Published in final edited form as:

Stereotact Funct Neurosurg. 2018 ; 96(4): 249–258. doi:10.1159/000492231.

Propofol Anesthesia Precludes LFP-based Functional Mapping of Pallidum during DBS Implantation

Mahsa Malekmohammadi^a, Hiro Sparks^a, Nicholas AuYong^a, Andrew Hudson^b, and Nader Pouratian^{a,c,d}

^aDepartment of Neurosurgery, University of California, Los Angeles, California, 90095

^bDepartment of Anesthesiology, University of California, Los Angeles, California, 90095

^cNeuroscience Interdepartmental Program, University of California, Los Angeles, California, 90095

^dBrain Research Institute, University of California, Los Angeles, California, 90095

Abstract

Background/Aims: There are reports that microelectrode recording (MER) can be performed under certain anesthetized conditions for functional confirmation of optimal deep brain stimulation (DBS) target. However, it is generally accepted that anesthesia affects MER. Due to potential role of local field potentials (LFP) in DBS functional mapping, we characterized effect of propofol on globus pallidus interna (GPi) and externa (GPe) LFP in Parkinson disease (PD) patients.

Methods: We collected LFP in twelve awake and anesthetized PD patients undergoing DBS implantation. Spectral power of β (13–35 Hz) and high frequency oscillations (HFO: 200–300 Hz) was compared across the pallidum.

Results: Propofol suppressed GPi power > 20 Hz while increasing power at lower frequencies. Similar power shift was observed in GPe however, power in the high β range (20–35 Hz) increased with propofol. Before anesthesia both β and HFO activity were significantly greater at GPi ($\chi^2=20.63$ and $\chi^2=48.81$, $P<0.0001$). However, during anesthesia, we found no significant difference across the pallidum ($\chi^2=0.47$, $P=0.79$ and $\chi^2=4.11$, $P=0.12$).

Conclusion: GPi and GPe are distinguishable using LFP spectral profiles in the awake condition. Propofol obliterates this spectral differentiation. Therefore, LFP spectra cannot be relied upon in the propofol-anesthetized state for functional mapping during DBS implantation.

Keywords

Deep brain stimulation; Globus pallidus; Propofol; General anesthesia; Local field potentials; Functional mapping

Introduction:

Deep brain stimulation (DBS) targeting the globus pallidus internus (GPi) is a well-established treatment for Parkinson Disease (PD) [1–3]. The efficacy of DBS is dependent on the accuracy of electrode targeting. Microelectrode recording (MER) along with micro- and macroelectrode stimulation testing are often used to provide functional confirmation of optimal DBS lead placement [4]. While several groups have reported “asleep” DBS lead implantation [5–8], most centers still perform DBS implants with patients under light sedation, using a combination of local anesthesia and analgesics to grossly preserve neuronal activity assessed by MER and allow the patient to participate in functional testing [9–12]. MER targeting relies on the identification of characteristic neuronal firing patterns of structures positioned along the implantation track and is useful for differentiating signals generated by neurons of the GPe from those of the GPi [13]. PD patients are typically off-medication for macro-stimulation testing and intraoperative symptom monitoring. This can result in exhaustion, discomfort, and anxiety [9]. Uncontrollable tremor or dystonic movements may further complicate patient comfort during awake implantation surgery [9].

A variety of “asleep” implantation protocols have been increasingly employed to enable either image-guided with or without intraoperative neurophysiological targeting, while optimizing patient experience [14–16]. It is well accepted that anesthesia can affect MER mapping, although several groups have reported the ability to perform MER under certain anesthetized conditions [10,17]. The development of a “hybrid” approach, where DBS lead implantation is performed with the patient anesthetized and with intraoperative neurophysiological targeting, requires signal markers that are both suitable for localizing boundaries of DBS target and are not fully suppressed by general anesthetics. Local field potentials (LFP), representing the sum activity of neuronal ensembles, are potential neurophysiological signals that maybe applicable for “hybrid” target localization in PD [18]. Compared to the single unit recordings, LFP are more robust but represent an integrated measure of local neuronal activity. Aberrant β (13–35 Hz) and high frequency oscillations (HFO: 200–300 Hz) are found in and can potentially be used for functional localization and verification of various nodes of the basal ganglia, such as STN [18,19] and GPi [20,21]. Recent studies use these oscillatory signals to predict the optimal targeting track in DBS implantation surgery in Parkinson disease [18,19,22,23]. Given the proposed role of LFP in successful target identification and recent surge in the literature to use “hybrid” procedures, it is important to understand the effects of anesthesia on LFPs recorded during DBS implantation surgery to assess how these signals are affected by anesthetic and whether LFP can be used to guide functional localization and mapping in an anesthetized patient. While there have been several studies of the effect of anesthesia on unit recordings, one cannot assume a similar effect of anesthetic on LFP. LFP and unit recordings are inherently related neurophysiological signals however, LFPs represent the summative synchronized oscillatory activity of neuronal populations rather than the activity of single neurons, as is measured with MER. Changes in MER, such as those induced by propofol, may not directly correlate with changes in LFP [24].

While there is some evidence to suggest that propofol decreases higher frequency (>20 Hz) power and increases lower frequency (<20 Hz) power in subcortical nuclei [25,26], there has

been no prior assessment of spectral power changes specific to the GPi following propofol administration in PD patients. Further, concurrent change in GPe LFP, which may be crucial for the clinical context of lead targeting, is poorly characterized. In this study the effect of propofol on GPi and GPe LFP oscillatory power in PD patients are characterized to fully evaluate the suitability of LFP for lead targeting in the anesthetized patient. Based on prior MER and LFP studies, we hypothesized that propofol-related changes in consciousness would be associated with loss of functional specificity of LFPs in the subcortical nuclei, including GPe and GPi.

Materials and Methods

Patients and surgical procedure.

Twelve subjects with idiopathic PD undergoing bilateral DBS lead implantation in the globus pallidus, provided written informed consent to participate in this study. Study protocol was approved by the institutional review board at the University of California, Los Angeles. We recorded concurrent deep brain LFPs from bilateral pallidum (both GPi and GPe, made possible by the trajectory that traverses both nuclei, see Fig 1) during rest while subjects were undergoing awake DBS implantation and after intravenous administration of propofol.

All patients underwent the surgical procedure in the off medication state: all long-acting and short-acting medications were withdrawn at least 12 hours prior to the surgical procedure. Subjects underwent clinical pre-and post-operative imaging. Pre-operative imaging included T1- weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) image (slice thickness = 1 mm, repetition time = 2100 ms, echo time, 2.98 ms, flip angle = 15°, 3T, Siemens Skyra). For implantation, a Leksell stereotactic head frame (Elekta Instruments, Stockholm, Sweden) was applied to the skull and a full head computed tomography (CT) scan was obtained using 0.6 mm slice thickness (Siemens Sensation 64). The DBS lead (Model 3387, 1.27 mm lead body diameter, contact length 1.5mm, inter-contact distance 1.5mm, Medtronic, Inc., Minneapolis MN, USA) was targeted to motor (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 (depending on individual anatomy, Fig. 1A). All trajectories were confirmed with intraoperative microelectrode recordings based on firing activity and kinesthetic tests [27] in addition to awake macrostimulation testing. Contact localization was based on a combination of MER results and postoperative image analysis, as described below, when available.

Data recording

LFPs were recorded with the lead in final implant position in all subjects using the lead's four ring electrode contacts (contacts 0, 1, 2 and 3, ventral to dorsal). Signal acquisition was performed using BCI2000 v3 connected to an amplifier (g.Tec, g.USBamp 2.0) with a sampling rate of 2400 Hz and online 0.1Hz-1000Hz band-pass filtering. Ground and reference contacts were connected to the scalp. Bipolar re-referencing was used for further signal analysis, yielding two bipolar signals to evaluate differences between GPi (bipolar

pair 0–1) and more dorsal signals (bipolar pair 2–3, collectively referred to as GPe, since contact 3 reaches to 10.5 mm above target which consistently include GPe).

We began recordings with patients resting awake with eyes open for 1 min, after which propofol was administered according to the attending anesthesiologist's clinical judgment. Recordings continued and patients were assessed verbally at least every 30 s after propofol administration to ensure and determine the timing of loss of responsiveness. We used the modified observer's assessment of alertness/sedation scale (MOAA/S) to evaluate the subject's level of alertness. Each patient included in the study reached a score of 0/1, after which recordings continued for 1 min. Recordings continued for an average of 5 min after the start of propofol administration. Due to variations in propofol dosing, cardiac output, and blood volume across subjects, we expected substantial differences in circulation time and anesthetic induction across subjects. Therefore, we focused our analyses on pre-bolus and post-induction steady state signals, using the last minute of recording as the time period when subjects were maximally anesthetized and no longer verbally responsive (hereafter referred to anesthesia period or Anes), and contrasted this with the preanesthesia (PreAnes) stage.

Localization of DBS electrodes in the MNI standard space

Pre-operative high-resolution MR structural scans were acquired in all subjects. In the subgroup of eight subjects post-operative high resolution computed tomography (CT) scan was acquired. The DBS electrodes for this subgroup were localized using the Lead-DBS software [28] (<http://www.lead-dbs.org>). Initially the post-operative CT scan was co-registered to the pre-operative structural MRI using two-stage linear registration (rigid followed by affine) as implemented in advanced normalization tools (ANTs) [29]. Next, All images were normalized to the MNI standard stereotactic space (ICBM152 2009b non-linear asymmetric) using the SyN registration approach as implemented in Advanced Normalization Tools [29]. Lead trajectories were pre-localized by Lead-DBS and manually adjusted to ensure optimal reconstruction in the standard space. All reconstructed leads from the left hemisphere were mirrored to the right side and data from all patients were aggregated for visualization (Fig. 1). DISTAL minimal atlas for the stereotactic targets was used to illustrate relative position of the leads with respect to the internal and external part of the pallidum [30]. Bipolar signals from contact pairs 0–1 (Marked in red, Fig.1 A–B) and 2–3 (Marked in black, Fig.1 A–B) were used for the analysis.

Data Preprocessing

Signal analysis was performed using custom made scripts in MATLAB (Version 8.6, The Mathworks Inc., Natick, MA) and Fieldtrip toolbox for EEG/MEG-analysis [31]. Data was converted to bipolar montage, and standardized using Z-transformation. Then it was parsed into PreAnes and Anes epochs excluding all the segments containing electrical or unwanted movement artifact using methods previously described [20]. Removed segments primarily featured power spectra with abnormally high values, excessive harmonics and time series with high rates of voltage change. Data were band pass filtered at 1–300 Hz using a 6th order Butterworth IIR filter (forward and backward to ensure no phase distortion was created

during band pass filtering). Line noise (60 Hz) and its harmonics (up to 300 Hz) were removed from the data using notch implemented in fieldtrip toolbox.

Power spectral density and peak estimation

Power spectral density (PSD) for PreAnes and Anes conditions were calculated using the Thomson's multitaper method in 1 second consecutive time windows with no overlap for frequencies of 2 to 300 Hz with ± 2 Hz frequency bandwidth (3 tapers) [32,33]. Group Average PSDs for both conditions were then calculated at each contact pair. Spectral peaks in the α - β range (8–35 Hz) were detected using a peak detection algorithm, similar to what previously described [21], as local maxima in the spectral power for each signal. Adjacent peaks in the same spectra had to be separated by at least 4 Hz to be considered separately. All detected peaks were visually inspected to identify potential false positives and negatives. To explore how propofol changes spectral peak distribution in pallidal signals, we then created a non-parametric probability density estimate [34] of detected peaks for GPi and GPe signals in PreAnes and Anes conditions separately (ksdensity.m, 2 Hz smoothing bandwidth).

Spectral peak in HFO (200–300 Hz, frequency range selected based on our prior work [20,21]) were extracted using the Matlab curve fitting toolbox. We fit a power law estimation to each spectrum using the 35 – 175 Hz frequency range (excluding line noise frequencies) to reduce the effect of spectral peaks on the model and then subtracted this estimation from the spectrum. We then used smoothing spline to detect the spectral peak of the resulting data within the HFO range. We confirmed all of the detected peak visually and calculated Peak power normalized to the total power in the HFO range (200–300 Hz) to account for variable baseline power at different contact pairs and also across the population. The normalized peak HFO power was used in subsequent group level analyses. Average band power was also calculated for frequency bands of α (8–12 Hz), low β (13–20 Hz), high β (21–35 Hz), low γ (40–80 Hz). These frequency bands were chosen based on our previous findings [21].

Statistical analysis

Statistical analysis was performed using SPSS (IBM Corp. Armonk, NY) and STATA (StataCorp LLC, College Station, TX). We calculated the mean group spectrum for each condition along with the corresponding Z statistics using asymptotic spectral probability distribution and the 95% confidence intervals using Jackknife estimation of variance [33]. Statistically significant differences in spectral power between two conditions (PreAnes/Anes) at each frequency (3–300Hz) and each contact (GPi, GPe) were assessed using the two group test of the spectrum [32,33], with a null hypothesis that conditions have equal spectra within the cohort.

To correct for multiple comparisons, we note that differences in spectra due to the chance are likely to be present at discrete frequencies, while neurophysiological differences span contiguous frequency ranges (e.g., α , β). Since spectral estimates at frequencies separated by less than the bandwidth of the multitaper method (4 Hz) are inherently correlated, we rejected the null hypothesis for all candidate frequencies constituting bands whose width is larger than 4Hz.

Another complementary method was used to assess the statistical significance of power changes. The average normalized band power values were calculated for the different frequency bands α , low β , high β , and γ . We used normalized peak power to compare HFO activity as described earlier. Because our sample size is < 50 , the Shapiro-Wilk test was used to assess normality of distribution prior to comparing power (at different frequency bands). Since this test could not reject the normality of distributions ($P > 0.05$), we used paired sample t- test to compare band power across pallidal contacts between conditions. All resulting p-values were corrected for multiple comparisons using Bonferroni or Holm's sequential Bonferroni method [35].

Finally, we used linear mixed-effect modeling (LMEM) to examine the difference in the average β power and HFO peak power ratio, between PreAnes/Anes states at each contact pair across the cohort. LMEM is the extension of linear regression method that models the linear relationship between a response variable and independent variables, with coefficients that vary with respect to grouping variables [36]. In this study, each subject contributed multiple samples (from two hemispheres and three contacts in the pallidum) in a repeated measures design. LMEM, unlike analysis of variance based techniques (i.e. ANOVA), is a robust statistical technique for repeated measures study design and accounts for the inherent correlation between repeated measures from each subject [37]. Models were constructed with three grouping factors including anesthesia state (PreAnes and Anes), contact pairs (0–1: GPi, 1–2 and 2–3: GPe), brain side (left or right hemisphere). We include “brain side” as a factor as recordings from bilateral hemispheres from individual subjects are not completely independent. The average values of the power (dB), as a function of these grouping variables were used as response variables. Interactions between effects were studied as part of the model and assessed for statistical significance ($P < 0.05$).

Results

Patient demographics and anesthetic induction and maintenance

Twelve subjects (i.e. 24 hemispheres) were evaluated (three female; average age, 65 ± 7 yr). Clinical evaluation of disease severity was done before the surgery while subjects were off medication. Unified Parkinson Disease Rating Scale (UPDRS) part 3 (motor examination) indicated mean $\pm$ SD of 41 ± 9 for severity of the motor symptoms. Average body weight across the cohort at the time of the recording was 78.6 ± 17.87 kg. Propofol was administered intravenously with an initial bolus of 0.53 ± 0.33 mg/kg, followed by an average continuous infusion rate of 63 ± 33 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Please refer to table 1 for detailed information. The two ventral and two dorsal contacts are consistently located within the GPi and GPe respectively (Fig. 1C).

Propofol causes a shift in the pallidal spectral power from higher to lower frequencies

Propofol administration resulted in a spectral power shift from high to low frequencies in both GPi and GPe (Fig. 2). In GPi, two-group test of spectra showed that power between 2–22 Hz increased while spectral power between 23–300 Hz decreased (Fig. 2A). In GPe, power between 2–38 Hz increased while spectral power between 43–300 Hz decreased (Fig. 2A). Band power analysis further confirmed significant suppression of low γ and HFO

power in both GPi and GPe. Similarly, α and low β power significantly increased in both GPi and GPe. Interestingly, propofol had opposite effects on high β power in GPi and GPe. Whereas high β power increased in GPe, high β was suppressed in the GPi recordings (Fig. 2B, Table 2). Given different direction of change for low and high β power within the GPi (as opposed to GPe), comparison of total β power between PreAnes and Anes states indicated no significant difference between the two conditions in GPi ($P=0.14$, paired t-test), while a significant increase in the total β power was identified in GPe ($P=0.003$, paired t-test).

Propofol administration was also associated with changes in distribution of spectral peaks for frequencies between 8 and 35 Hz (α/β range) from a bimodal to unimodal distribution (Fig. 2C). Specifically, GPi spectral profile changed from having bimodal spectral peaks at 15 and 24 Hz to have a single peak at 12 Hz. Likewise, the GPe spectral profile changed from having bimodal spectral peaks at 13 and 24 Hz to a unimodal peak at 13 Hz.

Spatial specificity of β and HFO oscillations is lost with propofol

Analysis of spatial specificity of β and HFO oscillations in the pallidal recordings was carried out by comparing β power across three contact pairs. LMEM analysis of spectral β band power/HFO normalized peak power as a full-factor combination of anesthesia condition (PreAnes vs Anes), brain side (left vs right), and contact ((0–1): GPi, (1–2), (2–3): GPe) was statistically significant ($\chi^2=25.57$, $P=0.0075$ and $\chi^2=163.32$, $P<0.0001$ for β and HFO respectively). During PreAnes period, LMEM identified a significant difference across three pallidal contacts for β ($\chi^2=20.63$, $P<0.0001$) and HFO ($\chi^2=48.81$, $P<0.0001$). After propofol administration, the model showed that β power and HFO peak power ratio were not significantly different across the pallidal signals ($\chi^2=0.47$, $P=0.79$ and $\chi^2=4.11$, $P=0.12$, respectively). We further explored pairwise contrast of mean β power and HFO peak power ratio between channel pairs. During PreAnes, β /HFO was significantly larger in channels (0–1): GPi relative to (2–3): GPe ($P<0.001$ / $P<0.001$) and relative to channel pair (1–2) ($P=0.03$ / $P=0.005$) (Fig 3). During Anes period β /HFO in the GPi were not significantly different relative to any of the other pallidal signals ($P>0.06$).

Due to opposite behavior of low and high β power in GPi as described above, we further used LMEM for the two β sub-bands separately. Such analysis showed that similar to the whole β band, during PreAnes period, there was a significant difference across the contacts for both low β ($\chi^2=17.92$, $P=0.0001$) and high β ($\chi^2=12.80$, $P=0.0017$). These differences however were found to be statistically insignificant after propofol administration ($\chi^2=0.56$, $P=0.76$ and $\chi^2=0.09$, $P=0.96$ for low and high β respectively).

Discussion

The potential role of LFP for DBS localization has been previously described and reinforced by the current results in the pre-anesthetized state. Previous studies in PD patients undergoing STN-DBS implantation suggest that features of spectral power in β band and HFO could be successfully used to distinguish the target location and track within the STN [18,19,22,23]. Similarly previous findings of our group indicated that both β and HFO

activities are strongest at the GPi target (compared to the more dorsal recording sites along the track) [20].

As reported in the present study, the GPi was characterized by significantly greater relative power in both β and HFO frequencies when compared to the GPe. The relative power difference that we observe along the pallidum in the awake state, is consistent with prior MER-SUA studies which describe a significantly greater mean discharge rate in the GPi versus GPe in PD patients at rest [38]. Altogether, these findings suggest that in the awake state, β and HFO activity could potentially serve as neurophysiological biomarkers of target engagement of GPi in awake patients. Given the recent interest of the field in using “asleep” DBS implantation protocols, we further tested these neurophysiological markers of the target location under propofol anesthesia, to determine whether the spatial specificity of LFP persists in the anesthetized stage and can therefore be used as a biomarker in anesthetized patients. Our findings indicate the obliteration of these major distinguishing features, that are, the relative difference in β and HFO power values, between the GPi and GPe under propofol general anesthesia.

The effects of propofol induced unconsciousness on the GPi MERs in PD patients are not settled. However, one study of 10 dystonia patients found a correlation between high dose propofol GA and decreased number of identified high frequency discharge neurons in the GPi [10]. In the STN of PD patients, propofol sedation has been generally associated with the dampening of neuronal spiking activity [17,39], although there have been reports of no significant effect [40]. A previous study used γ and HFO (45–450 Hz) power to estimate of the dorsal STN border when compared to MER estimates [22]. Additionally, these high frequency oscillations have been shown to correlate well with single neuronal spiking activity as measured by MER [41–44]. Following propofol induction, we observed a significant suppression of power in higher frequencies (i.e. > 40 Hz) and a coincident narrowing of relative power difference between the GPe and GPi. Thus, in the unconscious state, HFO activity may not be useful for characterization of the GPi. If HFO activity is indeed a surrogate for local neuronal spiking activity, our results are consistent with previous reports that propofol induced unconsciousness inhibits neuronal firing in both the GPe and GPi.

Although previous studies have demonstrated changes in microelectrode signals under general anesthesia [17,39], several groups have attempted using different regimens of general anesthesia under which MER can still be recorded from STN. These techniques included using less than 1% Sevoflurane concentration [45], a combination of inhalational nitrous oxide and isoflurane or intravenous propofol and remifentanyl [8], desflurane inhalation [46,47] sustaining the minimal alveolar concentration below 1% during MER [48]. These findings along with our current findings emphasize importance of anesthetic dose concentration and timings on the neurophysiological recordings. Our current results therefore do not imply that LFP cannot be used for target identification under all forms of general anesthesia, rather we suggest these oscillatory signals cannot be reliably used to identify the target area under greater doses of anesthesia (similar to the protocol we employed). Future studies need to investigate LFPs under suggested regimens of anesthesia

with reliable MER recordings to further explore utility of these signals in DBS target localization.

During propofol induced unconsciousness state, we observed a similar shift to low frequency predominance in both GPe and GPi; Coincident with changes in power, we also observed a shift of the spectral peak from in frequencies <35 Hz to the α range. A synchronization across the frontal cortex has previously been shown to correlate with the a propofol induced unconscious state [49–51]. This increased α synchrony has been implicated to involve deep nuclear structures, such as the thalamus [51]. The observed dominance of pallidal α oscillations within pallidum (Both GPi and GPe) would be consistent with a theory of BG involvement in the thalamocortical α synchrony given that decreased power is generally related to reduced coupling across regions [25,26,51].

Limitations

Propofol, a GABAergic sedative, is the most common anesthetic used for DBS electrode implantation [14,17]. The precise effect of propofol GA on basal ganglia activity may vary with a patient's disease state, time of sedation, and dosing strategy [10,14,26]. Propofol has previously been shown to suppress β power in the STN of PD patients in a “consciousness-independent”, dose-dependent manner [26]. Thus, conclusions regarding the contributory effect of propofol versus the patient's disease state on neuro-oscillatory activity may be limited. Also, macroelectrode recordings are performed with high temporal resolution; however, the assessment for level of a patient's consciousness using MOAA is prone to temporal error. There may have been periods of electrode recordings during which the patient was not fully unconscious. This may have altered LFP recordings during supposed states of unconsciousness.

Conclusion

In this study, we used LFP recordings from the GPi and GPe in awake and unconscious PD patients to assess the potential utility of LFP-guided targeting during propofol general anesthesia. Our results show that prior to anesthesia, the GPi and GPe are distinguishable using their LFP power spectral profiles, namely in β and HFO frequencies. With the administration of propofol, we observed the obliteration of these major distinguishing features; that is the relative β and HFO power difference delineating the GPi from the GPe. Our findings suggest that LFP spectra, in the propofol-anesthetized state, are most likely not suitable for functional mapping and localization during DBS implantation.

Acknowledgements

This work was supported by the National Institutes of Biomedical Imaging and Bioengineering [K23 EB014326], National Institutes of Neurological Disorders and Stroke [R01NS097782] and philanthropic support from Casa Colina Centers for Rehabilitation. NA was supported by National Institutes of Neurological Disorders and Stroke [R25-NS079198]. MM also was supported by postdoctoral fellowship from American Parkinson disease association (APDA, NY, USA). Authors would like to thank patients who consented to participate in this study without whom recording of local field potentials would not be possible

References

1. Williams NR, Foote KD, Okun MS: STN vs. GPi Deep Brain Stimulation: Translating the Rematch into Clinical Practice. *Movement disorders clinical practice* 2014;1:24–35. [PubMed: 24779023]
2. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks WJ, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ: Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *The New England journal of medicine* 2010;362:2077–2091. [PubMed: 20519680]
3. Mansouri A, Taslimi S, Badhiwala JH, Witiw CD, Nassiri F, Odekerken VJJ, De Bie RMA, Kalia SK, Hodaie M, Munhoz RP, Fasano A, Lozano AM: Deep brain stimulation for Parkinson's disease: meta-analysis of results of randomized trials at varying lengths of follow-up. *Journal of neurosurgery* 2017:1–15.
4. Abosch A, Timmermann L, Bartley S, Rietkerk HG, Whiting D, Connolly PJ, Lanctin D, Hariz MI: An international survey of deep brain stimulation procedural steps. *Stereotact Funct Neurosurg* 2013;91:1–11.
5. Brodsky MA, Anderson S, Murchison C, Seier M, Wilhelm J, Vederman A, Burchiel KJ: Clinical outcomes of asleep vs awake deep brain stimulation for Parkinson disease. *Neurology* 2017;89:1944–1950. [PubMed: 28986415]
6. Saleh S, Swanson KI, Lake WB, Sillay KA: Awake Neurophysiologically Guided versus Asleep MRI-Guided STN DBS for Parkinson Disease: A Comparison of Outcomes Using Levodopa Equivalents. *Stereot Funct Neurosurg* 2015;93:419–426.
7. Ostrem JL, Galifianakis NB, Markun LC, Grace JK, Martin AJ, Starr PA, Larson PS: Clinical outcomes of PD patients having bilateral STN DBS using high-field interventional MR-imaging for lead placement. *Clin Neurol Neurosurg* 2013;115:708–712.
8. Harries AM, Kausar J, Roberts SA, Mocroft AP, Hodson JA, Pall HS, Mitchell RD: Deep brain stimulation of the subthalamic nucleus for advanced Parkinson disease using general anesthesia: long-term results. *J Neurosurg* 2012;116:107–113. [PubMed: 21999316]
9. Venkatraghavan L, Manninen P, Mak P, Lukitto K, Hodaie M, Lozano A: Anesthesia for functional neurosurgery: review of complications. *J Neurosurg Anesthesiol* 2006;18:64–67. [PubMed: 16369142]
10. Venkatraghavan L, Rakhman E, Krishna V, Sammartino F, Manninen P, Hutchison W: The Effect of General Anesthesia on the Microelectrode Recordings From Pallidal Neurons in Patients With Dystonia. *J Neurosurg Anesth* 2016;28:256–261.
11. Ho AL, Ali R, Connolly ID, Henderson JM, Dhall R, Stein SC, Halpern CH: Awake versus asleep deep brain stimulation for Parkinson's disease: a critical comparison and meta-analysis. *J Neurol Neurosurg Psychiatry* 2017
12. Burchiel KJ, McCartney S, Lee A, Raslan AM: Accuracy of deep brain stimulation electrode placement using intraoperative computed tomography without microelectrode recording Clinical article. *Journal of Neurosurgery* 2013;119:301–306. [PubMed: 23724986]
13. Starr PA: Placement of deep brain stimulators into the subthalamic nucleus or globus pallidus internus: Technical approach. *Stereot Funct Neurosurg* 2002;79:118–145.
14. Kwon WK, Kim JH, Lee JH, Lim BG, Lee IO, Koh SB, Kwon TH: Microelectrode recording (MER) findings during sleep-awake anesthesia using dexmedetomidine in deep brain stimulation surgery for Parkinson's disease. *Clin Neurol Neurosurg* 2016;143:27–33. [PubMed: 26895206]
15. Duff J, Sime E: Surgical interventions in the treatment of Parkinson's disease (PD) and essential tremor (ET): medial pallidotomy in PD and chronic deep brain stimulation (DBS) in PD and ET. *Axone* 1997;18:85–89. [PubMed: 9295483]
16. Hertel F, Zuchner M, Weimar I, Gemmar P, Noll B, Bettag M, Decker C: Implantation of electrodes for deep brain stimulation of the subthalamic nucleus in advanced Parkinson's disease with the aid of intraoperative microrecording under general anesthesia. *Neurosurgery* 2006;59:E1138; discussion E1138. [PubMed: 17143204]

17. Raz A, Eimerl D, Zaidel A, Bergman H, Israel Z: Propofol decreases neuronal population spiking activity in the subthalamic nucleus of Parkinsonian patients. *Anesth Analg* 2010;111:1285–1289. [PubMed: 20841416]
18. Kolb R, Abosch A, Felsen G, Thompson JA: Use of intraoperative local field potential spectral analysis to differentiate basal ganglia structures in Parkinson's disease patients. *Physiol Rep* 2017;5
19. Telkes I, Jimenez-Shahed J, Viswanathan A, Abosch A, Ince NF: Prediction of STN-DBS Electrode Implantation Track in Parkinson's Disease by Using Local Field Potentials. *Frontiers in Neuroscience* 2016;10
20. Tsiokos C, Hu X, Pouratian N: 200–300Hz movement modulated oscillations in the internal globus pallidus of patients with Parkinson's Disease. *Neurobiol Dis* 2013;54:464–474. [PubMed: 23388190]
21. Tsiokos C, Malekmohammadi M, AuYong N, Pouratian N: Pallidal low beta-low gamma phase-amplitude coupling inversely correlates with Parkinson disease symptoms. *Clin Neurophysiol* 2017;128:2165–2178. [PubMed: 28942154]
22. Telkes I, Ince NF, Onaran I, Abosch A: Localization of subthalamic nucleus borders using macroelectrode local field potential recordings. *Conf Proc IEEE Eng Med Biol Soc* 2014;2014:2621–2624. [PubMed: 25570528]
23. Chen CC, Pogosyan A, Zrinzo LU, Tisch S, Limousin P, Ashkan K, Yousry T, Hariz MI, Brown P: Intra-operative recordings of local field potentials can help localize the subthalamic nucleus in Parkinson's disease surgery. *Exp Neurol* 2006;198:214–221. [PubMed: 16403500]
24. Krishna V, Elias G, Sammartino F, Basha D, King NKK, Fasano A, Munhoz R, Kalia SK, Hodaie M, Venkatraghavan L, Lozano AM, Hutchison WD: The effect of dexmedetomidine on the firing properties of STN neurons in Parkinson's disease. *Eur J Neurosci* 2015;42:2070–2077. [PubMed: 26108432]
25. Swann NC, de Hemptinne C, Maher RB, Stapleton CA, Meng L, Gelb AW, Starr PA: Motor System Interactions in the Beta Band Decrease during Loss of Consciousness. *J Cogn Neurosci* 2016;28:84–95. [PubMed: 26401814]
26. Martinez-Simon A, Alegre M, Honorato-Cia C, Nunez-Cordoba JM, Cacho-Asenjo E, Troconiz IF, Carmona-Abellan M, Valencia M, Guridi J: Effect of Dexmedetomidine and Propofol on Basal Ganglia Activity in Parkinson Disease A Controlled Clinical Trial. *Anesthesiology* 2017;126:1033–1042. [PubMed: 28492384]
27. Israel Z, Burchiel K: Microelectrode recording in movement disorder surgery. Thieme, 2004.
28. Horn A, Kuhn AA: Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. *Neuroimage* 2015;107:127–135. [PubMed: 25498389]
29. Avants BB, Epstein CL, Grossman M, Gee JC: Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal* 2008;12:26–41. [PubMed: 17659998]
30. Ewert S, Plettig P, Li N, Chakravarty MM, Collins DL, Herrington TM, Kuhn AA, Horn A: Toward defining deep brain stimulation targets in MNI space: A subcortical atlas based on multimodal MRI, histology and structural connectivity. *Neuroimage* 2017
31. Oostenveld R, Fries P, Maris E, Schoffelen J-M, Oostenveld R, Fries P, Maris E, Schoffelen J-M: FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data, FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Computational Intelligence and Neuroscience*, Computational Intelligence and Neuroscience 2010;2011, 2011:e156869–e156869.
32. Malekmohammadi M, AuYong N, Price CM, Tsolaki E, Hudson AE, Pouratian N: Propofol-induced Changes in alpha-beta Sensorimotor Cortical Connectivity. *Anesthesiology* 2018;128:305–316. [PubMed: 29068830]
33. Bokil H, Purpura K, Schoffelen JM, Thomson D, Mitra P: Comparing spectra and coherences for groups of unequal size. *Journal of Neuroscience Methods* 2007;159:337–345. [PubMed: 16945422]
34. Hill PD: Kernel Estimation of a Distribution Function. *Commun Stat-Theor M* 1985;14:605–620.

35. Holm S: A simple sequential rejective multiple test procedure. *Scandinavian Journal of Statistics* 1979;6:65–70.
36. Heil SF: Multilevel and Longitudinal Modeling Using Stata, 2nd edition *J Educ Behav Stat* 2009;34:559–560.
37. Wainwright PE, Leatherdale ST, Dubin JA: Advantages of mixed effects models over traditional ANOVA models in developmental studies: A worked example in a mouse model of fetal alcohol syndrome. *Developmental Psychobiology* 2007;49:664–674. [PubMed: 17943976]
38. Starr PA, Turner RS, Rau G, Lindsey N, Heath S, Volz M, Ostrem JL, Marks WJ, Jr.: Microelectrode-guided implantation of deep brain stimulators into the globus pallidus internus for dystonia: techniques, electrode locations, and outcomes. *J Neurosurg* 2006;104:488–501. [PubMed: 16619651]
39. Lefaucheur JP, Gurruchaga JM, Pollin B, von Raison F, Mohsen N, Shin M, Menard-Lefaucheur I, Oshino S, Kishima H, Fenelon G, Remy P, Cesaro P, Gabriel I, Brugieres P, Keravel Y, Nguyen JP: Outcome of bilateral subthalamic nucleus stimulation in the treatment of Parkinson's disease: correlation with intra-operative multi-unit recordings but not with the type of anaesthesia. *Eur Neurol* 2008;60:186–199. [PubMed: 18667827]
40. Kim W, Song IH, Lim YH, Kim MR, Kim YE, Hwang JH, Kim IK, Song SW, Kim JW, Lee WW, Kim HJ, Kim C, Kim HC, Kim IY, Park HP, Kim DG, Jeon BS, Paek SH: Influence of propofol and fentanyl on deep brain stimulation of the subthalamic nucleus. *J Korean Med Sci* 2014;29:1278–1286. [PubMed: 25246748]
41. Miller KJ, Leuthardt EC, Schalk G, Rao RP, Anderson NR, Moran DW, Miller JW, Ojemann JG: Spectral changes in cortical surface potentials during motor movement. *J Neurosci* 2007;27:2424–2432. [PubMed: 17329441]
42. Manning JR, Jacobs J, Fried I, Kahana MJ: Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *J Neurosci* 2009;29:13613–13620. [PubMed: 19864573]
43. Rasch MJ, Grettton A, Murayama Y, Maass W, Logothetis NK: Inferring spike trains from local field potentials. *J Neurophysiol* 2008;99:1461–1476. [PubMed: 18160425]
44. Mukamel R, Gelbard H, Arieli A, Hasson U, Fried I, Malach R: Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science* 2005;309:951–954. [PubMed: 16081741]
45. Fluchere F, Witjas T, Eusebio A, Bruder N, Giorgi R, Leveque M, Peragut JC, Azulay JP, Regis J: Controlled general anaesthesia for subthalamic nucleus stimulation in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2014;85:1167–1173. [PubMed: 24249783]
46. Lin SH, Chen TY, Lin SZ, Shyr MH, Chou YC, Hsieh WA, Tsai ST, Chen SY: Subthalamic deep brain stimulation after anesthetic inhalation in Parkinson disease: a preliminary study. *J Neurosurg* 2008;109:238–244. [PubMed: 18671635]
47. Tsai ST, Chuang WY, Kuo CC, Chao PC, Chen TY, Hung HY, Chen SY: Dorsolateral subthalamic neuronal activity enhanced by median nerve stimulation characterizes Parkinson's disease during deep brain stimulation with general anesthesia. *J Neurosurg* 2015;123:1394–1400. [PubMed: 26024004]
48. Lin SH, Lai HY, Lo YC, Chou C, Chou YT, Yang SH, Sun I, Chen BW, Wang CF, Liu GT, Jaw FS, Chen SY, Chen YY: Decreased Power but Preserved Bursting Features of Subthalamic Neuronal Signals in Advanced Parkinson's Patients under Controlled Desflurane Inhalation Anesthesia. *Front Neurosci* 2017;11:701. [PubMed: 29311782]
49. Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, Ching S, Kopell NJ, Tavares-Stoeckel C, Habeeb K, Merhar R, Brown EN: Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci U S A* 2013;110:E1142–1151. [PubMed: 23487781]
50. Supp GG, Siegel M, Hipp JF, Engel AK: Cortical hypersynchrony predicts breakdown of sensory processing during loss of consciousness. *Curr Biol* 2011;21:1988–1993. [PubMed: 22100063]
51. Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ: Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness. *Proc Natl Acad Sci U S A* 2010;107:22665–22670. [PubMed: 21149695]

Fig. 1.

Post-operative reconstruction of DBS leads implanted in the pallidum (A) Sagittal view of the ICBM152 2009b non-linear asymmetric standard space with DISTAL atlas (Blue: GPe, Green: GPi) and reconstructed DBS leads for a group of eight subjects (please see materials and methods). All leads from the right side were mirrored to the left side. (B) a close-up view of panel (A) showing that the two ventral contacts (i.e. contacts 0, 1) shown in red and the two dorsal contacts (i.e. contacts 2,3) shown in dark gray (C) Cloud of the contacts. Contacts 0 and 1 are shown with big red circles and contacts 2 and 3 are indicated by small red circles.

Fig. 2.

Spectral power changes in GPi/GPe recordings before and after propofol anesthesia **(A)** Group average power spectral density for GPi (bottom panel) and GPe (top panel), during per-bolus period (black curve) and anesthetized state (red curve). Statistically significant power difference between the two states is indicated by vertical shade, where red and gray colors indicate power was significantly greater during anesthetized and pre-bolus period respectively (GPi: bottom panel, GPe: top panel). **(B)** Boxplots comparing average band power for different frequency bands before and during anesthetized state. Pairwise comparison indicated that all changes were significant (see Table. 2 for details). **(C)** Kernel density estimate of the α/β frequencies (8–35 Hz) before (PreAnes) and after (Anes) induction of anesthesia. Arrows indicate the modes of density estimates showing emergence of a dominant α spectral peak during Anes state. This change happened similarly in GPi (bottom) and GPe (top).

Fig. 3.

Spatial specificity of β and HFO spectral power across pallidal recordings, is lost with propofol anesthesia. Boxplots showing β band power (panel A) and HFO normalized peak power (panel B) for three bipolar contacts across the DBS lead during pre-bolus state (PreAnes) and anesthesia period (Anes). Asterisk signs (*) and (**) indicate statistically significant difference at $p=0.05$ and 0.01 levels respectively.

Table. 1

Subjects' demographic and relevant clinical information

Subject	Gender	Age	MDS-UPDRS-III off (PD)/Tremor Score (ET)	Weight (kg)	Propofol dose (Bolus (mg)/Infusion (mcg/kg/min))
PD1	M	63	32	89.2	40/50
PD 2	M	66	35	69.2	25/50
PD 3	M	64	51	77.1	0/20
PD 4	M	69	36	111	40/25
PD 5	F	75	39	44	0/125
PD 6	M	72	43	82.6	40/30
PD 7	M	52	58	69	75/100
PD 8	M	60	21	102.5	60/50
PD 9	M	70	42	93.4	100/60
PD 10	M	69	52	73.2	30/100
PD 11	F	73	NA	57.6	30/100
PD 12	F	57	47	74.8	60/50

Table 2:

Summary of percent and significance of change in the band power with Propofol anesthesia

		Frequency Band				
		α	Low β	High β	Low γ	HFO
GPe	Percent change (mean $\pm$ SD)	42.75 $\pm$ 39.43	61.33 $\pm$ 46.05	11.79 $\pm$ 46.76	-6.71 $\pm$ 7.54	-16.22 $\pm$ 9.62
	p-value	<0.001	<0.001	0.013	<0.001	<0.001
GPi	Percent change (mean $\pm$ SD)	27.72 $\pm$ 33.32	28.53 $\pm$ 36.06	-27.08 $\pm$ 44.25	-14.20 $\pm$ 11.25	-28.02 $\pm$ 16.10
	p-value	0.001	0.001	0.004	<0.001	<0.001