Cover Page

Document: Study Protocol and Statistical Analysis Plan

Official Title of Study: Subcortical-cortical network dynamics of anesthesia and consciousness

NCT04502550

Date of Document:

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Form A

IRB #	STU 2021-0396

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

Our *overall hypothesis* is that the mesocircuit model of consciousness, which was original proposed to characterize recovery after brain injury, can be generalized to understand mechanisms of consciousness more broadly. The protocol focuses on experimentally probing the mesocircuit in neurosurgical patients, taking advantage of differences in patient populations with respect to basal ganglia disease (e.g., Parkinson disease [PD] vs essential tremor [ET]), the ability to synchronously acquire high resolution basal ganglia (BG) and cortical neurophysiology, and the opportunity to modulate the circuit in a targeted fashion with deep brain stimulation (DBS) to interrogate brain-behavior relationships. Our *overall goal* is to use neurosurgical opportunities to gain an understanding for the role of the basal ganglia in regulating consciousness, using a pharmacological model of consciousness. We propose four separate studies under one clinical trial, which we present here in sequence, titled and labeled according to the organization of the grant as Aim 1, Aim 2, Aim 3A and Aim 3B.

In Specific Aim 1, we aim to demonstrate differences in propofol sensitivity across 2 patient cohorts based on the presence of absence of basal ganglia pathology (Parkinson disease [PD] and essential tremor, respectively). By characterizing and demonstrating differences in group level pharmacokinetic/pharmacodynamics of propofol (primary endpoints), we will provide evidence suggesting basal ganglia pathology is associated with differential response to propofol suggesting the basal ganglia are an important part of brain circuitry regulating consciousness. This aim will be completed entirely at UCLA.

In Specific Aim 2, we aim to characterize the temporal evolution of brain signals (recorded from the cortex and the basal ganglia) with propofol induced loss and recovery of consciousness to identify network level changes correlating with consciousness. All subjects will have PD and will be assigned to the same intervention of propofol administration and withdrawal, while we invasively record brain signals from key nodes in the hypothesized brain networks regulating consciousness. The primary endpoint/outcome will be neurophysiologic data.

In Specific Aim 3A, we aim to demonstrate the role of the basal ganglia in regulating consciousness by focally modulating the network with deep brain stimulation (DBS). Patient with PD and previously implanted DBS will be randomly assigned to undergo anesthetic induction either with or without DBS. Primary endpoint will be the characterization of the pharmacokinetics/pharmacodynamics with and without stimulation with PD. We expect to see shifts in the kinetics and dynamics associated with DBS, suggesting focal modulation of the circuit alters consciousness regulating circuitry of the brain.

In Specific Aim 3B, we will conduct a final clinical trial in which we will, as in Aim 3, record from the brain of patients undergoing DBS implantation, now with or without DBS on during both induction and emergence from propofol anesthesia. The primary outcome will be neurophysiological signals and observing perturbations of the evolution of the brain signals with vs without DBS.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

For "Background" see grant application under "Research Strategy" – sections 1.1 – 1.5.

Electrode grids will be obtained from AdTech Medical which manufactures FDA-approved electrode grids that are used daily in regular neurosurgical practice. In patients undergoing DBS implantation, grids will be placed for research purposes using the same technique as is usually done for clinical purposes, placing the grid under the dura and over the cortex, taking great care to protect bridging veins. Note, that grid placement is for research purposes only. The grids will be removed prior to closing, such that the patient will end up with the identical implant they would otherwise have. These electrode grids have also been approved under a 510K letter and are approved for research. They are approved under the same letter as the NeuroOmega system (below).

In all cases, electrical signals collected by the electrodes will be transmitted to an FDA-approved amplifier system for amplification, and digitization. Neurophysiological signals will be amplified (AlphaOmega, NeuroOmega) using a sampling rate of 44 kHz (microelectrode recordings) and 1.3 kHz (macroelectrode and ECoGs recordings). This amplifier is used for research purposes, and is approved for such use under a 510K letter.

Propofol will be used as the general anesthetic for this study. It will be used for FDA-approved purposes only: as anesthesia for patients undergoing surgery. Propofol is administered for standard of care, and also for the research study. Propofol infusion will be administered by an anesthesiologist. For research, propofol will be administered via Target-Controlled Infusion protocol. It will be infused via Harvard PHD 22 Infusion/Withdrawal Pump, controlled by STANPUMP software and monitored by the anesthesiologist.

b. Current practice

Not Applicable

3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

Specific Aim 1: The overall goal for this aim is to assess the population level pharmacokinetic-pharmacodynamic (PK-PD) model for propofol sedation in *PD patients (who have BG pathology) in contrast to a control group (essential tremor, ET, who do not have BG pathology).* The PK-PD model will be used to predict the time course of plasma and effect site concentration of propofol and establish differential anesthetic sensitivity profiles. This assessment will be done during battery placement surgeries for individuals already implanted with DBS electrodes.

Specific Aim 2: These experiments will be performed during the initial DBS implantation surgery. The overall goal for this aim is to assess neural correlates, with specific attention to network parameters/states, during LOC/LOR and ROC/ROR using direct, high-resolution invasive recordings from the basal ganglia (GPi/GPe) and frontoparietal cortices in humans. *There is only one study group in this aim – PD patients (no stimulation of GPi/GPe).*

Specific Aim 3a: These experiments will be performed during the DBS generator exchange surgeries, as in Aim 1. All study participants will have PD in this set of experiments and results will be compared across *experimental cohorts (GPi vs GPe stim)* as well as to PD patients anesthetized with propofol off stimulation (from Aim 1). During data analysis, the rater will be blinded to stimulation assignment.

Specific Aim 3b: These experiments will be performed during the initial DBS implantation surgery. Recordings and behavioral assessments will be made during both induction and emergence of anesthesia with *either GPi or GPe stimulation*, comparing results with those acquired in Aim 2 (no stimulation). As in Aim 3a, the rater will be blinded to stimulation assignment.

4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

Some information in responses below is taken from grant protocol section 3 “Approach”. See figures referenced and citations in grant protocol.

RESEARCH METHODS

For all specific aims:

Prior to conducting any research related tests / procedures, the patient will be consented. The consent process will be facilitated by the IRB approved research coordinator and will occur in a private room in the pre-operative area prior to surgery. Once in the operating suite, the patient will be put under anesthesia for clinical purposes for surgery. Privacy will be maintained by limiting the individuals in the operating room to only necessary IRB approved research personnel. In addition, all data collected during the study will be immediately de-identified and stored on an encrypted, password protected server.

Behavioral Assessments. For each experiment, three behavioral responses will be evaluated: (1) loss/recovery of spontaneous movement (i.e., loss and recovery of responsiveness (LOR/ROR)) (2) loss/recovery of movement in response to stimuli (separately to clicks [non-salient] and verbal stimuli [salient], as per prior work by Purdon and colleagues4), and (3) loss/recovery of movement to command (verbal command with patient name with instruction to show different numbers of fingers, as proxy of loss/recovery of consciousness (LOC/ROC)). Stimuli will be presented in an interleaved fashion every 4 seconds binaurally via headphones (15 presentations of each stimuli at each dose, total 5 min per dose, or until failure to respond 3 times in a row to a certain stimulus). We use these separate measures because of the literature and our hypothesis that circuits mediating responsiveness and consciousness are separable. Namely, numerous studies highlight that consciousness (defined as ability to interact with the environment, most often measured by the isolated forearm test) can be maintained even with loss of responsiveness.[39, 56]

Target-Controlled Infusion (TCI) Anesthesia protocol. We will use a syringe pump controlled by STANPUMP implementing the Eleveld Pharmocokinetics-Pharmacodynamics (PK-PD) model for propofol as a TCI system to achieve plasma target propofol concentrations.[57] Two intravenous cannulae will be used in each patient, one for propofol infusion and one for blood draws. Supplemental oxygen will be delivered as needed by nasal canula. Propofol serum concentrations will be confirmed via blood sampling to confirm the TCI performance. Blood samples will be stored on ice until they can be centrifuged, and the plasma fraction isolated by centrifuge and stored at -20 deg C until analyzed. Propofol concentration will be determined by a high performance liquid chromatographic method (HPLC).[58] The attending anesthesiologist will be able to override the pump at any point should there be evidence of airway obstruction, hemodynamic compromise, or other clinical issue, though the long track record of safety of TCI systems outside of the United States suggests this should not be a major issue, and TCI models appear safe to use in PD patients.[47] Per prior published work[48], target effect-site concentration of propofol will be started at 1.4 µg/mL (below expected level required for LOC/LOR) and will be increased by 0.3 µg/mL with reassessment until endpoints are achieved. ROC/ROR will be assessed with gradual reduction in propofol dose as with assessment of relevant endpoints. Due to clinical and invasive neurophysiological requirements, in all cases, ROC/ROR will be evaluated after LOC/LOR.

Specific Aims 1 & 3a:

Data collection for these aims will occur during IPG placement / replacement surgery for individuals with DBS. Specific Aim 1 will occur solely at UCLA following these guidelines. Specific Aim 3a will be collected at both UCLA and UTSW following the same protocol.

Surgeries are performed under monitored anesthesia care, using propofol anesthetic. Once patients are positioned, propofol is administered per a target-controlled infusion (TCI) anesthesia protocol detailed above. Participants will also complete the Behavioral Assessments outlined above. Assessment will be completed at the end of every propofol infusion (every 5 minutes). Blood draw will also occur at this time. If data is being collected for **Specific Aim 1**, no DBS stimulation will occur. If data is being collected for **Specific Aim 3a,** the patient will receive either GPi or GPe stimulation during study tasks. Once stable anesthesia is established, local anesthetic is infused and the generator is replaced, prior to closing the skin. Behavioral assessments will be made during induction and / or emergence.

Specific Aims 2 & 3b:

Data collection for these aims will occur during DBS implantation surgery. Data will be collected at UCLA and UTSW following the same protocol.

Surgical procedure Intraoperative Recordings (Specific Aim 2, 3). For DBS implantation for PD, the DBS lead is targeted to ventral posterolateral GPi using image-guided targeting (2-4 mm anterior, [19-24] mm lateral, and 4-6 mm inferior to the mid-commissural point [MCP], Figure 4). All trajectories are confirmed with intraoperative microelectrode recordings, based on firing activity and kinesthetic tests[52] in addition to intraoperative awake macrostimulation testing, clinically assessed by Dr Pouratian. LFP will be recorded from deep brain targets from the DBS lead’s four or eight contacts (dependent on clinical selection of DBS

lead) at the therapeutic target. Unilateral ECoG recordings are obtained from the right frontoparietal region by advancing a subdural ECoG strip with eight 4 mm platinum contacts (1 cm inter-contact spacing) posteriorly through the burr hole used for DBS implantation and an additional lead (4 contact) anteriorly towards the prefrontal cortices (Figure 4). Unilateral ECoG is planned to mitigate risk. Intraoperative fluoroscopy is used for anatomical localization as extensively described in our previous work.[50] We use the Freesurfer cortical parcellation and the Desikan-Killiany atlas[53] to identify pre and postcentral gyri and middle frontal gyrus and select the contacts for analysis respectively. DBS leads are localized postoperatively with lead-DBS[54] (Figure 4) using preoperative structural MRI and postoperative CT scan. For M1, we identify the first ECoG contact anterior to the central sulcus and completely overlying the precentral gyrus. Anterior scalp reference and left retroauricular ground are used, to enable subsequent re-referencing. Neurophysiological signal acquisition, stimulus presentation, and recordings of behavioral responses are controlled via a single computer running BCI2000.[55] Signals are amplified (AlphaOmega, NeuroOmega) using a sampling rate of 44 kHz (microelectrode recordings) and 1.3 kHz (macroelectrode and ECoGs recordings).

The following timeline will be followed during the above surgerical procedure:

The patient will emerge from anesthesia for clinical placement of the left DBS electrode and neurological testing done by Dr. Pouratian and the neurologist. Once clinical testing is complete, the ECoG strip will be placed on the right side for research purposes. Then, Dr. Pouratian will continue with the clinical procedure and place the right DBS electrode and conduct neurological testing to confirm placement. The researchers will connect ECoG and DBS leads to the Neuro-Omega system to record brain signals throughout research related tasks. Once all clinical testing has been completed, the research team will simultaneously record cortical ECoG and pallidal LFP from GPi/GPe during both induction and emergence with target-controlled infusion of propofol detailed above. During induction and emergence, the participant will also complete the behavioral task detailed above. If data is being collected for **Specific Aim 2**, ECoG /LFP recordings and behavioral assessments will take place with no stimulation. If data is being collected for **Specific Aim 3b,** recordings and behavioral assessments will be made during both induction and emergence of anesthesia with either GPi or GPe stimulation. When the research portion is complete, the ECoG strips will be removed and the surgery will finish per clinical standard of care.

DATA ANALYSIS

LFP Analyses:

Signal analysis is performed in MATLAB (The Mathworks Inc., Natick, MA). Data is parsed into various behavioral and stimulation state epochs, excluding any sections containing electrical or movement artifact using methods previously described. [41, 50] Bipolar re-referencing of adjacent contacts is used in order to emphasize local and minimize global signals, which is critical for the proposed network coupling analyses across brain regions. 60 Hz line noise is rejected using a notch filter. 60 Hz line noise is rejected using a notch filter.

Power spectra are obtained by applying non-overlapping windows in time series using Thomson's multi-tapering method59 or Welch method and 1 Hz frequency resolution. To minimize stimulus artifact during stimulation trials, we employ the following critical steps: (1) bipolar referencing to minimize common stimulation artifacts in adjacent contacts (2) monopolar deep brain stimulation with current return at the shoulder (analogous to chronic generator implant) (3) bipolar recordings flanking the site of deep brain stimulation in order to minimize differential stimulation artifact between the two recordings leads (4) amplifier grounding on the contralateral hemibody (5) high frequency sampling (to minimize aliasing) (4) signal preprocessing to filter stimulation frequency and (6) employing Hampel filters to eliminate residual stimulus related noise. The Hampel filter uses the outlier robust Hampel identifier to detect peaks in the power spectra attributable to the stimulation frequency and replaces them with the median value of local, adjacent values.60 Using this multi-tiered approach to recording and signal processing, we have successfully recorded cortical activity during subcortical stimulation. [41, 42]

Measures of Network Coupling (bivariate, assessed over time and trials) In our approach, when we refer to analyzing "network coupling," we will investigate a broad range of coupling measures. The measures and their rationale are summarized here. Coherence, the most commonly used measure of LFP coupling, is used to describe the degree of co-variability between signal pairs over different frequency ranges.[61] To find the time-frequency representation of coherence for pairs of signals, we use a moving window approach and multi-taper method. Phase synchrony index, a measure of consistency of phase differences between two signals, is used to separately evaluate the specific role of phase difference on neurophysiological observations. Phase locking is of particular interest as fixed phase relationships may be particularly detrimental to information transfer across nodes.[62] Phase-Amplitude Coupling (PAC) is assessed both locally and across nodes and across time and across trials and is quantified using modulation index (MI).[63] PAC is a critical measure that has been identified as a putative pathophysiological mechanism and our group has previously shown to be a potential mechanism for long distance coordination of physiological signals.[16] MI is a method based on Kullback-Liebler (KL) divergence used to extract PAC, described previously. In order to extract the phase from phase signals corresponding to the peak of amplitude signal which we refer to as preferred phase, the weights of the phaseamplitude histogram were used as amplitudes of a vector, while the center phase of each bin constituted the phase of the vector. Statistical significance of MI values is evaluated using surrogate data analysis (by circularly shifting one series relative to the other). MI values are then converted into z-scores and false discovery rate (FDR) is used to correct p-values for multiple comparisons.*64* Phase lag index (PLI) is used to determine if one signal consistently leads or lags another signal, using non-zero iCoh which indicates an interaction between signals that cannot be due to volume conduction. PLI measures the

extent to which a distribution of phase angle differences is distributed toward the positive or negative side of the imaginary axis on the complex plane. Specifically, we employ unbiased weighted PLI[62] in which angle differences are weighted according to their distance from the real axis. We emulate the moving window approach used in the spectral analyses described above, allowing evaluation of patterns of changes in these measures over time. Phase slope index is also used as a measure of the consistency of directional flow within a frequency by determining if the slope of the phase lag between two processes is positive or negative over several adjacent frequency bins, suggesting the direction of signal flow. To assess directionality of the changes, we will perform multivariate granger causality analysis[65] Similar to the power, connectivity analysis will be performed both across the time[16, 41-43, 50, 66] and the trials[67] and with frequency and time resolution similar to the spectral analysis.

Graph theory is used to characterize global network architecture and the inter-relatedness of the nodes.[68] We will employ weighted connectivity measures to construct functional network diagrams and extract metrics using the Brain Connectivity Toolbox.[69] Given only 5 nodes, we will compare the following measures across conditions: node degree, clustering, pathlengths, and identification of hubs. Dynamic Causal Modeling (DCM), implemented in SPM70, is used to evaluate causal network architecture rather than separately evaluating pairs of nodes. DCM identifies the most likely among a set of competing models that best accounts for observed neural dynamics, allowing modeling of missing nodes which is critical since human studies preclude evaluation of every node.

Statistical Analysis is done using SPSS. We assess the significance of connectivity measures by shuffling data to create a permutation distribution and calculating Monte-Carlo estimates of the significance probabilities and/or critical values using parametric/nonparametric statistical tests. We will explore the correlation between behavioral and LFP metrics, and clinical scores (total and lateralized UPDRS-III) using a multiple linear regression model. To confirm generalization to new data points, a "leave one-out" procedure will be employed and finally a coefficient of determination (R2) and RMS of errors will be calculated for all generalization data. T-tests will be used to compare between conditions. To investigate interactions, two factor ANOVA will be used. Gaussian "v-test" and Rayleigh tests will be used to compare the preferred phase angle of connectivity with the uniform distribution to infer phase specificity.[71] The Watson-Williams two-sample test (i.e. circular analogue of the two-sample t-test) will be used to assess whether the mean directions of two groups are identical.

Specific Aim 1:

Behavioral data analysis and constructing propofol dose response curve. Behavioral data will be collected from both PD and ET patients undergoing generator replacement surgery. Propofol will be administered using a recently published, unified PK-PD for propofol developed to predict the BIS (bispectral index) response to propofol for a broad, diverse population by Eleveld and colleagues, which includes age adjustment, allometric scaling, and parameters for arterial and venous sampling.[57] (Although not a focus of our work and its value questionable given our underlying hypothesis of altered mesocircuit function in PD, we will record BIS in all patients as an additional data point.) From a range of studies, we expect that in a healthy population loss of responsiveness in 50% of healthy patients will occur with an age-adjusted effect site concentration (Ce50)between 2.71–3.44 µg/ml.[74] The only published pharmacodynamic studies in PD patients reported a Ce50 of 2.05 and 2.28 µg/ml.[47, 48] We therefore expect that the dose-response curve for PD patients will be shifted to the left compared to ET patients, who lack basal ganglia pathology. To test this hypothesis, propofol infusion will be initiated with an effect-site concentration (Ce) target of 1.4 µg/ml for 5 min, incremented by 0.3 µg/ml steps every 5 min until loss of behavioral responses (as defined in 3.1.4). One additional incremental step will be performed after loss of responses. Venous serum samples will be drawn at the end of each 5 min step before the next increment. After conclusion of the procedure, target Ce would decrement by 0.3 µg/ml every 5 min until recovery of behavioral responses. Serum sampling will be used to confirm that the Eleveld unified TCI model is functioning as predicted.

PK-PD Model Fitting. The pharmacodynamic responses for both behavioral endpoints will be modeled with a sigmoidal Emax function: $Fraction_{responsive} = 1 - C_e^{\gamma}/(C_{e50}^{\gamma} + C_e^{\gamma})$; Where Ce is the effect site concentration, Ce50 is the effect site concentration at which half of the population is no longer responsive, and ɣ is the Hill coefficient governing the slope of the sigmoid. Fitting will be done using NONMEM (ICON Development Solutions) and parameter estimation. Comparison of Ce50 values between PD and ET populations will be made using 95% confidence limits on the resulting parameter fits. Additional exploratory analyses of the model will attempt to account for heterogeneity in the PD population by constructing candidate models that nest the PD effect by both UPDRS scores and covariates of cognitive function (MoCA), utilizing a drop of corrected Akaike Information Criterion (AIC) by 20 points as a threshold for a significant improvement from adding a parameter to the model.

Specific Aim 2:

We will temporally correlate the evolution of behavioral measures of LOC/LOR (including loss of spontaneous movement and loss of movement to command, with digital synchronization with neurophysiological recordings through digital event recording) with l changes in GPi vs GPe pallidocortical circuits. Techniques outlined in LFP analyses above will be implemented to complete assessment.

Specific Aim 3a:

Statistical analysis pipeline outlined in Aim 1 will be replicated in Aim 3a.

Specific Aim 3b:

Recordings and behavioral assessments will be compared to results acquired in Aim 2. Techniques outlined in LFP analyses above will be implemented to complete assessment.

SAMPLE SIZE

Aim 1: We estimate our sample size using a Monte Carlo simulation based on predicted differences in propofol sensitivity as defined in prior studies,[47, 48, 57, 75] which suggest a 20% difference in Ce50 with 20% intersubject variability and an additive measurement error. We performed the Monte Carlo simulation by constructing two population response curves from N patients whose response to propofol was determined by the sigmoidal Emax model while varying only the Ce50 between the populations. The nonlinear fitting was performed for both populations and this process was repeated 1000 times, with the fraction correctly identifying the underlying difference in the model used as our power estimate. N was then incremented until 80% power was obtained, which required approximately 24 patients per arm (total of 48 patients). Similar studies have targeted enrollments of 18-31 subjects per arm.[47, 48, 76] To account for an estimated 20% dropout rate or protocol error, we plan to recruit a total of 58 subjects. All patients will be recruited from / data collection will occur at UCLA for Specific Aim 1.

Aim 2: Our experiments are purposefully designed to ensure proper power and that experiments can be completed within intraoperative time constraints. Using our prior LFP recordings in PD as well as the published literature[43, 78, 79], we conducted a power analysis based on average α/β power modulation between rest and anesthetized state observation (Figure 1). Power analysis indicates a total of 16 patients is required to achieve significant results (one-sample t-test with d=0.75, p=0.8, α=0.05). To account for an estimated 20% dropout rate or protocol error, we plan to recruit at least 20 subjects. Data collection will occur at UTSW and UCLA.

Aim 3a: We estimate our sample size using a Monte Carlo simulation based on predicted differences in propofol sensitivity as defined in prior studies,47, 48, 57, 75 which suggest a 20% difference in Ce50 with 20% intersubject variability and an additive measurement error. We performed the Monte Carlo simulation by constructing two population response curves from N patients whose response to propofol was determined by the sigmoidal Emax model while varying only the Ce50 between the populations. The nonlinear fitting was performed for both populations and this process was repeated 1000 times, with the fraction correctly identifying the underlying difference in the model used as our power estimate. N was then incremented until 80% power was obtained, which required approximately 24 patients per arm (total of 48 patients). Similar studies have targeted enrollments of 18-31 subjects per arm.47, 48, 76 To account for an estimated 20% dropout rate or protocol error, we plan to recruit a total of 58 subjects. Data collection will occur at UTSW and UCLA.

Aim 3b: Our experiments are purposefully designed to ensure proper power and that experiments can be completed within intraoperative time constraints. Using our prior LFP recordings in PD as well as the published literature43, 78, 79, we conducted a power analysis based on average α/β power modulation between rest and anesthetized state observation (Figure 1). Power analysis indicates a total of 16 patients is required to achieve significant results (one-sample t-test with d=0.75, p=0.8, α=0.05). To account for an estimated 20% dropout rate or protocol error, we plan to recruit at least 20 subjects. Data collection will occur at UTSW and UCLA.

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4.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Affiliate Place a check next to institution(s) where the intervention will be performed	Local Standard Practice? Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	Propofol administration	☒ UTSW	☒ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☒ Other: UCLA	☒ Yes
2	GPi/GPe high frequency stimulation	☒ UTSW	☒ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☐THR	☐ Yes
		☐TSRH	☐ Yes
		☒ Other: UCLA	☒ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

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4.c. **Study Intervention #1** **Propofol Administration**	
List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
All groups	No benefit

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

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4.c. **Study Intervention #2** **GPi/GPe high frequency stimulation**	
List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
Aims 2, 3a, 3b	none

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

	4.d. List ALL other research procedures or components not listed in table 4.b. ***The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.*** Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)

#	**Research component** • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Research Component**			
	Blood Draw	0	3-5 times (dependent on # infusions)	
	Behavioral assessment	0	3-5 times (dependent on # infusions)	
	UPDRS – III Data Analysis	0	1	
2				
	Increased Intraoperative time	0	~40 min	
	Insert procedure here			
	Insert procedure here			
3	**Insert component 3 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			
4	**Insert component 4 here**			
	Insert procedure here			
	Insert procedure here			
	Insert procedure here			

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5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Anesthesia will be administer by an anesthesiologist and vitals will be monitored at all times. Research will stop if the anesthesiologist believes the patient is having an adverse reaction to propofol.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

Advanced Cardiac Life Support certified personnel, code blue team, anesthesia team, and neurocritical care team will all be available in the case of an adverse event.

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No

If yes, describe here