Effect of Dexmedetomidine and Propofol on Basal Ganglia Activity in Parkinson Disease

A Controlled Clinical Trial

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ABSTRACT

Background: Deep brain stimulation electrodes can record oscillatory activity from deep brain structures, known as local field potentials. The authors' objective was to evaluate and quantify the effects of dexmedetomidine (0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) on local field potentials in patients with Parkinson disease undergoing deep brain stimulation surgery compared with control recording (primary outcome), as well as the effect of propofol at different estimated peak effect site concentrations (0.5, 1.0, 1.5, 2.0, and 2.5 μg/ml) from control recording.

Methods: A nonrandomized, nonblinded controlled clinical trial was carried out to assess the change in local field potentials activity over time in 10 patients with Parkinson disease who underwent deep brain stimulation placement surgery (18 subthalamic nuclei). The relationship was assessed between the activity in nuclei in the same patient at a given time and repeated measures from the same nucleus over time.

Results: No significant difference was observed between the relative beta power of local field potentials in dexmedetomidine and control recordings (–7.7; 95% CI, –18.9 to 7.6). By contrast, there was a significant decline of 12.7% (95% CI, –21.3 to –4.7) in the relative beta power of the local field potentials for each increment in the estimated peak propofol concentrations at the effect site relative to the control recordings.

Conclusions: Dexmedetomidine (0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) did not show effect on local field potentials compared with control recording. A significant deep brain activity decline from control recording was observed with incremental doses of propofol.
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DEEP brain stimulation (DBS) is a standard treatment to combat the symptoms of Parkinson disease (PD).[1–3] In most centers with surgery for PD, the surgical implantation of the electrodes for DBS follows a well-established technique that combines microelectrode recordings (MERs), microstimulation, and neurologic intraoperative testing to localize the target nuclei.[4–8]

A variety of anesthetic approaches are used when DBS electrodes are implanted, including local anesthesia, conscious sedation, "asleep-awake," or "asleep-awake-asleep" protocols.[6,9,10] With the exception of local anesthesia, one important drawback is that all the sedative drugs used to achieve anesthesia in this surgery affect the quality of MERs, lowering the firing rate of basal ganglia neurons while simultaneously suppressing or altering symptoms of PD.[11–13]

What We Already Know about This Topic

- In patients undergoing implantation of deep brain stimulation electrodes for Parkinson disease, microelectrode recordings from the target nuclei are used to guide proper electrode placement. The selection of anesthetic agents that have the least impact on microelectrode recordings is therefore important.
- The effect of dexmedetomidine on activity of subthalamic nuclei was compared with that of graded doses of propofol in patients undergoing placement of deep brain stimulation electrodes.

What This Article Tells Us That Is New

- Activity in the subthalamic nuclei was similar to the control, unsedated state in patients who received dexmedetomidine. By contrast, propofol produced a dose-dependent reduction in neuronal activity, especially in the beta frequency range.
- The data support the use of dexmedetomidine for sedation in patients undergoing deep brain stimulator implantation.

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Propofol is the drug most often used for sedation during DBS surgery for PD, although how it affects MER quality and symptoms of PD during this type of surgery remains unclear. It has been reported to dampen the rate of neural discharge in the subthalamic nucleus (STN), interfering with optimal MER localization to the target nucleus,[11,14] although there is other evidence that it does not alter MERs significantly.[15,16] In recent years, dexmedetomidine has been used increasingly in DBS surgery for PD.[9] Dexmedetomidine is an α2-adrenergic receptor agonist that does not affect GABA receptors and that has a strong anxiolytic effect through its activity in the subcortical areas of the brain.[17] Moreover, low maintenance doses of dexmedetomidine do not appear to interfere with MERs.[12,18]

To date, the influence of dexmedetomidine and propofol on basal ganglia–mediated motor symptoms and clinical recording in humans has not been clearly established. Clinical outcome, measured as the clinical situation or long-term stimulation parameters, has been analyzed, yet without the obtaining of electrophysiologic data to support the results.[16,19] Elsewhere, MERs from different patients[20] or from contralateral nuclei targets in the same patient have been compared.[15] In many of these studies, however, the influence of the anesthetic drug on MERs is based solely on the opinion of the neurologist or neurophysiologist.[12,14,21,22] Indeed, there are only a few studies that have analyzed how a sedative drug affects electrophysiologic data from the same target nucleus.[11,23] Thus, because there are currently no data comparing MERs in the same nucleus at baseline (without sedation) and at different levels of sedation, how these sedative agents interfere with deep brain activity remains largely unknown.

Previously implanted DBS electrodes provide a unique opportunity to record electrical oscillatory activity from deep brain structures. These oscillations are considered to be a summation of the synchronized postsynaptic changes surrounding the electrode, and they are referred to as local field potentials (LFPs).[24–28] A better understanding of the effects of sedative drugs on LFPs is important to improve the management of sedation in patients undergoing DBS placement surgery for PD. The objective of this controlled clinical trial was to evaluate and quantify the effects of dexmedetomidine (0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) on the LFPs in patients with PD undergoing DBS surgery and to assess the influence of different estimated peak effect site concentrations of propofol (0.5, 1.0, 1.5, 2.0, and 2.5 μg/ml) relative to control LFPs recordings.

Materials and Methods

This study involved a nonrandomized, nonblinded controlled clinical trial approved by the institutional review board of Navarra (Pamplona, Spain) and by the Spanish Agency of Medicines and Medical Devices (EudraCT 2014-000868-17), and it was also registered at http://www.clinicaltrials.gov (NCT-02256319). Eligible participants were adult patients with PD who underwent surgery for unilateral or bilateral DBS electrode placement at the University of Navarra Clinic (Pamplona, Spain) between October 2014 and December 2015 (n = 12 patients). The recruitment procedure was carried out entirely by the principal investigator. All potential participants were informed orally and in writing during the interview to obtain consent. No incentives were offered for participating in the study. The name and contact information of three anesthesiologists (including the principal investigator) were provided to solve any questions of the participant during the consent process or later. Interviews were conducted in a private room. Exclusion criteria included specific contraindications to the use of dexmedetomidine or propofol, uncooperative patients, and/or the concomitant use of other sedative drugs (benzodiazepines, opiates, or ketamine).

The surgical procedure was carried out in two phases. In a first intervention, the DBS electrodes were put in place *via* an "asleep-awake-asleep" anesthetic protocol with dexmedetomidine as the sole anesthetic drug. In the second phase, the DBS device was tunneled and connected to the implantable pulse generator by the use of propofol-based general anesthesia. As such, three types of LFPs recordings were obtained from the DBS electrode: a dexmedetomidine recording, administered at 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$, during DBS placement in the first surgical phase; a control recording, obtained in the absence of any influence of sedative on a day between the first and second surgical intervention; and a propofol recording at different estimated peak effect site concentrations (0.5, 1.0, 1.5, 2.0, and 2.5 μg/ml), before the induction of general anesthesia in the second surgical phase (see table, Supplemental Digital Content 1, http://links.lww.com/ALN/B405, which is a table showing the schedule of LFP recordings). Patients were in an "off" medication state during both phases of surgery and for all LFP recordings, meaning that at least 12 h had elapsed since the last administration of antiparkinsonian drugs.

Anesthesia

During the first phase of surgery, standard monitoring of anesthesia (electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry) was established on entry into the operating theater. Supplemental oxygen (2 l) was provided by the use of a nasal cannula and in association with capnography. A 20-gauge catheter was inserted into a vein in each hand, and a urinary catheter was put in place.

All patients received a loading (1 μg/kg in 10 min) and maintenance dose (0.2 to 1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) of dexmedetomidine to achieve a Ramsay Sedation Score (RSS) of 3 to 4 in preparation for the surgical intervention (positioning, skin incision, and burr hole). In every case, the sedative effect of the loading dose determined the concentration at which the maintenance dose was started. Before durotomy, the maintenance dose was decreased progressively to 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in function to ensure the patient's comfort without interfering with the neurologic examination (RSS of 2). Dexmedetomidine infusion was stopped temporarily in patients who did

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not display their usual clinical motor signs (tremor) or who could not cooperate adequately, and it was reestablished only if the patient recovered previous motor clinical symptoms and could respond adequately to verbal stimuli. Before electrode implantation, the maintenance dose was adjusted to 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ in all patients. In bilateral surgery, maintenance dose was adjusted before the insertion of the second DBS electrode. Once the electrode was implanted, a 2-min LFP recording of the target nucleus (unilateral or bilateral recording of the STN or internal globus pallidus [GPi]) was obtained (dexmedetomidine recording). Once this was achieved, the dose of dexmedetomidine was adjusted (0.2 to 1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) to achieve a RSS of 3 to 4 for the rest of surgery, and its administration was finished before the patient was transferred to the intensive care unit.

For the second phase, the same monitoring of anesthesia was used but only a peripheral vein catheter was put in place; a bladder catheter was not considered necessary. A 2-min recording of the LFPs (STN or GPi) from the DBS electrode was obtained during the induction of general anesthesia with propofol (propofol recording). We used target-controlled infusion (TCI Alaris; BD, USA) to administer propofol according to a Marsh model. The estimated effect site peak concentrations of propofol were 0.5, 1.0, 1.5, 2.0, and 2.5 μg/ml. If spontaneous breathing was lost by the patient at any point during the recording, general anesthesia was induced and no further recording took place. The tunneling procedure and battery placement were carried out following the standard procedures of anesthesia for this type of intervention.

Surgical Technique

An image fusion procedure (magnetic resonance imaging and computed tomography) was carried out routinely by our group to obtain the stereotactic coordinates of the STN and GPi.[29] The day before surgery, a magnetic resonance image of the brain was obtained for each patient with different magnetic resonance sequences for each surgical target. On the day of surgery, and once the CRW stereotactic frame (Cosman-Roberts-Wells, Radionics, USA) was put in place under local anesthesia, a computed tomography scan of the brain was obtained and the imaging data were fused with magnetic resonance imaging by the use of BrainLab software (iPlan Stereotaxy 2.6 and 3.0 Brain Lab, Germany). The coordinates for the STN or GPi were determined by direct targeting methods, and the motor region of the target structure was defined during surgery through the MERs (200 to 600 K platinum/iridium microelectrodes; FHC, USA), and based on the neuronal discharge pattern at rest, during tremor-related activity, and in response to passive and active movement "driving," as well as through the effects of microstimulation (changes in tremor amplitude, rigidity and/or bradykinesia, and side effects).

After the motor region was defined, the electrode (Medtronic 3389 in the STN; Medtronic 3387 in the GPi; Medtronic, USA) was placed at the selected coordinates in the target structure, each electrode having 4 active contacts: 0, 1, 2, and 3 from ventral to dorsal. This electrode was placed with the most ventral contact at the ventral portion of the STN or GPi.[29] After clinical testing to verify that stimulation yielded antiparkinsonian efficacy and no adverse effects, the electrode was fixed with a burr hole ring and cap and connected to percutaneous connectors with extension wires that exited through a small incision in the skin. Before finishing the surgery, a 2-min LFPs recording was obtained through percutaneous extensions (dexmedetomidine registration). All the surgical interventions were performed by the same senior surgeon (J.G.).

Control Recordings

The control LFPs recordings from the DBS electrode were obtained during a visit to the neurophysiologist on a day between the first and second operation (and therefore, free of any effect of the anesthetic drugs) using the standard protocol established at our center (Supplemental Digital Content 1, http://links.lww.com/ALN/B405).[26] The patients were studied early in the morning after overnight withdrawal of antiparkinsonian medication, as in the other two conditions. A minimum 2-min LFP recording was obtained at rest for each patient.

Recording and Signal Analysis

LFPs activity was recorded through the DBS electrodes with a bipolar montage. The DBS electrode has four contacts (0 to 3, ventral to dorsal) that can be recorded in three consecutive bipolar combinations (0 to 1, 1 to 2, and 2 to 3). In the propofol and dexmedetomidine recordings, only one channel per side was recorded. For the STN, the intermediate bipolar channel (contacts 1 to 2) was selected to ensure that the activity originated within the nucleus. For the GPi recordings, the most ventral contact pair (0 to 1) was chosen to avoid recording activity from the external globus pallidus. In the control recordings, the three contact pairs were recorded on each side, although only the same combination as that used in the other two recordings (1 to 2 in the STN, 0 to 1 in the GPi) was analyzed.

In all conditions, the LFP signal was amplified ×100,000, filtered at 0.3 to 1,000 Hz, and sampled at 2,000 Hz. Two-minute segments of the LFP recordings were selected for the spectral analysis. The frequency content of the signals were characterized by means of the Welch periodogram[30] using a Fast Fourier transform with a 4,096 points Hanning window (~2 s), giving a resolution of ~0.5 Hz per bin. The power spectra (in the 5 to 130 Hz range) were normalized individually by dividing each value by the mean power and multiplying it per 100. The mains artifact (48 to 52 Hz) and its first harmonic (97 to 104 Hz) were excluded from the mean, and the global power in the alpha (8 to 12 Hz) and beta band (13 to 30 Hz) was then measured in the normalized spectra for each patient, side, and condition.

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Pharmacokinetics of Dexmedetomidine

During the current trial, the pharmacokinetics of dexmedetomidine was not evaluated; however, given that the complete dosing history and body weight were recorded for each of the subjects, the corresponding typical plasma concentration *versus* time profile was generated through the full surgery period, based on the population pharmacokinetics model published by Hannivoort *et al.*[31] Simulations of the typical pharmacokinetic plasma profiles were performed with the software NONMEM, version 7.2.[32] The graphical representation was performed with the R software (http://cran.r-project.org, version 2.6.0).

Sample Size

A sample of at least 11 patients was necessary to detect a standardized mean difference effect size of 0.95, considering a within-subjects design, with a two-sided test, and assuming a 5% significance level and a power level of 80%.

Statistical Analysis

Descriptive data are reported as the median (range) unless otherwise stated. Paired *t* test and multilevel mixed-effects linear regression were used to assess the change in LFPs activity over time (dexmedetomidine recording at 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ *vs.* control recording [primary outcome]; and propofol recording at the estimated peak effect site concentrations of 0.5, 1.0, 1.5, 2.0, and 2.5 μg/ml from control recording). This model was used to assess the association between the nuclei in the same patient at a given time and between repeated measures from the same nucleus over time. A three-level model with random intercepts by patient and nucleus was used, allowing correlation between the random slopes and intercepts. An unstructured covariance matrix was assumed. The intervention variable was modeled as a fixed factor, and the between-patient and between-nuclei variability was modeled as a random effect. Sensitivity analyses were carried out considering only the more and the less affected nuclei. A type I error rate of 0.05 was assumed. Bonferroni correction was used for multiple comparisons (individual test critical $P = 0.017$). All analyses were conducted with Stata 14 (StataCorp LP, USA).

Results

A total of 12 patients with PD were invited to participate in this study. The participation rate was 100%. One patient was excluded due to an intraoperative adverse event. This patient experienced pharyngeal dystonia and developed dyspnea before DBS implantation, leading to a change in the anesthesia from cooperative sedation to general anesthesia. We also excluded from the analyses the unique patient whose target nucleus was GPi. Table 1 shows the demographic and surgical data of the remaining 10 patients.

We administered a median (range) initial dose of 0.5 (0.2 to 1.0) $\mu g \cdot kg^{-1} \cdot h^{-1}$ dexmedetomidine and a maximum maintenance dose of 0.6 (0.2 to 1.0) $\mu g \cdot kg^{-1} \cdot h^{-1}$. In only two patients was the maintenance dose stopped due to a reduction or suppression of their usual tremor, and it was reinstated before recording in both cases. Nine patients were adjusted to the maintenance dose of 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ more than 90 min before the dexmedetomidine recording, with a median time of 223.5 min, but one patient (case 11) was adjusted only 10 min before dexmedetomidine recording. We tried to adjustment the dexmedetomidine maintenance dose to 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ long before recording (more than 100 min), but this patient began to feel uncomfortable, and we needed to increase the dose to 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$. It was not possible decrease the maintenance dose to 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ until 10 min before the recording. A lack of cooperation or agitation was not observed in any case.

Table 1. Demographic, Clinical, and Surgical Characteristics

N	10
Median age, yr (range)	58.5 (47–69)
Male/female, n (%)	9 (90)/1 (10)
Median BMI, kg/m^2 (range)	29.2 (22.6–33.4)
Median time from PD diagnosis, yr (range)	8 (4–14)
Number of target nuclei for DBS	18
Type of target nuclei, n (%)	
Unilateral STN	2 (20)
Bilateral STN	8 (80)
Median number of unilateral tracks, n (range)	3 (2–5)
Median functional surgery duration, min (range)	330.5 (228–433)

BMI = body mass index; DBS = deep brain stimulation; PD = Parkinson disease; STN = subthalamic nucleus.

We simulated the dexmedetomidine plasma concentrations in our studied population (see figure, Supplemental Digital Content 2, http://links.lww.com/ALN/B406, which shows the predicted dexmedetomidine plasma concentration *vs.* time profiles). The predicted plasma concentration values during dexmedetomidine recording were between 0.36 and 0.63 ng/ml (table 2). The values of dexmedetomidine in plasma reported by Hannivoort *et al.*[31] ranged approximately between 0.1 and 10 ng/ml. Those levels are similar to those obtained with the current simulation. Some dispersion is expected around each pharmacokinetic profile due to intersubject variability; however, the magnitude of intersubject variability was reported to be low for total plasma clearance and the apparent volume of distribution of the deep peripheral compartment, both parameters driving mainly the concentration value at the end of surgery, where drug distribution approximates to steady-state.

In total, 18 dexmedetomidine and control recordings were obtained. We also obtained a total of 77 propofol recordings from nine patients. A protocol violation occurred in one patient during the administration of propofol (case 2) that made it impossible to obtain the propofol recording from this subject. Respiratory depression and a need for airway manipulation occurred in two cases before reaching the 2.5 μg/ml target.

The characteristic STN beta peak observed in PD patients in the off state was evident in the normalized

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Table 2. Dexmedetomidine-predicted Plasma Concentration during Dexmedetomidine Recording

Case	Time of Administration of Dexmedetomidine, h:min			Dexmedetomidine Recording, (h:min)*	Dexmedetomidine-predicted Plasma Concentration during Recording, ng/ml
	Loading Dose	Initial Maintenance Dose*	Adjustment to 0.2 μg·kg^{-1}·h^{-1}*		
1	00:00	00:10	00:10	03:33	0.394
2	00:00	00:10	00:15	06:26	0.366
3	00:00	00:10	00:10	05:36	0.360
4	00:00	00:10	00:35	05:11	0.392
6	00:00	00:10	01:13	04:24	0.427
7	00:00	00:10	01:10	03:02	0.445
9	00:00	00:10	01:05	04:35	0.476
10	00:00	00:10	01:03	05:02	0.423
11	00:00	00:10	05:33	05:43	0.631
12	00:00	00:10	03:29	05:09	0.342

*Time since starting the loading dose of dexmedetomidine.

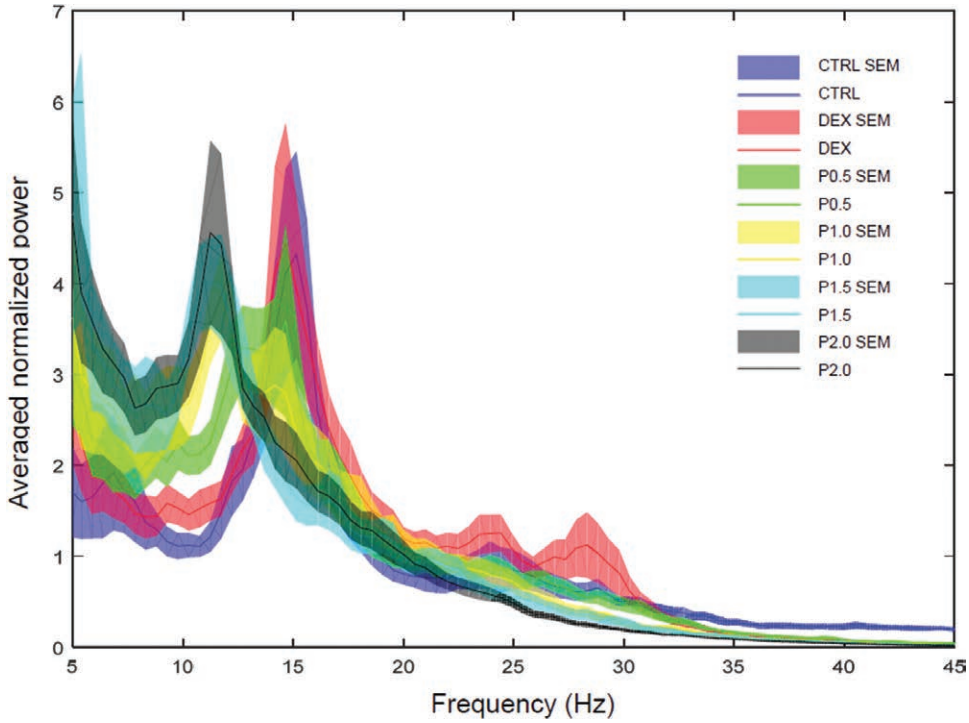

Fig. 1. Averaged normalized spectra of the subthalamic nucleus local field potentials recorded at the different conditions. Please note that the SEM indicates intersubject variability, whereas the statistical analysis is based on intrasubject variability. The power spectra from the propofol recording at 2.5 μg/ml was not included because this dose was not reached in two of the patients. CTRL = control recording; DEX = dexmedetomidine recording at 0.2 μg·kg^{-1}·h^{-1}; P0.5 = propofol recording at 0.5 μg/ml; P1.0 = propofol recording at 1.0 μg/ml; P1.5 = propofol recording at 1.5 μg/ml; P2.0 = propofol recording at 2.0 μg/ml.

power spectra of the control recording from all the patients with this target (fig. 1). The administration of propofol caused a progressive dose-dependent decrease in the amplitude of this peak, together with the appearance of a new peak in the alpha range. Conversely, dexmedetomidine administration at 0.2 μg·kg^{-1}·h^{-1} caused minimal changes in the power distribution. Accordingly, no significant difference was observed when comparing the relative beta power of LFPs (RBP-LFPs) between dexmedetomidine and control recordings (table 3, fig. 2), with a mean difference in the RBP-LFPs between dexmedetomidine and control recordings of −7.7 (95% CI, −18.9 to 3.8) when all nuclei were analyzed. In addition, the mean differences of RBP-LFPs between dexmedetomidine and control recordings were −7.1 (95% CI, −22.7 to 8.4) and −4.8 (95% CI, −17.3 to 7.6) in the analyses restricted to nuclei of clinically more and less affected sides, respectively.

A significant 12.7% (95% CI, 4.1 to 21.3) decline in the LFPs relative to the control recordings was evident for each

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Table 3. Comparison between Local Field Potential Activity in Control and Dexmedetomidine Recordings*

	Patients, n	Nuclei, n	Mean Difference	95% CI	*P* Value
Nuclei of clinically more affected side	10	10	−7.1	−22.7 to 8.4	0.327
Nuclei of clinically less affected side	8	8	−4.8	−17.3 to 7.6	0.389
All nuclei	10	18	−7.7	−18.9 to 3.8	0.190

*Dexmedetomidine was administered at 0.2 μg·kg^{-1}·h^{-1}.

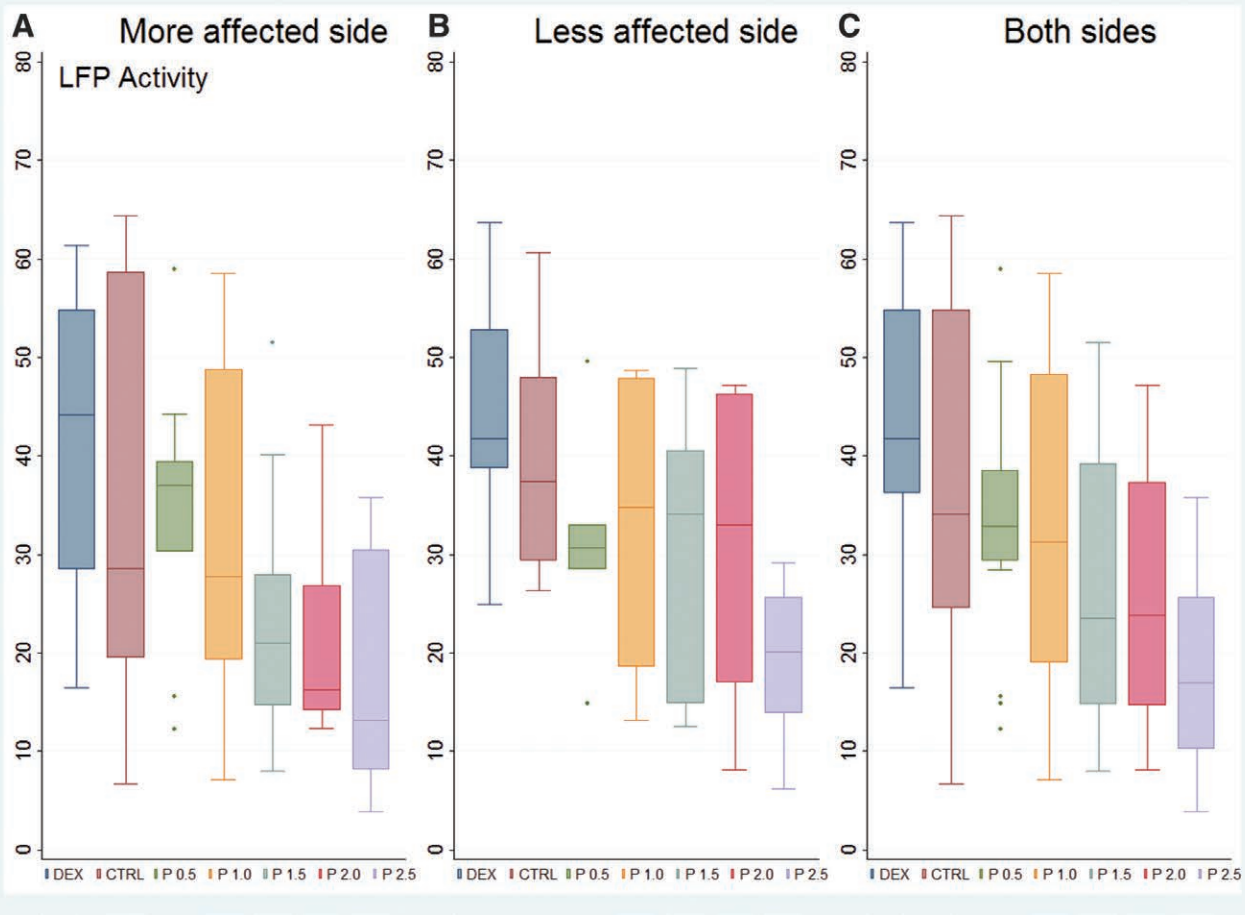

Fig. 2. Mean beta power of the local field potential (LFP) under the different conditions. CTRL = control recording; DEX = dexmedetomidine recording at 0.2 μg·kg^{-1}·h^{-1}; P0.5 = propofol recording at 0.5 μg/ml; P1.0 = propofol recording at 1.0 μg/ml; P1.5 = propofol recording at 1.5 μg/ml; P2.0 = propofol recording at 2.0 μg/ml; P2.5 = propofol recording at 2.5 μg/ml.

increment in the estimated peak effect site concentration of propofol (0.5, 1.0, 1.5, 2.0, and 2.5 μg/ml) when all nuclei were analyzed. Similar results also were seen when these analyses were restricted to nuclei of clinically more and less affected sides (table 4, fig. 2), even though the subanalysis of nuclei of the less affected side yielded a significance level that was slightly above the threshold of statistical significance level after Bonferroni correction.

A significant (and progressive) increase in relative alpha power was observed with recordings at all doses of propofol compared with control (see table, Supplemental Digital Content 3, http://links.lww.com/ALN/B407).

Discussion

To our knowledge, this is the first study to analyze and quantify the effect of dexmedetomidine and propofol on basal ganglia neuronal activity through the LFPs generated in patients who underwent DBS surgery for PD. We did not find significant differences between the RBP-LFPs in control and dexmedetomidine (0.2 μg·kg^{-1}·h^{-1}; simulated plasma concentrations 0.36 to 0.63 ng/ml) recordings, yet we did observe a significant and progressive loss of beta LFP activity as the propofol dose increased. For every 0.5 μg/ml increase of the estimated peak concentration of propofol at the effect site, the beta LFP activity decreased by 12.7% relative to the control recording.

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Table 4. Estimated Change in Local Field Potential Activity for One Category of Change in Propofol Level Relative to the Controls

	Patients, n	Nuclei, n	Average Change, %	95% CI	*P* Value
Nuclei of clinically more affected side	9	9	−14.6	−24.8 to −4.3	0.005
Nuclei of clinically less affected side	7	7	−11.3	−21.4 to −1.4	0.026
All nuclei	9	16	−12.7	−21.3 to −4.1	0.004

*The categories of the intervention variable are ordered according to the administration protocol in the following sequence: control recording and propofol recording (0.5, 1.0, 1.5, 2.0, and 2.5 μg/ml).

DBS provides a unique opportunity to record oscillatory activity from deep brain structures.[24–28] Such oscillations are considered to be a summation of the synchronized postsynaptic changes around the electrode and referred to as LFPs. LFPs are composite signals that are divided into different frequency bands: delta (0 to 3 Hz), theta (4 to 7 Hz), alpha (8 to 12 Hz), beta (13 to 30 Hz), and gamma (31 to 200 Hz). In the basal ganglia of patients with PD in the "off" state at rest, LFP activity is dominated by prominent beta oscillations.[24–28] These LFP signals are more resistant to physiologic fluctuations than MERs (impedance, cerebrospinal fluid, and blood).[24] Unlike other studies that focused on MER recordings, we have analyzed the effects of dexmedetomidine and propofol on the LFP activity obtained with the DBS electrodes at different moments, comparing this with the control recordings without anesthesia. Although intraoperative mapping of the STN/GPi can be carried out through LFPs,[27] this usually is achieved by MER. Indeed, LFPs are thought to represent the grand-average of the postsynaptic activity around the electrode, whereas action potentials recorded by MER represent the output of the specific structure recorded. Thus, it is highly likely that any interference in the postsynaptic activity of a structure, in principal through the "input" to that structure, will change the output in terms of action potentials. Accordingly, a change in the LFPs should reflect changes in the MERs.

Effects of Propofol on Neuronal Activity in the Basal Ganglia

Many neurosurgeons and neurologists prefer to avoid sedation in patients undergoing DBS placement for PD because some anesthetic drugs may abolish MER recordings and symptoms of PD. This is particularly applicable to GABAergic drugs like propofol. In a study comparing 24 patients with local anesthesia with 30 who received general anesthesia with propofol (peak effect site concentration 1.5 to 2.3 μg/ml),[16] the administration of propofol did not appear to influence the clinical outcome, although MERs were not analyzed. Elsewhere, low doses of propofol (25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and fentanyl (25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were administered to eight patients, which did not interfere significantly with the MER signal[15]; however, the MER signal was compared with that in the contralateral STN, which may not be truly comparable. When MER data from the same nucleus were analyzed in patients with and without sedative drugs, a propofol bolus of 0.3 mg/kg had only a minimal effect on the action potential discharge activity.[23] The bolus used was predicted to represent a peak effect site concentration of 1.3 μg/ml at 1 min, said to be comparable with 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Propofol (50 $\mu g \cdot kg^{-1} \cdot min^{-1}$) also was shown to significantly decrease spiking and background electrical activity, as well as the root mean square power in the STN when recordings from the same target nucleus and coordinates were compared[11]; however, this effect was reversible after 9.3 ± 4 min of stopping propofol and the median infusion time was only 11.9 ± 3 min, well below that usually used in clinical practice. Thus, it is possible that longer exposure times would probably be associated with a longer time to reversal. Our results indicate that neuronal activity in the basal ganglia of patients with PD, as reflected by the RBP-LFPs, decreased by 12.7% relative to the control recordings with every increase of 0.5 μg/ml in the estimated peak effect site concentration; however, the clinical implications of this decrease in the identification of the target nucleus for DBS placement will require further study.

A collateral finding of our study was the gradual increase of subthalamic alpha activity with the different doses of propofol. Alpha synchronic oscillations in the frontal cortex have been reported as the electroencephalogram signature for loss of consciousness under propofol anesthesia.[33,34] The finding of increased alpha oscillatory activity in the basal ganglia under propofol suggests that these nuclei also might play a role in this process.

Effects of Dexmedetomidine on Neuronal Activity in the Basal Ganglia

Dexmedetomidine is a selective pre- and postsynaptic α2-adrenergic receptor agonist whose action in the locus coeruleus is responsible for arousal, sleep, anxiety, and withdrawal symptoms from drug addiction. Dexmedetomidine does not interact with the GABA system, differentiating it from GABA-mimetic sedatives and anesthetics. A study of 11 consecutive cases of continuous or discontinuous dexmedetomidine administration during DBS implantation for PD indicated that a maintenance dose greater than 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$ suppressed neuronal firing in the STN[12]; however, this was based on observational analysis of neuronal activity. In a similar approach, when 11 consecutive cases of unilateral DBS placement for PD with continuous dexmedetomidine infusion (0.3 to 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$) were assessed, no interference in the MERs was evident on the

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basis of an observational analysis of neuronal activity.[21] Quantitative MER data from seven patients who received dexmedetomidine while undergoing DBS implantation for PD were compared with those from 11 who received no anesthesia, highlighting a significantly lower percentage of burst spikes, a lower burst index, and mean interspike interval outside bursting in the patients who received dexmedetomidine.[20] Although it was proposed that these parameters are mediated by intrinsic mechanisms, quantitative MER data from patients under different dexmedetomidine maintenance doses (between 0.1 and 0.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$), or without anesthesia, led to the conclusion that high doses of dexmedetomidine might compromise intraoperative MER identification. The possible effect of at low maintenance doses of dexmedetomidine, however, remained unclear. Here, we did not find any significant difference in the RBP-LFPs between control and dexmedetomidine (0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$; simulated plasma concentrations 0.36 to 0.63 ng/ml) recordings, so it seems safe to conclude that this anesthetic agent drug can be used safely during target nucleus identification for the placement of DBS electrodes in PD.

Although it has been proposed that there is no benefit in maintaining sedation throughout the whole procedure,[35,36] the basal status of some patients in conjunction with the length and discomfort of the procedure might make continuous sedation helpful. Indeed, sedation may even be essential to obtain a rested and cooperative patient in some cases.[37] All our patients cooperated optimally during the intraoperative recording and neurologic examination. Infusion was only stopped in two patients due to the reduction or suppression of tremor. This is an unusual effect that has been reported elsewhere.[38]

Some weaknesses should be considered. First, the recordings for each intervention were carried out on different days (see table, Supplemental Digital Content 1, http://links.lww.com/ALN/B405, which shows the schedule of LFP recordings), which could hinder our interpretation of the results of this study. Second, the implantation of the electrode might induce edema around the area of the implant,[7,28] potentially affecting the recordings on different days; however, this does not appear to substantially influence our conclusions. Indeed, although the presence of edema around the electrode might decrease the global power recorded in the spectra, the normalization of the power spectra minimizes any potential influence of edema on the recordings. Moreover, there is evidence that LFP recordings, and beta LFP recordings in particular, are stable in time regardless of any "impact,"[39,40] Third, one patient was adjusted to the dexmedetomidine dose of 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ only 10 min before dexmedetomidine recording. This patient had slightly greater simulated plasma concentrations (0.63 ng/ml) during the recording (table 2). This could be underpowered to detect a difference of that one subject's response from the mean response. However, we did not find a statistical difference between control and dexmedetomidine recording. Therefore, we think that the slightly greater level of effect site concentration during the recording in this patient does not interfere with the conclusion of ours results. Fourth, final data from 10 patients were analyzed. Despite a slight loss of statistical power for the prespecified standardized mean difference effect size (76.2 *vs.* 80%), results have not been affected substantially and conclusions from the study remain unchanged. Fifth, our protocol design did not allow us to analyze the effect of higher doses of dexmedetomidine on LPFs. Further investigation to study the potential effects of doses greater than 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ on LPFs may be warranted.

In conclusion, we quantified the effect of dexmedetomidine and propofol on basal ganglia neuronal activity by measuring LFPs. We did not find significant differences between the RBP-LFPs in control and dexmedetomidine (0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) recordings; however, we observed a significant decrease in LFP activity for each increment in the propofol dose. The estimated decline in beta LFP activity was of 12.7% relative to the control recording for every 0.5 μg/ml increase of the estimated peak effect site concentration of propofol. These findings may have relevant clinical implications to improve the sedation and management of patients undergoing DBS placement for PD.

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Competing Interests

The authors declare no competing interests.

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Following the Civil War, American concern mounted about the anesthetic safety of ether and of chloroform. After reviving the use of nitrous oxide for brief anesthetics, dentists and physicians had to hurdle new obstacles. Because most nitrous oxide administrations lacked supplementary oxygen, a roughly 50-s inhalation of 100% laughing gas might yield as little as 30 s procedurally for tooth extraction or other minor surgeries. To combat this problem, entrepreneurs in the 1880s began marketing proprietary formulations of herbally supplemented nitrous oxide. Early on, valerian (*Valeriana officinalis*, *left*) became a botanical candidate for extending the otherwise fleeting anesthetic duration of laughing gas. Known to both Hippocrates and Galen, this mildly sedative herb, valerian, has been peddled to the public for more than 24 centuries (McMahon's "Oil of Valerian," *right*). Sadly, unscrupulous practitioners soon began reassuring patients who wished to avoid nitrous oxide that herbally supplemented laughing gas was a completely unrelated gas…when that was just not the case at all. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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