subjects over the age of 40 with MCI or mild dementia using the Movement Disorder Task Force 2012 criteria and a Clinical Dementia Rating scale score (CDR) less than 2.[39, 40] All study visits will be performed in subjects' best dopaminergic On state. PD MCI and mild dementia subjects will be tested on anticholinesterase therapy if already taking these medications given the potential difficulty of finding drug naïve subjects; long half-life of these medications; and desire to find measures robust to medication effects as seen in prior MEG studies.[41]

Exlusion criteria:
1) features suggestive of other neurological disorders
2) DBS
3) evidence for active depression or Hospital Anxiety Depression Scale[42] score $\geq$ 11
4) motor symptoms expected to interfere with scanning
5) contraindications to TMS:

- history of seizures or status epilepticus,
- unstable coronary artery disease
- hydrocephalus
- implantable electrodes, cerebral spinal fluid shunts, skull plates or other intracranial metal
- medical devices including pacemakers or other implantable stimulators or pumps
- subjects taking medications known to lower seizure threshold
- pregnancy

In order to complete recruitment including consent screen failures, drop-outs and unusable datasets we request the capacity to recruit up to 150 participants.

C. Study Design and Research Methods

Aim 1 Rationale and Design: Even while not engaged in a task the brain exhibits spatially and temporally organized patterns of activity.[84] The past 15 years has seen remarkable progress in understanding these intrinsic functional networks (also termed resting-state networks) in both health and disease.[85] Intrinsic networks are consistent within and across individuals, correlate with behavioral and clinical outcomes, and can be analyzed with graph theory measures to define global and local aspects of network organization.[59] MEG can be used to identify multiple intrinsic networks similar to fMRI but with additional information regarding the power spectra of connections.[86, 87] Importantly, MEG measures of intrinsic activity can sensitively discriminate AD from other neurological disorders and correlate with cognitive function in both AD and multiple sclerosis.[40, 47, 64] Prior studies of PD suggest changes in cortical connectivity may be associated with dementia but did not define network organization using graph theory.[88] Our *objective* for this experiment is to determine whether graph theory measures of intrinsic MEG activity correlate with cognitive dysfunction in PD. We *hypothesize* that loss of small-world architecture contributes to cognitive dysfunction in PD through loss of local efficiency and increased randomness. To test this hypothesis, 25 PD subjects with MCI and 25 with normal cognition will undergo neuropsychological testing and a resting MEG scan for analysis for this aim. MEG and neuropsychological testing may be done on the same day or separate days, not to exceed 1 week in between. We will use graph theory measures to model the

relationship between network connectivity and cognitive function. The data generated by this Aim will fundamentally advance our understanding of the role of cortical physiology in PD cognitive dysfunction, will provide a modern network framework for future studies in this field and may provide insights leading to future therapeutic targets.

Aim 2 Rationale and Design: While finding group differences or clinical associations in brain connectivity using MEG will improve our understanding of the pathophysiology of PD cognitive dysfunction it is unlikely to provide sufficient discriminant ability to serve as a useful diagnostic or predictive biomarker. Machine learning algorithms offer several advantages in terms of biomarker development including: 1) Characterization of data at the level of the individual; 2) Ability to simultaneously optimize multiple features from complex datasets; and 3) Allows data to drive feature selection rather than theoretical assumptions.[72] Support Vector Machine (SVM) is a machine learning method that works by determining the maximum separation between classes in a high dimensional space composed of the features of interest.[119] Our *objective* for this Aim is to develop a novel state-defining biomarker for PD-MCI based on MEG measures of regional activity and network connectivity using SVM. We *hypothesize* that cognitive dysfunction in PD can be characterized through a unique combination of MEG regional and network features and optimized through SVM. To test this hypothesis, we will reanalyze the MEG data collected in Aim 1 using SVM to classify PD patients with and without MCI.

AIM 3 Rationale and Design: rTMS can improve cognition in PD without dementia[52], PD with depression[80], older adults[122] and in AD[123] but has not been tested in PD-MCI. Given the need for improved cognitive treatments and possible differences in rTMS effects on PD-MCI pathophysiology it is important to specifically test rTMS in this population. Prior studies as well as our own pilot data suggest that rTMS modulates cortical connectivity;[16,17] thus rTMS provides not only a potentially effective intervention but an important causal test of our associative data and theoretical link between cortical connectivity and cognitive dysfunction in PD. Our *clinical objective* for this experiment is to determine whether rTMS improves cognitive outcomes in PD-MCI. Our *mechanistic objective* is to determine whether rTMS normalizes patterns of cortical connectivity. We *hypothesize* that high-frequency bifrontal rTMS will partially normalize patterns of cortical connectivity linked to frontal nodes and will improve cognitive measures. To test this hypothesis 55 PD-MCI subjects will be randomized to a 10-day course of real or sham bifrontal high frequency rTMS. We will measure cognitive and MEG outcomes pre-treatment and on the day of the last treatment (neuropsych testing and MEG procedures may be separated by 1 day if patient is fatigued) and repeat cognitive measures 28 days post rTMS to assess the durability of cognitive changes.

TMS: TMS will be administered using a 70-mm diameter air-cooled figure-of-8 coil and SuperRapid^2 Magstim Stimulator. We will first define the subject's resting motor threshold (MT) by localizing the hand area of motor cortex and determing the minimal TMS amplitude needed to produce a motor-evoked potential of 50 microV on 4 of 8 trials measured by EMG over the first dorsal interosseous muscle (Biopac, Goleta, CA). Once the MT is determined, repetitive pulses will be delivered to the right and left pre-frontal cortex (Brodman area 46) using a frameless stereotactic navigation system and the subject's MRI in Brainsight software. Depending on our preliminary results from Aim 1, we may change our target if it is evident that a particular frontal node shows high clustering within beta or theta frequency bands. This type of targeting based on functional data has been previously performed and may enhance TMS effects on intrinsic connectivity.[16] Stimuli will be delivered at 20 Hz at 90% rMT for 25 trains of 30 pulses per train, inter-train

interval of 30 seconds for a total of 750 pulses per hemisphere, which is well within the most recent international TMS safety guidelines.[129] This dose and duration of rTMS is based on physiological studies of healthy adults and treatment studies of cognition in PD and Alzheimer's disease.[52, 123] Side of first stimulation (left vs right hemisphere) will be counterbalanced across subjects. Sham stimulation will be delivered using a sham coil fitted with electrodes to mimic both the auditory and somatic sensation of real TMS as I have performed in prior TMS trials.[19]

Schedule of Procedures

		← 2 weeks →			
	Baseline Procedures[2]	rTMS Session 1[1,]	rTMS Sessions 2-9[1]	rTMS Session 10[1]	28 days post-rTMS Session 10[1]
Informed consent	X				
MRI (anatomical and optional functional scans)	X				
MEG	X			X[1]	
Neuropsych tests	X			X[1]	X[1]
rTMS (real or sham)[1]		X[1]	X[1]	X[1]	
Randomization to real or sham TMS[1]	X				

[1]PD-MCI subjects only

[2]Baseline procedures to be completed within 1 week of rTMS Session 1

D. Description, Risks and Justification of Procedures and Data Collection Tools:

PD-MCI and mild dementia patients may be considered a vulnerable population due to cognitive dysfunction but are necessary to answering our research questions. We are cognizant of this issue and will carefully assess potential participant's understanding of the study, particularly of study activities and risks. If there are any concerns on the part of the investigator or potential participant, we will require that their guardian participate in the consenting process and sign an informed consent. We will also require that PD-MCI subjects give consent, or at minimum assent if fully informed consent is not possible. Our protocol and consent forms will be approved by our local IRB before approaching any potential subjects.

After enrollment and screening assessment, PD and PD-MCI subjects will undergo neuropsychological testing, magnetoencephalography (MEG) recordings, and MRI. PD-MCI subjects will then be randomized in a 1:1 ratio to real or sham TMS groups using MAPLE 9.0 software (Waterloo, Canada). Baseline neuropsychological testing, MEG, and MRI may be performed over multiple days, but all will be completed within 1 week and within 1 week of first TMS session for PD-MCI subjects.

TMS will consist of 10 sessions (over two weeks) of 20 Hz repetitive TMS given at 90% of motor threshold in 25 trains of 30 pulses per train with a 28.5 second inter-train interval to each prefrontal cortex (Brodman area 46) localized using MRI and Brainsight software. There will be a total of 750 pulses per hemisphere per session. These TMS parameters are well within the most recent published safety guidelines.[129] This dose and duration was chosen on the basis of prior physiological studies in healthy adults[78] and in treatment studies of cognition in PD[52] and Alzheimer's Disease.[123]

There are minimal risks involved in the proposed research. There are no known risks from MEG recordings. In appropriately screened subjects, the primary risk of MRI is claustrophobia and anxiety which is remediable by removal from the scanner. Cognitive testing as proposed in this study may induce boredom or restlessness. Any new neuropsychiatric diagnoses detected during screening (e.g. depression) will be referred for appropriate treatment, including emergent treatment if indicated. TMS as proposed in this study has a minimal risk (less than 1 in 1000) of inducing seizures in appropriately screened subjects or other adverse events.[129] Noatbly, there have no cases of epilepsy (recurrent seizures) or status epilepticus (prolonged seizure considered a medical emergency) with TMS. The risks of TMS in PD are similar to that of the general population.[3] Transient motor worsening has been reported with supplementary motor area TMS in PD, but not with the frontal targets we have proposed. There have been reports of hearing loss with repeated TMS pulses and thus all subjects will be required to wear ear plugs, similar to MRI. There is a slight risk of headache and neck pain which is typically self-resolving and/or treatable with over the counter analgesics.

All subjects will be required to wear hearing protection and will be supervised by study personnel during all aspects of this study. A neurologist will be available either in person or on-call within the building in the event of a seizure or other adverse study event. Study personnel involved in human subject interactions will be trained not only in human subjects protection but will be also BLS or ACLS certified and specifically trained in seizure safety and what to do in the event of other medical emergencies. There is a COR cart available outside of the TMS and MEG laboratories. All adverse events will be reported to the IRB within 5 days and seizures or other significant adverse events associated with TMS will additionally be reported to the FDA.

E. Potential Scientific Problems:

Prior TMS trials are often questioned regarding the adequacy of patient blinding with certain sham procedures. Our sham involves both auditory and tactile stimulation, and in fact resulted in a similar improvement in depression as real TMS in our recent trial.[19] Subject retention, particularly with PD-MCI, may be difficult with 2 weeks of daily treatment. We will use similar procedures to our PD apathy rTMS trial where we maintained 100% retention. Finally, our sample size is relatively small to detect clinically significant changes. This is in part due to budgetary imitations and one goal of this trial is to serve to develop a more definitive, larger trial with longer-term follow-up. Changes in sensor location over repeated recordings may result in false attribution of brain activity

changes. To address this issue, sensors will be realigned to a common sensor array to allow repeated group level analysis in a shared brain space.[109]

F. Data Analysis Plan:

AIM 1 Statistical Analysis and Sample Size: To address our primary research question, Spearman correlations will be used to identify frequency spectra small-worldness measures associated with the MDRS in eyes-closed data with a false detection rate set at 0.05 to handle the issue of multiple comparisons. We will then use linear regression to determine whether small-worldness in these specified frequency bands remain associated with the MDRS when controlling for each other as well as other important covariates, namely age and motor severity. A *sample size* of 45 (allowing for 5 drop-outs and/or unusable data-sets from the original 50) will allow us to detect correlations of 0.18 or higher between our MEG features and MDRS with 80% power 0.05 significance. This is comparable to correlations of 0.19 and higher seen in other resting state MEG studies of cognition.[115] Planned secondary analyses will parallel our primary analysis to determine whether global efficiency, nodal efficiency or degree distribution are significantly associated with MDRS in linear regression models. Exploratory analyses will assess reactivity of these measures between eyes open and closed conditions and assess whether domain specific neuropsychological test scores are associated with connectivity within networks defined by domain related nodes (e.g. occipital nodes and visuospatial tests).

AIM 2 Statistical Analysis and Sample Size: We will use SVM to determine what combination of MEG features yields the most robust classifier for discriminating PD with and without MCI. The principle behind SVM learning is that features of interest can be modeled in a high-dimensional feature space (see Figure 2 for a visualization of a very simple 2 feature space). SVM then uses a recursive algorithm to define a hyper-plane of select features creating the greatest distance between groups of interest.[119] Given the large potential combination of MEG features and sensors this will be a computationally intensive but tractable SVM application. As the optimal number of features to build an SVM classifier is not known a priori, we will use a procedure called bagging-cross-validation to determine the optimal number of features and maximize the information gained from SVM in this relatively small sample size.[121] This approach uses a boot-strap leave one out procedure to create n – 1 training sets and n test subjects, where n is the total sample size, to optimize feature number and maximize the final receiver operating curve. Given the large effect sizes seen in our pilot data and other MEG studies of PDD[58], we anticipate that our *sample size* of 45 (allowing for 5 unusable data-sets from the original 50) will allow us to create a classifier with an area under the ROC curve (AUC) of 0.95 or higher comparable to AUCs seen in other SVM applications in dementia and MCI populations with as few as 15 subjects per group.[68]

AIM 3 Statistical Analysis and Sample Size: We will address our primary clinical research question by determining whether there is a significant group difference between the real and sham treated PD-MCI patients on the MDRS change following rTMS using repeated measures ANOVA. We will address our primary physiologic research question by determining whether there is a significant difference between the real and sham treated PD-MCI patients on change in MEG measures of small-worldness using a repeated measures ANOVA. Planned secondary analyses will include determining group differences in change on measures of quality of life, domain specific neuropsychological results and durability at the 28-day post-TMS time point. If cognition is improved we will use regression modeling to determine if these improvements were associated in changes

in small-worldness or other MEG features. With a total *sample size* of 50 (25 per group allowing for 5 drop-outs from original 55) we will be able to determine a between group difference of 10 points on the MDRS (assuming a SD of 13 as per prior trials and an effect size 0.77)[124] with 80% power and 0.05 significance. This sample size is comparable to prior PDD studies. For example, a study of rivastigmine in PDD detected significant change on the Mattis with only 28 subjects.[124]

Exploratory Aim Statistical Analyses and Sample Size: We will address our exploratory research questions by looking at Spearman correlations or linear models of MEG and MRI measures. Power considerations are similar as for Aim 1 with detection of correlations of 0.18 or higher between our MEG and MRI features with 80% power 0.05 significance.

G. Summarize Knowledge to be Gained:

PD is the second most common neurodegenerative disease, affecting over one million Americans and dementia is the most common cause of nursing home placement in this population.[53, 54] Our understanding of the neurobiological mechanisms of cognitive dysfunction in PD are limited and we do not have efficacious treatments. This research with address this significant public health issue in three major ways: 1) Identify abnormalities in cortical connectivity associated with cognitive dysfunction in PD; 2) Develop a MEG biomarker for cognitive dysfunction in PD; and 3) Evaluate the potential for TMS to induce durable changes in PD cognitive function and connectivity. Given the burden of dementia in this population, we feel that the minimal risks involved are justified both to individual PD and PD-MCI subjects, the larger population of PD and PD-MCI patients, and to society as a whole. Recent TMS studies using published safety guidelines suggest that the risks of TMS may be even lower than previously described. Even using conservative estimates and anticipating some discomfort from prolonged sitting and cognitive testing, we argue that this research is imperative to advance this field and ultimately to provide relief to these patients and their caregivers.

H. References:

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