ANESTHESIOLOGY

Sevoflurane and Parkinson's Disease

Subthalamic Nucleus Neuronal Activity and Clinical Outcome of Deep Brain Stimulation

Sheng-Tzung Tsai, M.D., Guo-Fang Tseng, Ph.D., Chang-Chih Kuo, Ph.D., Tsung-Ying Chen, M.D., Shin-Yuan Chen, M.D.

ANESTHESIOLOGY 2020; 132:1034–44

陳宗鷹

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Accurate stimulating electrode placement is essential for clinically effective subthalamic nucleus brain stimulation in patients with Parkinson's disease
- General anesthetics-induced changes of electrical oscillations in the basal ganglia may render the identification of the stimulation targets difficult
- The effects of sevoflurane-based general anesthesia on the electrophysiologic properties of subthalamic neurons, electrode placement efficacy, and long-term clinical outcomes in Parkinson's disease have not been previously reported

What This Article Tells Us That Is New

- When compared to local anesthesia, sevoflurane-based general anesthesia decreased beta-frequency oscillations and induced coherent lower frequency oscillations in the subthalamic nucleus of patients with Parkinson's disease undergoing electrode placement for deep brain stimulation
- These sevoflurane-induced changes in electrical activity patterns did not reduce electrode placement accuracy or clinical outcome
- These observations suggest that electrode placement for deep brain stimulation under sevoflurane anesthesia is a feasible clinical option

ABSTRACT

Background: General anesthetics-induced changes of electrical oscillations in the basal ganglia may render the identification of the stimulation targets difficult. The authors hypothesized that while sevoflurane anesthesia entrains coherent lower frequency oscillations, it does not affect the identification of the subthalamic nucleus and clinical outcome.

Methods: A cohort of 19 patients with Parkinson's disease with comparable disability underwent placement of electrodes under either sevoflurane general anesthesia (n = 10) or local anesthesia (n = 9). Microelectrode recordings during targeting were compared for neuronal spiking characteristics and oscillatory dynamics. Clinical outcomes were compared at 5-yr follow-up.

Results: Under sevoflurane anesthesia, subbeta frequency oscillations predominated (general *vs.* local anesthesia, mean ± SD; delta: 13 ± 7.3% *vs.* 7.8 ± 4.8%; theta: 8.4 ± 4.1% *vs.* 3.9 ± 1.6%; alpha: 8.1 ± 4.1% *vs.* 4.8 ± 1.5%; all $P < 0.001$). In addition, distinct dorsolateral beta and ventromedial gamma oscillations were detected in the subthalamic nucleus solely in awake surgery (mean ± SD; dorsal *vs.* ventral beta band power: 20.5 ± 6.6% *vs.* 15.4 ± 4.3%; $P < 0.001$). Firing properties of subthalamic neurons did not show significant difference between groups. Clinical outcomes with regard to improvement in motor and psychiatric symptoms and adverse effects were comparable for both groups. Tract numbers of microelectrode recording, active contact coordinates, and stimulation parameters were also equivalent.

Conclusions: Sevoflurane general anesthesia decreased beta-frequency oscillations by inducing coherent lower frequency oscillations, comparable to the pattern seen in the scalp electroencephalogram. Nevertheless, sevoflurane-induced changes in electrical activity patterns did not reduce electrode placement accuracy and clinical effect. These observations suggest that microelectrode-guided deep brain stimulation under sevoflurane anesthesia is a feasible clinical option.

(ANESTHESIOLOGY 2020; 132:1034–44)

Sevoflurane is a widely used volatile anesthetic with a complex mechanism of action including positive allosteric modulation of γ-aminobutyric acid receptors and two-pore-domain K^+ channels.[1] Although the effects of sevoflurane anesthesia on electroencephalographic (EEG) activity have been described, it is unclear if sevoflurane modulates single neuron activity in human patients.[2]

Subthalamic nucleus deep brain stimulation is an effective treatment for patients with Parkinson's disease with motor fluctuations, but clinical outcomes are critically dependent on accurate placement of the stimulating electrode.[3] Microelectrode recordings in awake patients under local anesthesia allow refinement of targeting within the sensorimotor subthalamic nucleus. Further, such recordings have also revealed critical aspects of Parkinson's disease pathophysiology, including pathologic beta band (13 to 30

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). The work presented in this article has been presented at the American Association of Neurological Surgeons annual scientific meeting in Los Angeles, California, April 26, 2017.

Submitted for publication May 29, 2019. Accepted for publication January 6, 2020. Published online first on February 6, 2020. From the Department of Neurosurgery (S.-T.T., S.-Y.C.) and Department of Anesthesiology (T.-Y.C.), Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation/Tzu Chi University, Hualien, Taiwan; and the Institute of Medical Sciences (S.-T.T., S.-Y.C.), and the Department of Anatomy (G.-F.T.) and Department of Physiology and Master Program in Medical Physiology (C.-C.K.), School of Medicine, Tzu Chi University, Hualien, Taiwan.

 Anesthesiology 2020; 132:1034–44. DOI: 10.1097/ALN.0000000000003177

Hz) oscillations in neuronal firing and local field potentials that correlate with disease severity, response to medical therapy, and deep brain stimulation efficacy.[4–6] However, patients with severe tremor, painful off-state dystonia, or high levels of anxiety may not tolerate awake stereotactic surgery.[7]

For such patients, recordings of subthalamic neurons under propofol or dexmedetomidine general anesthesia may be a feasible alternative.[8] Indeed, several studies have also reported comparable clinical outcomes for patients with Parkinson's disease receiving subthalamic nucleus–deep brain stimulation electrode placement surgery using different approaches, such as real-time image guidance and microelectrode recording, under local anesthesia or general anesthesia.[9–12] However, microelectrode recording under general anesthesia presents a unique challenge. Propofol and dexmedetomidine may degrade the quality of microelectrode recordings.[13,14] While the molecular mechanism of sevoflurane and propofol may overlap, EEG analysis revealed a distinct higher theta band (4 to 7 Hz) power under sevoflurane compared to propofol.[2] Therefore, it is critical to characterize the effects of different general anesthetics on single neuron spiking properties as well as on population activity as these properties are essential for guidance of deep brain stimulation electrode placement.

The major objective of this study was to compare the electrophysiologic properties of subthalamic neurons in patients with Parkinson's disease during deep brain stimulation surgery under either sevoflurane general anesthesia or local anesthesia. Based on previous EEG findings, we speculated that sevoflurane would shift the power spectrum to lower frequency oscillations spanning delta, theta, and alpha bands. However, it is unclear whether sevoflurane can also influence the bursting features of subthalamic neurons used for guidance of electrode placement. If not, dorsal and ventral subthalamic borders should be detected under sevoflurane general anesthesia, allowing for electrode placement accuracy comparable to that achieved under local anesthesia. Therefore, in addition to comparing electrophysiologic properties, we also compared electrode placement coordinates, stimulation parameters, and long-term clinical efficacy between patients with Parkinson's disease receiving subthalamic nucleus electrode placement surgery under sevoflurane general anesthesia or local anesthesia.

Materials and Methods

Patient Selection and Imaging

The study was approved by the institutional review board of Tzu Chi General Hospital (Hualien, Taiwan), and written informed consent was collected from all patients. From March 2006 to February 2009, 19 patients with Parkinson's disease with comparable disease severity underwent subthalamic nucleus deep brain stimulation at Tzu Chi General Hospital. These patients were in our study to prospectively compare long-term clinical outcomes between patients with Parkinson's disease receiving general anesthesia or local anesthesia for deep brain stimulation.[15] Patients were recruited based on our previous experience with analyzing microelectrode recording from patients with Parkinson's disease.[16] No formal statistical power calculation was conducted to guide sample size. All participants fulfilled surgical criteria of subthalamic nucleus deep brain stimulation. The benefits and risks of local anesthesia and general anesthesia were explained to each patient, and the choice of anesthesia was made on clinical grounds and patient preference. The study was nonrandomized, and each patient was evaluated blindly using the Unified Parkinson's Disease Rating Scale in four different conditions: on and off medication, and with and without deep brain stimulation. There were no missing data. We evaluated cognitive status with the Cognitive Abilities Screening Instrument and Mini-Mental Status Examination. The Beck Depression Inventory was used to assess patients' depressive mood. The dosage of dopamine replacement medication was expressed as levodopa equivalent daily dose.[17]

The preoperative magnetic resonance imaging images were obtained with a 1.5-tesla unit (SIGNA HDXT 1.5T, General Electric, USA). The protocol consisted of T1-weighted axial pre- and postcontrast images (1 × 1 × 0.7 mm voxels) and T2-weighted axial images (0.5 to 1.0 × 0.5 to 1.0 × 2 mm). Stereotactic planning was conducted using a neuronavigation workstation (BrainLAB, Germany). The surgical target was selected to place the tip of the permanent implantable electrode at the ventral border of the posterior subthalamic nucleus. A Leksell G-frame (Elekta Instrument Inc., USA) was used for the stereotactic procedure. The frame was placed under local anesthesia for both groups. Patients then underwent preoperative computed tomography with frame-mounted stereotactic fiducials in place for fusing stereotactic images to the preoperative magnetic resonance imaging.

Anesthetic Procedure

All general anesthesia group patients received sevoflurane general anesthetics with endotracheal intubation. Anesthesia was initiated by administration of fentanyl (1 to 2 μg/kg), propofol (1 to 2.5 mg/kg), and a muscle relaxant (rocuronium at 0.6 to 1.5 mg/kg or cisatracurium at 0.15 to 0.2 mg/kg). Immediately after the patient's loss of consciousness, the anesthesiologist stopped propofol infusion and started sevoflurane anesthesia to keep the patient unconscious. Sevoflurane inhalation was maintained for the entire recording period. To prevent inadvertent patients' responses due to inadequate anesthesia depth, minimum alveolar concentration was maintained around 1.0 to 1.2 before electrophysiologic recordings, gradually decreased over 30 min, and maintained at 0.5 to 0.6 during recording. End-tidal anesthetic concentration was around 0.7 to 0.8 at a minimum alveolar concentration of 0.5 to 0.6.[18]

Intravenous anesthetics and analgesics demonstrated to dampen subthalamic neuronal firing were avoided for deep brain stimulation surgery.[8,14,19] Patients were closely monitored for heart rate and blood pressure changes during the microelectrode recording procedure.[20] If the blood pressure increased beyond 140 mmHg, the anesthesiologists administered intravenous nicardipine or labetalol to control it. Passive movements of the contralateral limb were tested and monitored in both anesthesia groups during the microelectrode recording in the subthalamic nucleus to identify movement-related neuronal firing changes (kinematic responses). We did not encounter any intraoperative awareness. The selection of the final trajectory for electrode implantation depended on the length of the subthalamic neuronal firings and the presence of passive movement-related activity of the subthalamic neurons. Macrostimulation tests were not performed for the patients in the general anesthesia group since there were no parkinsonian symptoms detected during anesthesia.

Microelectrode Recording Procedure and Localization of the Stimulation Electrode

The microelectrode was 10 to 40 μm in diameter and 200 mm in length, with a less than 50 μm tungsten tip (FHC, Inc., USA) and recording impedance between 0.5 and 1 MΩ. The microelectrode signal was recorded using an intraoperative microelectrode recording system (LeadPoint, Medtronic, USA). The raw signals were amplified (×10) and band-pass filtered (300 Hz to 3 kHz). Recording started 10 mm above the planned target coordinates, and the microelectrode was advanced in steps of 200 to 500 μm with pauses at sites of robust neuronal firing. The discharge from each depth was recorded for at least 10 s.

A typical microelectrode trajectory passes through the thalamus, zona incerta, subthalamic nucleus, and substantia nigra. For both groups, passive movement of the contralateral limbs was tested during microelectrode recording in the subthalamic nucleus to assess for kinematic responses.[20] The final trajectory was selected for electrode implantation based on the length of the subthalamic nucleus recording and the presence of kinematic responses. In the local anesthesia group, macrostimulation testing was performed after the deep brain stimulation electrode (Medtronic 3389) was inserted to test for adverse effects and clinical effectiveness. Postoperative brain computed tomography scanning was performed in both groups to check for the presence of intracranial hemorrhage and determine postoperative electrode coordinates. The implantable pulse generator was implanted during a second operation typically 1 week after the initial operation. Detailed clinical evaluation, targeting, surgical procedures, and recording methods are described in our previous publication.[21]

Offline Analysis of Subthalamic Nucleus Spike Firing

Raw spike recordings from the implanted trajectories were analyzed using custom-written scripts in MATLAB R2014b (Mathworks, USA). Raw recordings were visually inspected by a neurophysiologist blind to patient anesthesia group to exclude artifacts (*e.g.*, mechanical artifacts or spike bursts from neurons damaged by the recording microelectrode). Background spiking activity was estimated using the normalized root mean square of each subthalamic nucleus recording.[6] The root mean square value of each recording was also normalized by the root mean square value of the baseline presubthalamic nucleus recording of each tract (excluding thalamus, zona incerta, and other recordings with prominent spikes) to control for factors such as electrode impedance and electrical noise that vary between subjects.

To estimate the oscillatory entrainment of the population spiking activity, we calculated the power spectral density of the raw recorded subthalamic nucleus population spike firing as previously described.[22] The time series was full-wave rectified and the mean subtracted.[22,23] The power spectral density of the resulting time series was analyzed by the Welch method with a 1-s Hamming window (50% overlap) and zero-padding, yielding a spectral resolution of 1/3 Hz. The power spectral density at each recording depth was normalized by the total power between 0.3 to 100 Hz (excluding ±2 Hz of the 60 Hz line artefacts). We then determined the raw and normalized spectral power from delta (0.1 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 13 Hz), beta (13 to 30 Hz), and gamma (30 to 100 Hz) band ranges in each patient. Each recording's depth was converted to the relative depth to average across patients. Zero percent was designated as the dorsolateral border of subthalamic nucleus and 100% as ventromedial exit (presubthalamic nucleus represented as less than 0% and postsubthalamic nucleus as greater than 100%). For analysis of topographical distribution of subthalamic nucleus spike features, the subthalamic nucleus was arbitrarily divided into the dorsolateral (0 to 50%) and ventromedial (50 to 100%) components.

Single-neuron spike detection was performed using the voltage threshold method. Putative single neurons were identified offline using principal component analysis and the presence of a central trough in the autocorrelogram (Offline Sorter, USA). Isolation of the spike train was graded by evaluating the fraction of spikes within the refractory period of 1.5 ms out of the total number of spikes in the spike train, and only spike trains with a fraction of less than 1% were processed. Spikes degraded by obvious cardiobalistic or other artefacts were excluded.

Statistical Analysis

The Wilcoxon rank-sum test was used for comparing clinical scores, deep brain stimulation lead coordinates, stimulation parameters, and spike features across relative depths in the two groups. Significance was set at $P < 0.05$ (two-tailed) for all tests, corrected as needed for multiple comparisons, and two-tailed testing was used. We evaluated all variables for possible outliers and distribution abnormalities. The

Kruskal–Wallis test was used to assess groupwise differences in band power among the four combinations of dorsal *versus* ventral and local anesthesia *versus* general anesthesia. Pairwise comparisons were assessed using the Wilcoxon rank-sum test with correction for multiple comparisons (five bands and two groups, significance threshold of $P < 0.005$).

Results

Ten patients (four women/six men, mean age 47 ± 8 yr) underwent subthalamic nucleus deep brain stimulation electrode placement under sevoflurane general anesthesia with endotracheal intubation and nine patients (two women/seven men, mean age 45 ± 11 yr) while awake using local anesthesia. The demographic characteristics of the local anesthesia and general anesthesia patients were comparable. We conducted follow-up visits with patients at 5 yr after subthalamic nucleus deep brain stimulation (general anesthesia group: 62 ± 8 months; local anesthesia group: 60 ± 13 months). The mean duration from disease onset to deep brain stimulation surgery for the general anesthesia group was 11 ± 5 yr (mean age at surgery was 57 ± 6 yr) and for the local anesthesia group was 12 ± 9 yr (mean age at surgery was 57 ± 5 yr). Neither motor disability as assessed by Unified Parkinson's Disease Rating Scale scores nor responsiveness to dopamine replacement therapy (improvement in percentage) differed significantly between groups (table 1). All patients in both groups used monopolar stimulation. Further, anatomic coordinates of the surgical target and active stimulation contacts did not differ between groups, nor did the number of microelectrode recording tracts used for mapping (table 2).

Implants under general anesthesia and local anesthesia both utilized intraoperative microelectrode recording. Several previous studies have shown that propofol and dexmedetomidine can alter microelectrode recording features, raising doubts about the reliability of electrophysiologic features for target identification across anesthetic states. We analyzed intraoperative recordings with spontaneous activity of subthalamic nucleus units from both groups (19 microelectrode recording tracts with 299 recorded units under general anesthesia and 16 tracts with 224 units under local anesthesia). The mean normalized root mean square value, a metric of multiunit gray-matter spike activity, did not differ significantly between groups (general anesthesia, 2.3 ± 0.8; local anesthesia, 2.2 ± 0.9, $P = 0.39$; fig. 1A).

We next examined the oscillatory features of the spike trains. Sevoflurane general anesthesia shifted subthalamic nucleus spike oscillations toward lower frequencies. Under general anesthesia, the spectral power across delta, theta, and alpha bands was each significantly greater than in the local anesthesia group (general *vs.* local anesthesia, mean ± SD; delta: 13 ± 7.3% *vs.* 7.8 ± 4.8%; theta: 8.4 ± 4.1% *vs.* 3.9 ± 1.6%; alpha: 8.1 ± 4.1% *vs.* 4.8 ± 1.5%; all $P < 0.001$). In contrast, higher frequency beta and gamma band oscillations were more prominent in the local anesthesia

Table 1. Preoperative Dopaminergic Medication Response between General Anesthesia (n = 10) and Local Anesthesia (n = 9) Group

	General Anesthesia				Local Anesthesia				*P* Value	
	Medication Off	Medication On	Difference	Improvement (%)†	Medication Off	Medication On	Difference	Improvement (%)†	Difference‡	%§
Unified Parkinson's Disease Rating Scale										
Part I	4 ± 2	4 ± 2	1 ± 1	17 ± 33	4 ± 1	3 ± 1	1 ± 1	16 ± 18	0.461	0.554
Part II	19 ± 6	9 ± 4	10 ± 5	50 ± 19	17 ± 8	10 ± 6	6 ± 5	41 ± 31	0.128	0.368
Part III	42 ± 8	21 ± 9	22 ± 8	51 ± 16	34 ± 13	23 ± 9	12 ± 6	35 ± 15	0.011*	0.060
Brady	17 ± 4	10 ± 3	8 ± 4	42 ± 21	15 ± 5	11 ± 5	4 ± 2	30 ± 14	0.043*	0.153
Tremor	5 ± 5	2 ± 3	4 ± 3	63 ± 41	3 ± 4	2 ± 2	2 ± 4	41 ± 44	0.087	0.292
Rigidity	9 ± 2	3 ± 3	6 ± 2	68 ± 27	8 ± 5	5 ± 4	3 ± 2	53 ± 26	0.015*	0.235
Posture and gait	4 ± 2	2 ± 1	2 ± 1	47 ± 27	3 ± 1	2 ± 1	1 ± 0	42 ± 24	0.075	0.377
Axial	9 ± 4	6 ± 2	4 ± 3	38 ± 21	7 ± 3	5 ± 3	2 ± 1	30 ± 19	0.118	0.218
Part IV	7 ± 5	7 ± 5	0 ± 0	0 ± 0	3 ± 4	3 ± 4	0 ± 0	0 ± 0	1.000	1.000
Total	73 ± 15	41 ± 14	32 ± 12	44 ± 16	58 ± 21	39 ± 15	19 ± 10	32 ± 13	0.037*	0.102
Hoehn and Yahr stage	3 ± 1	3 ± 0	1 ± 0	16 ± 13	3 ± 1	3 ± 1	0 ± 0	9 ± 11	0.122	0.229
Activity of daily living score	77 ± 16	92 ± 4	−15 ± 15	−25 ± 31	90 ± 9	97 ± 5	−7 ± 9	−8 ± 11	0.212	0.146

Data are presented as mean ± SD.
*Indicates a significant difference with *P* value < 0.05.
†Improvement: medication off scores – medication on scores / medication off scores X 100%. ‡*P* value: Statistics for the difference of scores between general anesthesia and local anesthesia groups. §*P* value: Statistics for improvement (%) between general anesthesia and local anesthesia groups.§*P* value: Statistics for improvement (%) between general anesthesia and local anesthesia groups.

Table 2. Surgical Coordinates, Subthalamic Nucleus Recording Length, and Microelectrode Recording Tracts between General Anesthesia (n = 10) and Local Anesthesia (n = 9)

	Preoperative Subthalamic Nucleus Targeting*			Postoperative Active Contacts†			Anterior Commissure – Posterior Commissure (mm)	Subthalamic Nucleus Length in Microelectrode Recording (mm)	Microelectrode Recording Tract Number
	X	Y	Z	X	Y	Z			
General anesthesia	10.9 ± 0.7	3.1 ± 0.5	5.7 ± 0.8	12.0 ± 1.0	2.0 ± 0.6	2.5 ± 1.1	25.6 ± 1.3	4.9 ± 0.6	2 ± 1
Local anesthesia	11.0 ± 0.6	2.8 ± 0.7	5.4 ± 0.6	12.3 ± 1.5	2.1 ± 0.8	2.2 ± 1.0	25.6 ± 3.2	4.7 ± 0.6	3 ± 2
P value‡	0.328	0.149	0.192	0.279	0.870	0.268	0.978	0.348	0.117

Data are presented as mean ± SD; coordinates are illustrated according relative to midcommissural point.

*Coordinates of ventral border subthalamic nucleus from stereotactic computed tomography fused brain magnetic resonance imaging. †Coordinates of active contacts of deep brain stimulation electrode from postoperative computed tomography fused with preoperative magnetic resonance imaging. ‡*P* value: statistics for anatomical parameters between general anesthesia and local anesthesia groups.

compared to general anesthesia group (general *vs.* local anesthesia, mean ± SD; beta: 12.7 ± 5% *vs.* 18 ± 6.1%; $P < 0.001$; gamma: 53.6 ± 11.3% *vs.* 62.5 ± 9.7%; $P < 0.001$). In the local anesthesia group, we observed the characteristic gradient of decreasing beta-band power along the recording trajectory from dorsolateral (sensorimotor) to ventromedial (associative-limbic) subthalamic nucleus (mean ± SD; dorsal *vs.* ventral percent of beta band power: 20.5 ± 6.6% *vs.* 15.4 ± 4.3%; $P < 0.001$). This topographic pattern of beta oscillations was not found in the recordings under general anesthesia (fig. 1B, fig. 2). Alternatively, neuronal spiking characteristics were similar between anesthetic states, with no significant group differences in mean spike firing rate (general *vs.* local, 32 ± 4 Hz *vs.* 41 ± 5 Hz, $P = 0.17$), peak burst firing rate (56 ± 3 Hz *vs.* 60 ± 5 Hz, $P = 0.5$), and burst index[24] (4.5 ± 0.3 *vs.* 4.6 ± 1.2, $P = 0.87$). The coefficient of variation of the interspike interval was relatively higher in the general anesthesia group, but the difference did not reach significance (1.6 ± 0.1 *vs.* 1.4 ± 0.1, $P = 0.056$, fig. 3).

At 5 yr after subthalamic nucleus deep brain stimulation surgery, general anesthesia and local anesthesia groups also showed comparable improvements in Unified Parkinson's Disease Rating Scale scores relative to postoperative medication off/deep brain stimulation off and preoperative medication off conditions (Supplemental Digital Content, tables 1 http://links.lww.com/ALN/C246, and 2 http://links.lww.com/ALN/C247). The fractional improvement in off-levodopa Unified Parkinson's Disease Rating Scale part III (motor rating) with deep brain stimulation on did not differ between general and local anesthesia groups (45 ± 17% *vs.* 38 ± 16%, $P = 0.37$). The reductions in levodopa equivalent daily dose ($P = 0.41$) and motor complications (Unified Parkinson's Disease Rating Scale part IV, $P = 0.57$) were also comparable, with no significant differences between groups in subthalamic nucleus deep brain stimulation efficacy according to fractional changes. The disease progressed at a similar rate in both groups (Supplemental Digital Content, table 3, http://links.lww.com/ALN/C248), as evidenced by score changes from preoperative medication off to the postoperative medication off/deep brain stimulation off conditions. Similarly, neuropsychological evaluation results, including Mini-Mental Status Examination, Cognitive Abilities Screening Instrument, and Beck Depression Inventory scores, were comparable between groups at 5 yr (Supplemental Digital Content, table 4, http://links.lww.com/ALN/C249). Furthermore, adverse events frequencies were comparable across groups. One patient implanted under general anesthesia developed an intracerebral hematoma and presented with mild hemiparesis. Another patient implanted under general anesthesia developed infection at the electrodes and recovered fully after explantation and antibiotic treatment. He underwent successful reimplantation. Other stimulation-related adverse events included hypophonia (general anesthesia, two; local anesthesia, one), dysarthria (general anesthesia, two), dyskinesia (local anesthesia, two), and weight gain (general anesthesia, three; local anesthesia, one).

Stimulation parameters were comparable between groups at 5 yr follow-up. The mean stimulation parameters in the general anesthesia group were (left *vs.* right subthalamic nucleus) 3.8 ± 0.4 V and 3.5 ± 0.9 V, 60 ± 0 and 60 ± 0 microseconds, and frequency 123 ± 16 Hz and 123 ± 16 Hz. In the local anesthesia group, parameters were voltages 3.2 ± 0.6 V and 3.5 ± 0.3 V, 64 ± 11 and 64 ± 11 microseconds, and 128 ± 5 and 128 ± 5 Hz. There were no significant differences between groups (stimulation amplitude: $P = 0.15$, pulse width: $P = 0.35$, frequency: $P = 0.26$).

Discussion

Our study demonstrates that sevoflurane general anesthesia has no clinically significant impact on the spike bursting characteristics of subthalamic neurons recorded during deep brain stimulation electrode placement surgery for Parkinson's disease compared to local anesthesia. While sevoflurane did induce a shift in the power band spectrum of subthalamic

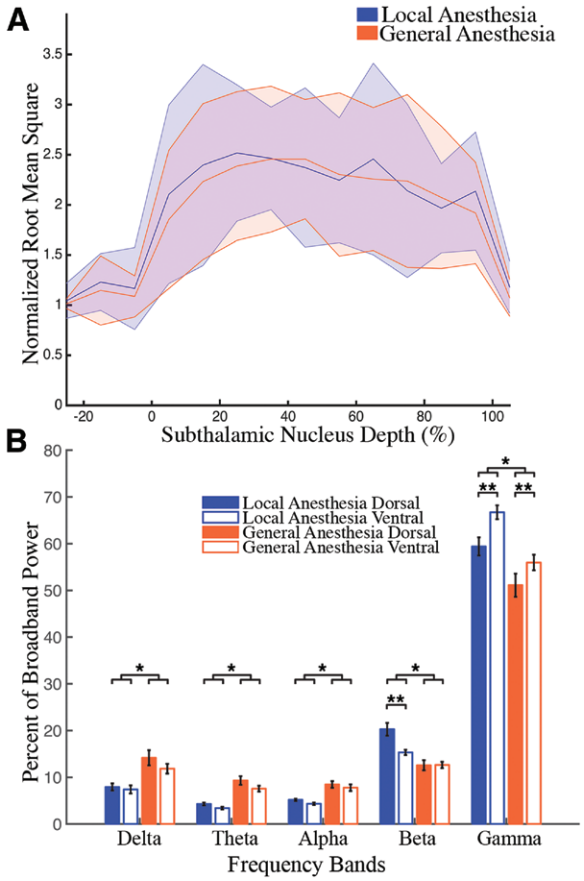

Fig. 1. Group analysis on power distribution of subthalamic nucleus firing. (*A*) Microelectrode recording revealed similar pattern of normalized root mean square values of raw subthalamic nucleus spike firing from both general anesthesia (n = 10) and local anesthesia (n = 9) groups of patients. Both groups have higher normalized root mean square values within subthalamic nucleus (0 to approximately 100%, dorsal to approximately ventral subterritory) compared with presubthalamic nucleus (less than 0%) and postsubthalamic nucleus (greater than 100%) depth recording. *Shaded color area* represents SD in each group. (*B*) Power ratio from individual frequency bands are compared between local anesthesia (n = 9) and general anesthesia (n = 10) groups and dorsal and ventral subthalamic nucleus subterritories. Power of beta band over dorsal subthalamic nucleus was significantly higher than over ventral subthalamic nucleus, and power of gamma band over ventral subthalamic nucleus was significantly higher than dorsal subthalamic nucleus in the local anesthesia group. These power differences in oscillation in topography were not found in the general anesthesia group. Conversely, subbeta band power (delta, theta, and alpha) was significantly higher in the subthalamic nucleus under sevoflurane general anesthesia. *Single asterisk (*)* indicates a significant difference of power between groups of designated bands with *P* value < 0.001. *Double asterisks (**)* indicate a significant difference between subterritories with *P* value < 0.001.

neuron spiking toward subbeta bands (delta, theta, and alpha) compared to local anesthesia, these changes did not influence stimulation electrode placement accuracy, deep brain stimulation parameters, or the clinical efficacy of deep brain stimulation for reducing motor symptoms at 5 yr postsurgery.

Effect of Sevoflurane on Neuronal Firings in the Subthalamic Nucleus

For microelectrode recording to be useful for electrode targeting under general anesthesia, one must be able to reliably identify the characteristic electrophysiologic features and transitions into and out of the target structure (such as the subthalamic nucleus for deep brain stimulation treatment of Parkinson's disease). We report that the fundamental subthalamic nucleus firing properties and gray–white matter transitions can be readily identified under sevoflurane anesthesia as precisely as under local anesthesia. While subthalamic nucleus mapping under inhalational anesthetics has been reported previously, there was no detailed electrophysiologic characterization to ensure preservation of features required for accurate electrode placement.[9,16,20] Further, no single anesthetic regimen has emerged in the literature as optimal for preserving the critical electrophysiologic features required for electrode target identification. For instance, the α-2-adrenergic receptor agonist dexmedetomidine has been reported to decrease bursting activity and variably alter subthalamic nucleus spike rates even at low doses.[13,25,26] Alternatively, propofol has been reported to qualitatively preserve subthalamic nucleus discharge patterns,[27] but several studies have reported that higher dosage reduces the discriminability of spike features in the subthalamic nucleus and globus pallidus.[14,19,24,28–30] Remifentanyl and ketamine anesthesia may also preserve the electrophysiologic properties of the subthalamic nucleus, but concerns about increased intracranial pressure and postanesthetic neuropsychiatric effects have limited use of ketamine.[31] Thus, sevoflurane may be an alternative choice for subthalamic nucleus deep brain stimulation patients intolerant of local anesthesia.

Effect of Sevoflurane on Neuronal Oscillation in the Subthalamic Nucleus

Although the fundamental spiking properties of the subthalamic neurons were similar under sevoflurane and local anesthesia, sevoflurane induced a shift in the oscillatory entrainment toward subbeta bands. Under general anesthesia, subthalamic nucleus spiking demonstrated increased power in the delta, theta, and alpha (less than 12 Hz) range, and decreased power in the beta (13 to 30 Hz) range. Despite distinct molecular targets, sevoflurane was shown to induce unconsciousness in a manner similar to propofol and ketamine by interfering with coherent oscillations between cortical layers of frontal and parietal

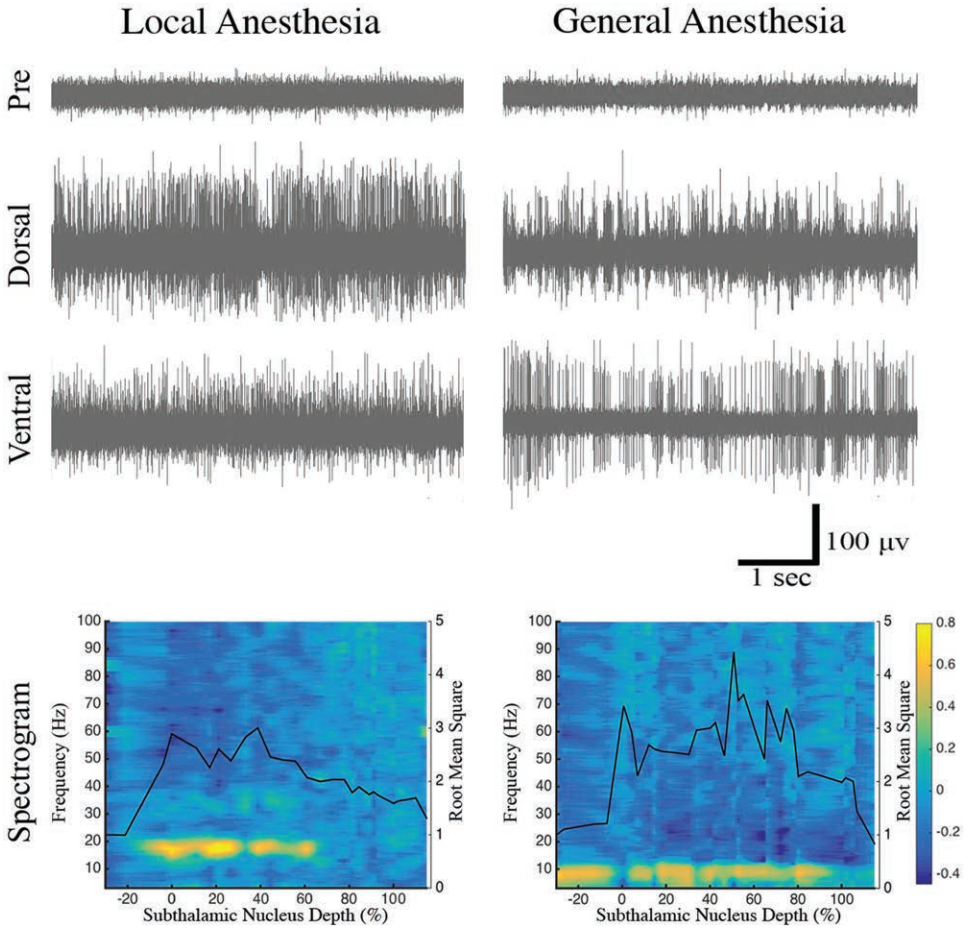

Fig. 2. Two illustrative cases from local anesthesia (*left column*) and general anesthesia (*right column*) groups. *Above* are the composite graphs that show representative microelectrode recordings from presubthalamic nucleus, dorsal, and ventral subthalamic nucleus of both groups. Analysis of power spectral density at *middle* revealed topographical changes of spectrogram in the local anesthesia group, while power spectral density of general anesthesia showed higher values over low frequency (subbeta) band oscillation. The overlying normalized root mean square curve derived from raw spike firing of individual patients from both groups still reveal distinctive boundary of subthalamic nucleus borders.

lobes.[31,32] These effects on the group oscillations of subthalamic neurons further confirm that sevoflurane has a similar influence on basal ganglia–related oscillatory dynamics and anesthesia as propofol. In contrast, Velly *et al.* suggested that sevoflurane and propofol produce unconsciousness and analgesia through distinct effects on cortical and subcortical structures.[33] A recent study using desflurane during microelectrode recording of deep brain stimulation surgery showed enhanced power over theta band range (4 to 8 Hz) oscillation only, which further indicates that different volatile anesthetics work through different mechanisms on drug-induced unconsciousness and analgesia.[32,34]

Under general anesthesia, we did not observe increased beta entrainment of the dorsolateral subthalamic nucleus compared to the ventromedial subthalamic nucleus. The inability to detect this electrophysiologic signature of sensorimotor subthalamic nucleus could potentially interfere with electrode placement accuracy for some applications. Beta band oscillations and beta-gamma phase-amplitude coupling have been proposed as biomarkers of Parkinson's disease neuropathology and have been demonstrated to correlate with severity of Parkinson's disease motor disability, response to levodopa, and response to deep brain stimulation.[35–39] In addition, the spatial extent of beta oscillations at the implanted deep brain stimulation site correlated with its efficacy.[6] Detection of such oscillations intraoperatively may be useful to refine optimal targeting and guide deep brain stimulation programming. Also, adaptive deep brain stimulation strategies triggered by beta-band oscillations may offer additional advantages including reduced battery consumption and side effects.[40] In this case, implantation at a site with an optimal control signal would be important. Thus, while we

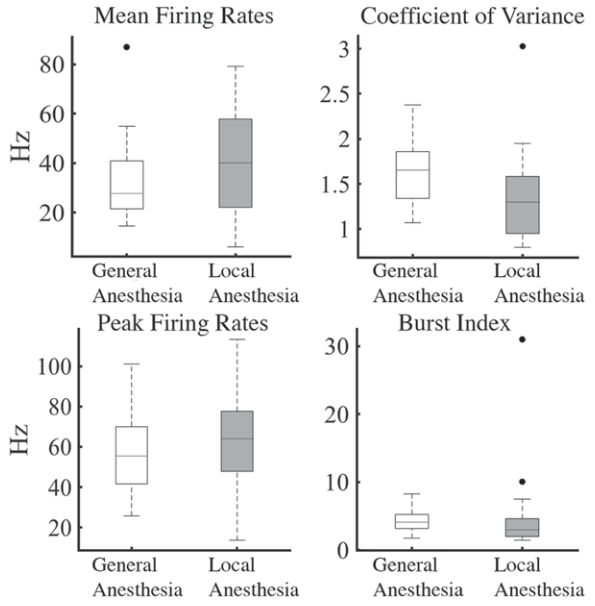

Fig. 3. Group analysis showing comparable subthalamic nucleus spiking characteristics in both general anesthesia (n = 10) and local anesthesia (n = 9) groups. *Box and whisker plots* from four different features of neuronal spiking, including mean firing rates, peak firing rates, coefficient of variance, and burst index did not reveal any significant difference between two groups.

found no differences in clinical efficacy at the 5-yr follow-up, we cannot exclude potential disadvantages of sevoflurane anesthesia for some deep brain stimulation applications.

Effect of Sevoflurane on Subthalamic Nucleus Targeting and Clinical Outcomes of Deep Brain Stimulation

Optimal clinical outcomes from subthalamic nucleus deep brain stimulation, including maximal motor benefit and minimal stimulation-related sided effects, depend on accurate placement of electrodes. Despite 30 yr of clinical experience, the optimal anatomic target and the best surgical approach to reach it are still debated.[41] Awake implantation facilitates microelectrode mapping and intraoperative assessment of the clinical response to stimulation. However, awake surgery is less comfortable for patients, and may be contraindicated for patients with painful dystonia, large-amplitude tremors, or severe anxiety. As advances in magnetic resonance imaging have improved direct targeting and real-time intraoperative imaging has become available, the relative benefits of awake surgery and microelectrode recording have been questioned.

In our study, surgical procedures were standardized between patients, save for anesthetic modality. Both anesthesia groups achieved approximately 50% improvement in off-levodopa Unified Parkinson's Disease Rating Scale part III score with stimulation at 5 yr postsurgery, comparable to long-term outcomes reported in other studies of deep brain stimulation under local anesthesia.[42,43] Thus, our results are consistent with the noninferiority of microelectrode recording-guided deep brain stimulation lead implantation under general anesthesia. Similarly, Fluchere *et al.* reported comparable 1- and 5-yr subthalamic nucleus deep brain stimulation outcomes for a large cohort of patients with Parkinson's disease implanted under general anesthesia with microelectrode recording.[9] The current results are also in line with several smaller studies and a meta-analysis reporting clinical outcomes at short- to midterm follow-up of deep brain stimulation under general anesthesia for Parkinson's disease.[10,11,27] Complication rates and hospital length of stay have also been reported to be comparable between anesthetic modalities.[44] However, these studies did not describe electrophysiologic changes to subthalamic neurons compared to local anesthesia. Given the importance of neuronal firing properties for defining the optimal stimulation target, the current findings provide a plausible explanation for the comparable clinical success of subthalamic nucleus deep brain stimulation under general anesthesia.

Our study has several limitations. First, patients were not randomized to the sevoflurane anesthesia and local anesthesia groups. All were included according to strict surgical criteria. Second, there were differences in some motor domains at baseline between groups, such as levodopa response, which may have influenced electrophysiologic features or clinical outcome.[4] For instance, it has been suggested that responsiveness to dopaminergic treatment correlates with deep brain stimulation efficacy.[45,46] Third, we did not assess differences in electrophysiologic properties according to the depth of sevoflurane anesthesia, and all surgical and recording procedures were standardized. Fourth, this relatively small cohort limits the statistical power to discern small differences in electrophysiologic responses and long-term clinical outcomes between anesthetic groups. Finally, as we mentioned, we were unable to perform trial stimulation tests to evaluate the initial effectiveness and possible side effects in the general anesthesia group. However, due to precise localization of subthalamic nucleus targets and similar postoperative active contacts coordinates, patients in both groups achieved comparable benefits and exhibited similar side effect profiles at the long-term follow-up.

In conclusion, we report that the basic firing properties of subthalamic neurons are preserved using sevoflurane anesthesia for deep brain stimulation electrode placement surgery. Alternatively, the characteristic beta oscillations in the dorsolateral (sensorimotor) subthalamic nucleus are obscured by sevoflurane-induced entrainment of delta, theta, and alpha oscillations. Nonetheless, this does not impair electrode placement accuracy or affect long-term clinical outcome. This study supports the application of electrophysiology-based approaches for deep brain stimulation implantation under inhalational anesthesia. Whether this combined approach is widely applicable will depend

on future deep brain stimulation platforms employing real-time electrophysiologic data to guide therapy.

Acknowledgments

The authors thank Todd Michael Herrington, M.D., Ph.D., Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, for helpful discussion and English grammar editing.

Research Support

This work was funded by the Buddhist Tzu Chi Medical Foundation (TCMF-MP 108-01-03), Ministry of Science and Technology, Taiwan (107-2314-B-303-002), Tzu-Chi University, Hualien, Taiwan (TCIRP 104001-05), and Hualien Tzu-Chi General Hospital, Hualien, Taiwan (TCRD106-32).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Chen: Mail: 707, Sec. 3, Chung-Yang Road, Hualien, Taiwan, 970. william.sychen@msa.hinet.net.

References

1. Lioudyno MI, Birch AM, Tanaka BS, Sokolov Y, Goldin AL, Chandy KG, Hall JE, Alkire MT: Shaker-related potassium channels in the central medial nucleus of the thalamus are important molecular targets for arousal suppression by volatile general anesthetics. J Neurosci 2013; 33:16310–22
2. Akeju O, Westover MB, Pavone KJ, Sampson AL, Hartnack KE, Brown EN, Purdon PL: Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. Anesthesiology 2014; 121:990–8
3. 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
4. Sharott A, Gulberti A, Zittel S, Tudor Jones AA, Fickel U, Münchau A, Köppen JA, Gerloff C, Westphal M, Buhmann C, Hamel W, Engel AK, Moll CK: Activity parameters of subthalamic nucleus neurons selectively predict motor symptom severity in Parkinson's disease. J Neurosci 2014; 34:6273–85
5. Patel SR, Sheth SA, Martinez-Rubio C, Mian MK, Asaad WF, Gerrard JL, Kwon CS, Dougherty DD, Flaherty AW, Greenberg BD, Gale JT, Williams ZM, Eskandar EN: Studying task-related activity of individual neurons in the human brain. Nat Protoc 2013; 8:949–57
6. Zaidel A, Spivak A, Grieb B, Bergman H, Israel Z: Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. Brain 2010; 133(pt 7):2007–21
7. Kocabicak E, Aygun D, Alptekin O, Guz H, Kurt M, Sarihasan B, Temel Y: Conversion of local anesthesia-guided deep brain stimulation of the subthalamic nucleus to general anesthesia. J Neurol Surg A Cent Eur Neurosurg 2013; 74:332–4
8. Martinez-Simon A, Alegre M, Honorato-Cia C, Nuñez-Cordoba JM, Cacho-Asenjo E, Trocóniz IF, Carmona-Abellán M, Valencia M, Guridi J: Effect of dexmedetomidine and propofol on basal ganglia activity in Parkinson disease: A controlled clinical trial. Anesthesiology 2017; 126:1033–42
9. 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; 85:1167–73
10. Chen SY, Tsai ST, Lin SH, Chen TY, Hung HY, Lee CW, Wang WH, Chen SP, Lin SZ: Subthalamic deep brain stimulation in Parkinson's disease under different anesthetic modalities: A comparative cohort study. Stereotact Funct Neurosurg 2011; 89:372–80
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 2018; 89:687–91
12. 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; 89:1944–50
13. Elias WJ, Durieux ME, Huss D, Frysinger RC: Dexmedetomidine and arousal affect subthalamic neurons. Mov Disord 2008; 23:1317–20
14. Hertel F, Züchner 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
15. Tsai ST, Chen TY, Lin SH, Chen SY: Corrigendum to "Five-Year Clinical Outcomes of Local *versus* General Anesthesia Deep Brain Stimulation for Parkinson's Disease". Parkinsons Dis 2019; 2019:2654204
16. 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; 123:1394–400

17. Fine J, Duff J, Chen R, Chir B, Hutchison W, Lozano AM, Lang AE: Long-term follow-up of unilateral pallidotomy in advanced Parkinson's disease. N Engl J Med 2000; 342:1708–14
18. Nickalls RW, Mapleson WW: Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. Br J Anaesth 2003; 91:170–4
19. 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; 111:1285–9
20. 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; 109:238–44
21. Tsai ST, Lin SH, Lin SZ, Chen JY, Lee CW, Chen SY: Neuropsychological effects after chronic subthalamic stimulation and the topography of the nucleus in Parkinson's disease. Neurosurgery 2007; 61:E1024–9; discussion E1029–30
22. Moran A, Bergman H, Israel Z, Bar-Gad I: Subthalamic nucleus functional organization revealed by parkinsonian neuronal oscillations and synchrony. Brain 2008; 131(pt 12):3395–409
23. Myers LJ, Lowery M, O'Malley M, Vaughan CL, Heneghan C, St Clair Gibson A, Harley YX, Sreenivasan R: Rectification and non-linear pre-processing of EMG signals for cortico-muscular analysis. J Neurosci Methods 2003; 124:157–65
24. Moll CK, Galindo-Leon E, Sharott A, Gulberti A, Buhmann C, Koeppen JA, Biermann M, Bäumer T, Zittel S, Westphal M, Gerloff C, Hamel W, Münchau A, Engel AK: Asymmetric pallidal neuronal activity in patients with cervical dystonia. Front Syst Neurosci 2014; 8:15
25. 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
26. Krishna V, Elias G, Sammartino F, Basha D, King NK, 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; 42:2070–7
27. 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; 116:107–13
28. Steigerwald F, Hinz L, Pinsker MO, Herzog J, Stiller RU, Kopper F, Mehdorn HM, Deuschl G, Volkmann J: Effect of propofol anesthesia on pallidal neuronal discharges in generalized dystonia. Neurosci Lett 2005; 386:156–9
29. Maciver MB, Bronte-Stewart HM, Henderson JM, Jaffe RA, Brock-Utne JG: Human subthalamic neuron spiking exhibits subtle responses to sedatives. Anesthesiology 2011; 115:254–64
30. Lee WW, Ehm G, Yang HJ, Song IH, Lim YH, Kim MR, Kim YE, Hwang JH, Park HR, Lee JM, Kim JW, Kim HJ, Kim C, Kim HC, Park E, Kim IY, Kim DG, Jeon B, Paek SH: Bilateral deep brain stimulation of the subthalamic nucleus under sedation with propofol and fentanyl. PLoS One 2016; 11:e0152619
31. Lettieri C, Rinaldo S, Devigili G, Pauletto G, Verriello L, Budai R, Fadiga L, Oliynyk A, Mondani M, D'Auria S, Skrap M, Eleopra R: Deep brain stimulation: Subthalamic nucleus electrophysiological activity in awake and anesthetized patients. Clin Neurophysiol 2012; 123:2406–13
32. 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
33. Velly LJ, Rey MF, Bruder NJ, Gouvitsos FA, Witjas T, Regis JM, Peragut JC, Gouin FM: Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. Anesthesiology 2007 Aug; 107:202–12
34. Ryu KH, Song K, Lim TY, Choi WJ, Kim YH, Kim HS: Does equi-minimum alveolar concentration value ensure equivalent analgesic or hypnotic potency?: A comparison between desflurane and sevoflurane. Anesthesiology 2018; 128:1092–8
35. de Hemptinne C, Swann NC, Ostrem JL, Ryapolova-Webb ES, San Luciano M, Galifianakis NB, Starr PA: Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. Nat Neurosci 2015; 18:779–86
36. Miocinovic S, de Hemptinne C, Qasim S, Ostrem JL, Starr PA: Patterns of cortical synchronization in isolated dystonia compared with Parkinson disease. JAMA Neurol 2015; 72:1244–51
37. Neumann WJ, Jha A, Bock A, Huebl J, Horn A, Schneider GH, Sander TH, Litvak V, Kühn AA: Cortico-pallidal oscillatory connectivity in patients with dystonia. Brain 2015; 138(pt 7):1894–906
38. van Wijk BC, Beudel M, Jha A, Oswal A, Foltynie T, Hariz MI, Limousin P, Zrinzo L, Aziz TZ, Green AL, Brown P, Litvak V: Subthalamic nucleus phase-amplitude coupling correlates with motor impairment in Parkinson's disease. Clin Neurophysiol 2016; 127:2010–9
39. Pogosyan A, Yoshida F, Chen CC, Martinez-Torres I, Foltynie T, Limousin P, Zrinzo L, Hariz MI, Brown P: Parkinsonian impairment correlates with spatially extensive subthalamic oscillatory synchronization. Neuroscience 2010; 171:245–57

40. Meidahl AC, Tinkhauser G, Herz DM, Cagnan H, Debarros J, Brown P: Adaptive deep brain stimulation for movement disorders: The long road to clinical therapy. Mov Disord 2017; 32:810–9
41. Hamel W, Köppen JA, Alesch F, Antonini A, Barcia JA, Bergman H, Chabardes S, Contarino MF, Cornu P, Demmel W, Deuschl G, Fasano A, Kühn AA, Limousin P, McIntyre CC, Mehdorn HM, Pilleri M, Pollak P, Rodríguez-Oroz MC, Rumià J, Samuel M, Timmermann L, Valldeoriola F, Vesper J, Visser-Vandewalle V, Volkmann J, Lozano AM: Targeting of the subthalamic nucleus for deep brain stimulation: A survey among Parkinson disease specialists. World Neurosurg 2017; 99:41–6
42. Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E: Ten-year outcome of subthalamic stimulation in Parkinson disease: A blinded evaluation. Arch Neurol 2011; 68:1550–6
43. Zibetti M, Merola A, Rizzi L, Ricchi V, Angrisano S, Azzaro C, Artusi CA, Arduino N, Marchisio A, Lanotte M, Rizzone M, Lopiano L: Beyond nine years of continuous subthalamic nucleus deep brain stimulation in Parkinson's disease. Mov Disord 2011; 26:2327–34
44. Chen T, Mirzadeh Z, Chapple K, Lambert M, Ponce FA: Complication rates, lengths of stay, and readmission rates in "awake" and 'asleep' deep brain simulation. J Neurosurg 2016:1–10 doi:10.3171/2016.6.JNS152946
45. Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, Arnulf I, Pidoux B, Dormont D, Cornu P, Agid Y: Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain 2002; 125(pt 3):575–83
46. Charles PD, Van Blercom N, Krack P, Lee SL, Xie J, Besson G, Benabid AL, Pollak P: Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 2002; 59:932–4