Effects of anesthesia drugs on neuronal activity in the basal ganglia and thalamus during deep brain stimulation electrode implantation surgery

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Summary

Deep brain stimulation (DBS) is a common procedure performed for multiple neurological and psychiatric disorders. During these procedures, microelectrode recording (MER) is often used to precisely identify the optimal location for electrode implantation. The effect of sedation and anesthesia on the neuronal activity in the target structures is not fully understood, and we do not have yet an optimal sedation protocol for this procedure. Hence, many of these procedures are performed with the patient fully awake, despite a substantial discomfort this may cause. In this study, we will measure the change in neuronal activity in target areas during MER while administrating three commonly used sedative drugs: propofol, remifentanil and dexmedetomidine. This will be performed following positive target identification with MER in an awake patient, and thus allow precise documentation of the effects of anesthetic drugs on the neuronal activity without affecting the clinical outcome of the procedure.

Contents

Summary 1

Abbreviations 3

Background and Significance 4

Study Objectives and Endpoints 6

Study Subjects – Enrollment and Withdrawal: 7

- Exclusion criteria: 7
- Protected populations: 7
- Screening and Recruitment: 8

Surgical and experimental procedures: 8

- Intraoperative management: 9
- Experimental phase: 11

Assessment of Safety: 12

- Study halting rules 12
- Minimizing risk to the patient: 13
- Benefit to patient 13

Data collection analysis and management: 14

- Demographic and clinical data collection and management: 14
- Data analysis: 15
- Sample size: 16
- Interim Analysis 16
- Data and Safety Monitoring Plan 16
- Study Monitoring, Auditing and Inspecting 17

References: 18

Abbreviations

DBS	Deep brain stimulation
MER	Microelectrode recording
STN	Subthalamic nucleus
UW	University of Wisconsin Hospital and Clinics
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
BIS	Bi-spectral index
OAA/S	Observer's assessment of alertness/sedation scale
RMS	Root mean square

Background and Significance

Deep brain stimulation (DBS) of different brain nuclei is evolving as an essential component of the treatment for multiple brain disorders[1,2]. The subthalamic nucleus (STN) and globus pallidus have been used to treat advanced Parkinson's disease for a long time[3-5]. The ventral intermediate nucleus of the thalamus is an effective target for treating essential tremor patients[6,7]. STN and the internal segment of the globus pallidus are useful targets for treating dystonia[8,9]. Aside from movement disorders DBS has demonstrated efficacy in the treatment of other conditions such as chronic pain[10], obsessive compulsive disorder[11], depression[12] and epilepsy[13-15]. For these illnesses the specific brain region targeted depends upon the illness and the patient's characteristics. As the indications for DBS increase in number, so grows the number of patients that may be helped by this treatment. Increasing numbers of patients are undergoing these procedures for various maladies at our center and at other locations throughout the nation.

To achieve optimal clinical results and avoid side effects, the DBS electrode has to be implanted precisely within the targeted region. This was demonstrated elegantly for parkinsonian patients and the dorsolateral STN[16,17], but is likely to be the case for most DBS indications. To achieve this optimal electrode localization, many centers perform electrophysiological mapping of the target nuclei using microelectrode recording (MER). This way they can achieve precise localization of the electrode[18,19]. During the mapping procedure, microelectrodes are passed through the target nuclei, and the electrical neuronal activity is observed and recorded. The surgical team can identify the precise location of the target nuclei and its borders according to the typical activity of its neurons[16,18].

The MER mapping procedure may take several hours. In some centers the patient's head is motionless and fixed inside a stereotaxic frame throughout the procedure, at others (e.g. our institution – University of Wisconsin Hospital and clinics; UW) a frameless navigation system is used, but even in this method the patient has to remain in a relatively static position throughout the procedure. Some centers use sedation or light general anesthesia during this surgery[20-22]. However, most centers do not routinely use any kind of sedation out of concern that it might change the activity of neurons in the target area, and interfere with the precise MER localization of the electrode[23-25]. Other centers (UW included) use sedation during the initial phase, and stop it 20-30 minutes before the MER so that the MER (that may take 1-4 hours) is performed with patients awake. It is therefore not uncommon for patients to complain of anxiety or discomfort during the operation[20].

Dexmedetomidine, propofol and remifentanyl are often used in awake neurosurgical procedures[26]. Dexmedetomidine provides sedation and amnesia with minimal respiratory depression, and improves perioperative hemodynamic stability in neurosurgical patients[26,27]. Propofol and remifentanil have a much shorter duration of action, and thus allow rapid titration. Both these agents allow reliable and safe sedation for awake craniotomies[28]. However, the effects of any of these three agents on the electrical activity, and whether they will allow safe sedation during DBS electrode implantation at different targets and in different clinical conditions is unclear.

The STN is a well-known and well-studied target for electrode placement that has been in wide-spread use for many years. As such there are reports of different drugs that have been used for sedation during electrophysiological mapping of the STN, including propofol[20,22,29], dexmedetomidine[21,29], remifentanil[20,30], midazolam[22,30] and even volatile anesthetics[31]. Reports comparing the clinical results of DBS electrode implantation in fully awake patients versus anesthetized patients have demonstrated conflicting results: some have shown inferior long term outcome in the anesthetized patients[32] while others have not shown a significant difference[20]. However, there is very limited data regarding the actual effects of the different anesthetic drugs on STN activity and its effect on the accuracy of MER guided electrode placement.

We demonstrated that propofol transiently decreases STN activity and the signal to noise ratio available for STN localization. Activity returned to normal 9±4 minutes after propofol administration stopped[33]. A more recent study from our group suggests similar results but with a much slower return to baseline with dexmedetomidine (manuscript in preparation). Others have also demonstrated that dexmedetomidine may interfere with MER accuracy[34]. By contrast, MacIver et al. demonstrated that lower doses of propofol and remifentanil exhibit only a minimal change on the firing rate of STN neurons[35]. It is clear than that even for the most studied target – the STN; we do not yet have an optimal anesthesia regimen. The information regarding the effects of anesthetic on other, newer or less frequently targeted nuclei is sparse, and thus recommendations regarding the optimal sedation protocols and their effect on the neuronal activity, the accuracy of MER and the clinical outcome are lacking.

In addition to identifying an effective sedation regiment for these procedures, recording the neuronal activity under sedation will enable us to study the effect of anesthetic drugs on the target brain structures. As the mechanisms underlying sedation, anesthesia, and loss of consciousness remain unclear, study of neuronal activity via MER may enhance our

fundamental understanding of the mechanisms underlying anesthetic induced loss of consciousness – a great question in our specialty and in our understanding of the brain and behavior in general.

Study Objectives and Endpoints

In this study, we will compare the activity of neurons in several DBS targets before, during and after sedation with propofol, remifentanil and dexmedetomidine. Our goal is to understand the effects of anesthetics on the neuronal activity in these targets, allowing us to choose the most appropriate sedation protocol to use during implantation of DBS electrodes in deep brain structures (bearing in mind that each structure may have a different optimal protocol). We will do so using each patient as his/her own control, thus eliminating the subjective report bias of MER quality that limits conclusions drawn using surgeons and physiologist reports of MER quality under different conditions. We will start with the areas that are commonly targeted during DBS procedures at UW: the ventral intermediate nucleus of the thalamus, the STN and the globus pallidus. However, as new targets are gaining popularity and are added to the clinical procedures offered to the public at UW, we will seek to study the effects of anesthesia on those new targets, and find the effects of anesthesia on each new target.

Our hypothesis is that propofol, remifentanil and dexmedetomidine change the firing rate and pattern of deep brain structures to different extent.

Primary aim: To document the effects of commonly used anesthetic drugs on the neuronal activity during MER in different brain structures that are used as targets for DBS implantation.

Secondary aims: 1) Identifying effective sedation regimens for the different DBS targets; 2) Documenting the time course of the different drug's effect on the neuronal activity. Having this information will allow planning and performing sedation during the procedure prior to the MER without affecting the quality of the MER. This may prove useful in cases where no sedation regimen is completely devoid of effect on the MER; 3) Creating a database that includes the neuronal activity changes at multiple brain regions under the effect of different sedation drugs to enable further study of the effects of anesthetics on brain regions and the mechanisms underlying loss of consciousness.

Each subject's participation is for the duration of the surgery. We typically see 30-40 patients for DBS electrode implantation surgery per year at UW, of which 70% are expected to consent to the study. Thus, assuming we'll need on average 10-15 patients per drug per target (i.e. a total

of 70-105 patients as we already have the data of the effects of propofol and dexmedetomidine on the STN) the project will require between two and five years to recruit patients.

New targets for DBS are continuously discovered and become a standard of care. Once a new target is added to the clinical procedures routinely performed at UW, we will add the new target to the protocol, and if necessary request a time extension and increase the recruitment goals to study these new targets. The change of protocol to add the new target will be reviewed and approved by the IRB first prior to implementing any new targets.

Study Subjects – Enrollment and Withdrawal:

All patients scheduled to undergo DBS electrode implantation surgery with MER that agree to participate in the experiment and sign an informed consent (supplement 1) are candidates to participate in the study, unless one of the exclusion criteria is met.

Exclusion criteria:

1. Known or suspected obstructive sleep apnea.
2. Suspected difficult intubation.
3. Pregnancy (pregnancy test is standard care for women of childbearing age)
4. Under 18 years of age or over 85 years of age
5. Cognitive disability impairing understanding the experiment or signing the informed consent form.

Protected populations:

Prisoners – Due to the complexity of state and federal requirements governing the participation of prisoners in research, patients who are prisoners will not be considered for participation in this trial.

Pregnancy – Pregnancy is an exclusion criteria

Cognitive disability – The ability of the patient to sign an informed consent will be evaluated by the consenting investigator (MD). A patient deemed impaired in his ability to consent will not participate in the study (this is also an exclusion criteria). It should be noted that many of the patients undergo routine psycho-cognitive evaluation as part of their evaluation prior to undergoing a DBS procedure.

Screening and Recruitment:

Candidates for participation in the study will be identified by Dr. Lake as patients are referred to him for the preoperative evaluation (Dr. Lake is a co-investigator, and is also the only physician performing these operations clinically at UW, so all patients are referred to him for evaluation). Dr. Lake will alert one of the investigators from the department of anesthesiology regarding the patient and the dates the patient is scheduled to arrive at UW (for preoperative evaluation, bone marker fiducial insertion and the day of their surgery).

Patients found suitable to participate in the study will receive an explanation and get the informed consent form from one of the physicians participating in this study (either neurosurgeon or anesthesiologist). Subjects will be given as much time as possible to consider participation. There will be a follow-up conversation with the subject to review information about the study and discuss the subject's questions after the subject has had time to read and consider the consent form. Study personnel will be available to answer any questions the subject may have about the study. Potential subjects will be approached to introduce the study and will be given the consent form to review during the preoperative evaluation, or when hospitalized for bone marker fiducial insertion, allowing them time to go over the consent form and make a decision before the day of surgery. The signed informed consent form may be collected either before the day of surgery, or on the morning of the surgery, before the patient is taken to the operating room.

Surgical and experimental procedures:

Patients will undergo the standard DBS implantation surgery practiced at UW. The procedure will differ only during the experimental phase, as specified below in the section, "Experimental Phase".

The standard surgical procedure is as follows. The patients will have had a recent bone marker fiducial placement and a CT / MRI prior to the DBS placement. They will come to the operating room, lines and monitors will be placed for the procedure at the discretion of the anesthesiologist (in accordance with UW accepted standards). The head will be prepped and draped. Surgery will be performed under local anesthesia with or without sedation as is usually performed at UW.

DBS electrode placement is often done on both sides (two electrodes are implanted). This is often done in one day (the patient gets two electrodes on both sides), but sometimes this is done in two separate sessions on two different dates (usually if the procedure took a long time, or there may be a shift in the brain due to CSF leak). For the purpose of the study, it doesn't

matter if this is the first or the second side. We will perform the experimental phase on the last mapping session of the day.

Intraoperative management:

When the patient initially enters the operating room, standard American Society of Anesthesiologists monitors and oxygen by nasal cannula are applied. Bi-spectral index (BIS) monitor is placed, and the awake level numerical value is noted.

Adequate peripheral venous access is secured and the first dose of prophylactic antibiotic is administered as indicated (e.g. cefuroxime 1.5 g IV). Lactated ringer solution is the preferred IV solution (except for patients in renal failure; normal saline is then used). Fluids are administered throughout the case at the anesthesiologist's discretion.

The surgeon then uses local anesthetic (Bupivacaine 0.25%) for the scalp incision, burr holes and craniotomy, and add local anesthesia as required to maintain the patient comfortable and pain free. Once electrodes are positioned, we'll perform the MER to identify the optimal location for the DBS electrode. The number of mapping electrodes will be at the discretion of the neurosurgeon as required for the procedure. The system we use at UW allows as many as 9 mapping electrodes that may be advanced and recorded simultaneously. The trade-off is that more electrodes will allow better mapping and lower the likelihood of need for extra trajectories, but will cause more damage to the brain as the electrodes are passed. Three electrodes are routinely used at UW, but this can change according to the surgeons decision and the clinical scenario.

Remifentanyl or propofol sedation may be used for the initial part of the procedure (skin incision, burr holes and craniotomy and initial insertion of the electrodes). The sedative dose will be at the anesthesiologist's discretion in consultation with the neurosurgeon to achieve optimal sedation. Sedation will be held 10-15 minutes before initiating the MER phase, and we will allow the patient to wake up and the BIS values to normalize to awake level for the MER.

We will use the Guideline 4000 system (FHC Inc., Bowdoin, ME) for data acquisition and recording. This system is currently being used at UW for MER during this type of surgery. MER will commence 15 to 30 mm above the expected target depth (or at the relevant depth for the specific target). During MER the electrode will be advanced in progressively smaller steps as the target is approached (usually 50-100μm). After each step we will measure the neuronal

activity at that depth for a few seconds. Once inside the target nuclei, responses of neuronal activity to stimuli may be assessed as required (assessment will be performed as recommended to identify the relevant nuclei). The experimental phase (see below) will take place during this stage after the target location has been confirmed. In case we do not find the target during the electrode pass, identifying other structures along the trajectory may help with planning the next trajectory. Once the target is confirmed, MER is continued to identify the ventral border of the target nucleus. This is usually detected by a decrease in the neuronal activity of the target nucleus, and in some cases identifying typical activity of neighboring nuclei. e.g. the substansia nigra below the ventral border of the STN. Identifying the ventral border allows targeting the stimulating electrode to the center of the target area. Macrostimulation is performed to estimate the clinical response and possible side effects (i.e. are the patient's symptoms addressed at the current electrode position). Following that, a single permanent stimulating electrode will be placed at the same location and fixed to the skull (the routine treatment is a single stimulating electrode per affected side \ target). The whole procedure may take from 30 minutes up to three hours per side, depending on the number of trajectories required for a successful implantation. Once the mapping is done, one stimulating electrode is left in the optimal target. For most patients this will be two electrodes in total (one in each side), but in certain cases the surgeon may choose to put only one electrode (some patients present with a unilateral disease, and get one electrode, and sometimes they may present for a second electrode placement on the other side years later after the disease has progressed). For the sake of the study, we will be performing the experimental phase on the last electrode trajectory of the day. If the patient is getting two electrodes on the same day, this will only be done during the mapping for the second electrode, whereas if he gets only one electrode (with a second electrode placement planned for a future date, or not even planned yet) we will perform the experimental phase on whatever side is done.

During the procedure, the anesthesiologist will maintain systolic blood pressure below 150 mm Hg throughout and below 140 mm Hg when actively passing electrodes. The drugs used to control blood pressure will be discussed with the surgeon, and agreed upon according to the disease and target nuclei (e.g. we'll avoid ß blockers in essential tremor patients). In cases of extreme hypotension (Systolic blood pressure below 90mmHg) or bradycardia (Heart rate below 50) at the initiation of the experimental phase, the patient will not receive dexmedetomidine or propofol and may be withdrawn from the study. In such a case, all data collected from the patient will be purged and not used for further analysis.

Experimental phase:

During the operation, following target identification by the MER and while the recording electrode is inside the target area, electrode advancement will be stopped. Following three minutes of recording the baseline neuronal activity at the selected location, an anesthetic drug will be administered as detailed below until stable sedation is achieved. The administration rate can be titrated at the anesthesiologist's discretion to achieve the optimal clinical sedation goal. Our goal is to achieve a drowsy but arousable (by calling his name or a light tap on the shoulder) patient – 3 on the observer's assessment of alertness/sedation (OAA/S) scale[36,37] BIS value of 60-80 may be used as an adjunct to assess sedation level.

Following 2-3 minutes of recordings at a stable sedation level, we will stop the sedation and allow the patient to recover. Once the patient is awake and cooperative (OAA/S = 4-5) we will record another 2-3 minutes of activity. After recording 2-3 minutes of activity in the recovered patient, we will resume electrode advancement and MER in order to identify the ventral border of the target area, and localize the stimulating electrode. We expect the experimental phase to add 30-40 minutes to the procedure. High frequency sampling of the voltage at the tip of the electrode will be recorded continuously throughout the experimental phase and saved into coded files for the research record.

We will use 3 sedation protocols for each target:

1. Propofol infusion will be started at 100 μg/Kg/min and titrated by the anesthesiologist to the appropriate sedation depth.
2. Remifentanyl infusion will be started at 0.05 μg/kg/min and titrated by the anesthesiologist to the appropriate sedation depth.
3. Dexmedetomidine infusion will be started with a loading dose of 0.8 μg/Kg over 10-15 minutes followed by a maintenance infusion starting at 0.7 μg/Kg/hr and titrated by the anesthesiologist to the appropriate sedation depth.

Each patient will receive only one of these protocols (i.e. each patient will receive only one anesthetic drug). For each DBS target we will go through the drugs in a consecutive order, i.e. we will recruit patients and treat them with one sedation drug until we have enough data regarding the effect of this drug on the target, and then switch to the next drug. This approach will enable us to sum the results and draw conclusions rapidly and efficiently.

Appropriate sedation level should be achieved within 10-20 minutes in all these protocols.

Standard practice at UWHC – All the sedation protocols detailed above are routinely used for procedural sedation at our department. Propofol sedation is sometimes given as part of the treatment for this procedure. It is stopped before MER as described. We monitor the sedation depth of our patients but we do not formally use OAA/S as part of standard care. In standard care, the doses as well as drugs used (dexmedetomidine, propofol and remifentanil, alone or in combination) vary at the anesthesiologist's discretion.

Assessment of Safety:

Study halting rules:

The study includes short periods of sedation with commonly used anesthesia drugs, under the accepted monitoring and supervision for such sedation, thus we consider it a low risk study and do not expect any serious side effects. However – any serious complication related to the sedation (significant aspiration or other pulmonary complication requiring intubation and mechanical ventilation, stroke, myocardial infarction or death) will be reported to the IRB during the next work day. The study will be halted until the case is reviewed by all the investigators and the data safety monitoring board. If the complication is indeed related to the study according to the review held, protocol changes to prevent the recurrence of such an event will be recommended, and the study will resume only after the necessary protocol amendments will be made.

Risks

During the trial the volunteers will receive sedative drugs as a part of the study. These drugs may cause bradycardia, hypotension, transient Hypertension, respiratory depression, apnea, airway obstruction, oxygen desaturation, muscle rigidity (remifentanil). Propofol emulsion may get contaminated with bacteria and cause severe infection if improperly treated or stored improperly. Theoretically, long term subclinical effects of the anesthetic drugs may interfere with the identification of the ventral border of the target structure, or even with clinical evaluation of macrostimulation effect performed at the end of the procedure. A significant miss is very unlikely, and the target will be identified prior to the sedation trial to prevent such a case, but minor changes in the final depth are theoretically possible. Such changes may drain the pulse generator battery slightly faster, as stronger current is required. This shouldn't be a problem with the newer pulse generators, as they have a transcutaneous charging option.

Minimizing risk to the patient:

Administration of anesthetics will be performed in an OR setting, with all the equipment necessary to monitor the patients and treat any untoward effect of these drugs. The sedation will be performed directly under the supervision of a board certified anesthesiologist experienced with administrating these drugs and while the patient is connected to standard ASA monitoring (which is routinely used in these cases). The attending anesthesiologist will be in charge of treating any untoward event (in case any such event occurs). It should be emphasized that the patient will receive sedation (most likely with the same group of drugs, or a combination of drugs) as part of their routine clinical treatment. Combining different sedative drugs is a well-accepted practice that should not present a problem to the treating anesthesiologists, Furthermore, our exclusion criteria (obstructive sleep apnea and suspected difficult intubation) and protocol (avoiding drug administration in cases of bradycardia or hypotension) are designed to avoid the risk of these complications.

Performing the experiment will increase the surgery duration by the time required to complete the experimental phase (estimated 30-40 minutes, depending on the sedation drug). However, the patients will be sedated during most of this time, so this should not increase their inconvenience and stress level. The added time is relatively short compared to the length of the whole procedure (usually 3-5 hours), so it should not have a significant effect on OR time or complications. Administrating sedation intermittently, i.e. sedation followed by wake up and then re-administration of the sedation is a routine practice in neuro-anesthesia that has been well described, and is not considered to be a significant added risk.

One possible risk of the research protocol is that sedation will affect the MER and thus the final position of the electrode. In order to minimize possible interference with target identification, the experimental phase will take place during MER of the last location that will be targeted for electrode placement on that day, and only after identifying the target area. Thus we will sedate the patient only after all the electrode targets for that day were identified, so that the risk for adversely affecting the electrode localization is minimal.

Benefit to patient:

No direct benefit to subjects are anticipated. This research study may benefit other people in the future by helping us learn more about how to perform sedation without affecting the electrical mapping of the brain. If we can identify a sedative drug that does not affect cell activity in the target region, we will be able to routinely use sedation during mapping and increase patient comfort during deep brain surgery.

Data collection analysis and management:

Demographic and clinical data collection and management:

Subject name, age, gender, right/left handedness, date of surgery, anesthesia details (drugs, doses, depth of sedation), surgery details (target area, electrode coordinates, structures encountered during MER), disease type and duration, primary symptoms, medications, and electrophysiological (electrical potential at the tip of the electrode at any point in time during MER) data will be collected from the patient chart during the surgical procedure. Data will be collected using a pre-defined table (supplement 2) by one of the investigators.

Collected data will be coded to prevent identification of subjects. The identifiable data (signed consent forms and a table of subject codes, names,) will be secured in a locked filing cabinet at the Department of Neurosurgery or Department of Anesthesiology for 12 years.

The rest, de-identifiable data (Anesthesia details, Surgery details, Disease type and duration, Primary symptoms, Medications and Electrophysiological data) will be extracted from the electronic medical record and entered into an Excel spreadsheet. The data that is entered into the spreadsheet will contain no personal health information and will be coded with a unique study ID number and transferred using an encrypted flash drive to analysis computers at the department of anesthesiology. This data will not contain any subject identifiers other than the subject code, and will the key to the code will be stored in a separate location from the coded data.

Only co-investigators involved in the treatment of the subject and data collection will have access to the identifiable patient data. Coded data will be managed by the co-investigators as well as students at the Department of Anesthesiology under the supervision of one of the investigators.

The investigators will use their laptops and the department of anesthesiology computers for data analysis. Only coded data will be placed on the password-protected laptops set up in consultation with data security personnel to ensure that they employ sufficient data security

protections. No subject identifiers other than study code will be placed on the laptop, and no links between subject codes and subject identifiers will be on the laptop. Anyone engaged in research activities (for example, participating in data analysis) using either identifiable or coded data will be listed as key personnel on the ARROW application.

Data analysis:

We will record the neuronal activity at every point along the electrode trajectory according to the routine MER protocol at UW. We will evaluate the effect of sedative drugs on the firing rate and temporal firing pattern of neurons in the target area at a single location, as well as compare the activity along the trajectories.

We will calculate the root mean square (RMS) of the electrical activity as a measure of the spiking rate of neurons in the vicinity of the electrode tip. The RMS has been shown to be a useful clinical guide for STN identification and electrode placement[16,38]. We will normalize the RMS to the baseline value recorded at the first 2-5 minutes of MER (before entering the target area) to compensate for differences between patients and recording electrodes. In order to calculate the change in the normalized RMS following sedation we will compare the mean RMS during 2 minutes of the stable recording of the pre-sedation baseline to the mean RMS during stable sedation and following recovery. We will use a paired t-test to determine the significance of this change. Alpha of 0.05 will be considered significant. If we do find a significant change we will use the continuously recorded data to calculate the average RMS as a function of time to examine time course of the change and recovery of the RMS. The time to change and the time to return to baseline will be considered as the time that the average RMS crosses the 95% confidence interval of the baseline value. We will measure the correlation between the RMS and the sedation depth measured by the BIS monitor.

The oscillatory firing pattern of neuronal activity is also an important indicator of optimal electrode placement in certain areas (e.g. STN)[17]. We will use frequency-domain analysis to measure these oscillatory firing patterns in the target area and determine changes following administration of sedation and their time course.

Time to sedation and recovery will be calculated from the clinical data tables recorded during the procedure. Mean and standard deviation of these values will be calculated.

Analysis will be performed using custom software written in Matlab (MathWorks, Natick, MA).

Sample size:

As we have learned during our last study on the effects of dexmedetomidine on the activity in the STN, the sample size calculation based on estimation from one drug effect to another, or from a certain brain area to another is prone to inaccuracy, leading to either too large or too small sample sizes. To avoid that, we will perform a pilot study using the first five patients of each target location and anesthesia protocol as a preliminary data collection and use the data obtained to calculate the magnitude of sedation effect. If no effect is seen for the first five patients, or if the effect is smaller than 10%, we'll use 10% change as a benchmark to rule out a clinically significant effect. We will than calculate the sample size required with alpha of 0.05 and power of 0.75.

From our previous experience and from other manuscripts published in the field, we assume we'll need on average 10-15 patients per drug per target, i.e. a total of 70-105 patients (as we already have the data of the effects of propofol and dexmedetomidine on the STN). We plan to recruit 180 patients to allow for modification of the sample size estimation in case we find out that we need more patients than estimated.

Table 1: Estimate of the number of patients required for the currently used clinical targets and drugs

	Propofol	Remifentanil	Dexmedetomidine
Thalamus (vi)	10-15	10-15	10-15
STN	Completed	10-15	Completed
Globus pallidus	10-15	10-15	10-15

Interim Analysis:

Interim analysis of the data will be conducted following the pilot phase (first five patients) of each target and drug combination, and then following the recruitment of either 50% of the required patients or every 10 patients per target and drug combination.

Data and Safety Monitoring Plan

The Data Safety Monitoring Board will consist of 3 members with expertise in anesthesia, neurosurgery and electrophysiology. DSMB members are not investigators on the study. The PI will report to the board via e-mail (since 1 member is a distance from Madison) following

recruitment of every 10 patients, and with every preliminary and interim analysis results. No protected health information (PHI) will be included in reports sent via email. The report will include the number and type of cases recruited and actually performed, any adverse effects, and any obvious effects on the MER reported by the surgeon during surgery. For the interim analysis the report will also include the analysis results. The DSMB will communicate via email its decisions on whether to continue the study at each of these time points.

Study Monitoring, Auditing and Inspecting:

The PI will be responsible to make sure that the data are complete and accurate and AE reporting is done per this protocol.

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