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Effects of dexmedetomidine on subthalamic local field potentials in Parkinson's disease

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Abstract

Background: Dexmedetomidine is frequently used for sedation during deep brain stimulator implantation in patients with Parkinson's disease, but its effect on subthalamic nucleus activity is not well known. The aim of this study was to quantify the effect of increasing doses of dexmedetomidine in this population.

Methods: Controlled clinical trial assessing changes in subthalamic activity with increasing doses of dexmedetomidine (from 0.2 to 0.6 μg kg^{-1} h^{-1}) in a non-operating theatre setting. We recorded local field potentials in 12 patients with Parkinson's disease with bilateral deep brain stimulators (24 nuclei) and compared basal activity in the nuclei of each patient and activity recorded with different doses. Plasma levels of dexmedetomidine were obtained and correlated with the dose administered.

Results: With dexmedetomidine infusion, patients became clinically sedated, and at higher doses (0.5–0.6 μg kg^{-1} h^{-1}) a significant decrease in the characteristic Parkinsonian subthalamic activity was observed ($P<0.05$ in beta activity). All subjects awoke to external stimulus over a median of 1 (range: 0–9) min, showing full restoration of subthalamic activity. Dexmedetomidine dose administered and plasma levels showed a positive correlation (repeated measures correlation coefficient=0.504; $P<0.001$).

Conclusions: Patients needing some degree of sedation throughout subthalamic deep brain stimulator implantation for Parkinson's disease can probably receive dexmedetomidine up to 0.6 μg kg^{-1} h^{-1} without significant alteration of their characteristic subthalamic activity. If patients achieve a 'sedated' state, subthalamic activity decreases, but they can be easily awakened with a non-pharmacological external stimulus and recover baseline subthalamic activity patterns in less than 10 min.

Clinical trial registration: EudraCT 2016-002680-34; NCT-02982512.

Keywords: deep brain stimulation; dexmedetomidine; local field potentials; Parkinson's disease; sedation; subthalamic activity

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Editor's key points

- When deep brain stimulation electrodes are implanted in the subthalamic nucleus (STN) in patients with Parkinson's disease, microelectrode recordings are commonly used to verify the position of the electrode tip.
- Low doses of dexmedetomidine are often used for sedation, but little is known about its effects on the electrical activity of the STN.
- The authors recorded local field potentials from electrodes implanted bilaterally in 12 patients whilst they received increasing doses of dexmedetomidine.
- With increasing sedation, the characteristic spectral patterns associated with Parkinson's disease disappeared, but subjects were easily and rapidly arousable, and after arousal, the characteristic patterns returned.

In the past two decades, the subthalamic nucleus (STN) and globus pallidus have become the main interventional therapeutic targets for Parkinson's disease (PD).[1] Deep brain stimulation (DBS) surgery on the STN (STN–DBS) is preferred in many centres,[1,2] both for patients with early motor complications[3] and for those with advanced PD.[2,4,5]

However, no consensus exists regarding the best surgical technique for STN–DBS electrode implantation.[1,6] Techniques to localise the target include intraoperative imaging, single or multi-microelectrode recordings (MERs), micro-/macrostimulation, and neurological intraoperative testing.[1,6,7] Moreover, the anaesthetic approach varies from monitored anaesthesia care to general anaesthesia depending on the preferences of the team at each centre.[6–9] At our centre, localisation is performed using a combination of MERs, microstimulation, and intraoperative neurological testing under conscious sedation with dexmedetomidine.[10–14]

Dexmedetomidine, an α_2-adrenoreceptor agonist, produces sedation similar to natural sleep. Patients administered dexmedetomidine become drowsy, but can be easily awakened. This helps ensure patient cooperation. Moreover, it does not affect the respiratory drive and causes only mild adverse events, including bradycardia and hypotension.[15–21] These properties make dexmedetomidine a good choice for STN–DBS electrode implantation. At low doses, dexmedetomidine does not appear to have a significant clinical effect on Parkinsonian symptoms.[10] However, the exact dose required to maximise patient comfort and improve surgical conditions without interfering with basal ganglia activity, neurological symptoms, or patient collaboration has not been described.[15–17]

In this study, we aimed to evaluate and quantify the effect of increasing dexmedetomidine doses (from 0.2 to 0.6 μg kg^{-1} h^{-1}) on STN activity in patients with PD and STN–DBS electrodes. These electrodes provide a unique opportunity to investigate the effects of anaesthetics on the electrical oscillatory activity of deep brain structures,[10] as the oscillations recorded (local field potentials [LFPs]) are considered a summation of the synchronised postsynaptic changes surrounding the electrodes.[22–24]

Methods

The Spanish Agency of Medicines and Medical Devices and the Ethics Committee of Navarra approved this clinical trial (EudraCT 2016-002680-34) in March 2017. It was also registered at ClinicalTrials.gov (NCT-02982512). The study included patients with PD who underwent STN–DBS electrode implantation at the Clinica Universidad de Navarra between May 2017 and November 2018. All patients provided written informed consent before the surgery. The exclusion criteria were contraindications to dexmedetomidine use and patient non-cooperation.

In the first intervention, the DBS electrodes were placed under conscious sedation with dexmedetomidine.[10] Five days later, and at least 12 h after the last administration of anti-Parkinsonian drugs (off-medication state), the patients were transferred to the post-anaesthesia care unit (PACU) to conduct the study. The patients were fasted and prepared for surgery, and once the study was completed, they were transferred to the operating theatre (OT) where the DBS device was tunneled and connected to the battery under general anaesthesia.

Study protocol

Upon admission to the PACU, all patients underwent ECG, noninvasive arterial blood pressure, and pulse oximetry monitoring. A 20-gauge i.v. catheter was inserted into a vein of the right hand for drug administration, whilst another 20-gauge i.v. catheter was inserted into the left radial artery for blood sampling. Supplemental oxygen (2 L) was administered and capnography was performed through a dual nasal cannula. Sedation depth was measured using the bispectral index (BIS) (BIS™ Monitor; Medtronic, Minneapolis, MN, USA). Continuous LFP activity was measured through the DBS electrodes using a BrainAmp ExG amplifier (Brain Products GmbH, Gilching, Germany). The 'basal' state was defined as the clinical state before dexmedetomidine administration.

Based on the pharmacokinetic model developed by Hannivoort and colleagues[25] to obtain stable plasma dexmedetomidine levels during LFP recordings, all patients received an initial loading dose (0.5 μg kg^{-1} over 10 min) followed by a maintenance dose starting at 0.2 up to 0.6 μg kg^{-1} h^{-1}, with increments of 0.1 μg kg^{-1} h^{-1} every 45 min (Fig. 1). During dexmedetomidine infusion, some patients reached a 'sedated' state, defined by a BIS <80 and closed eyes. Five minutes before increasing the dose, all patients were subjected to an external stimulus to achieve an 'awake' state (open eyes and adequate response to verbal tasks) (Fig. 1). The stimulus and time needed were registered. In this awake state, 2 min segments of continuous LFP and BIS signals were marked for later analysis. Additional 2 min BIS segments were selected in the sedated state 5 min before applying the external stimulus for each dexmedetomidine dose, and additional 2 min LFP segments were marked in the sedated state at higher doses (0.5 or 0.6 μg kg^{-1} h^{-1}) (Fig. 1).

Local field potential recording and signal analysis

For the two STN, three consecutive bipolar derivations from the four contacts of the DBS electrodes were obtained: 0–1,

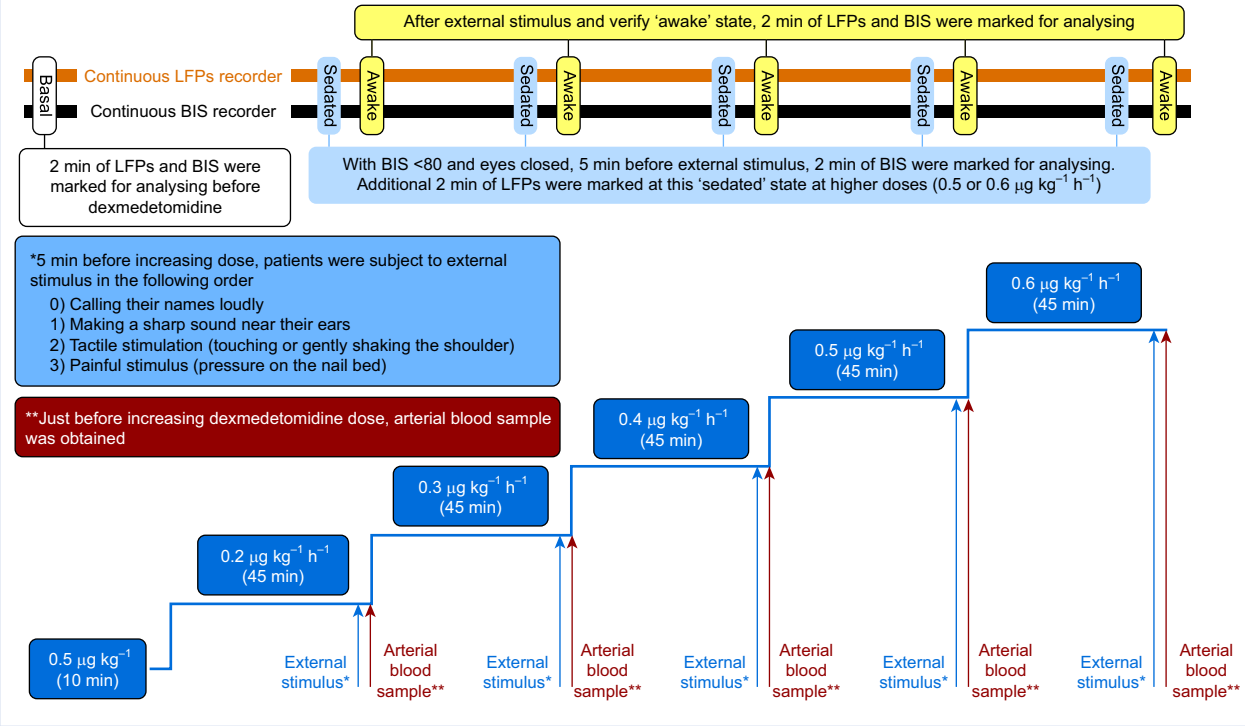

Fig 1. Protocol study. BIS, bispectral index; LFP, local field potential.

1–2, and 2–3 in the right STN and 4–5, 5–6, and 6–7 in the left STN (with contacts 0 and 4 being the most ventral). The signals were amplified, filtered at 0.3–1000 Hz, sampled at 2000 Hz with a resolution of 0.1 μV, and stored for later analysis using BrainVision Recorder (Brain Products GmbH).

Spectral characterisation was obtained from the 2 min LFP segments recorded in the basal state, right after verifying the awake state at the end of each increment of dexmedetomidine, and in the sedated state at higher doses (0.5 or 0.6 μg kg^{-1} h^{-1}) (Fig. 1). The frequency content of the signals between 0 and 400 Hz was estimated using multi-taper spectral techniques implemented with the *mtspectrumc* function of the Chronux toolbox.[26] Once obtained, the spectral values were normalised by dividing them by the average of the spectrum and multiplying by 100. The mains artifacts were removed by cancelling the values around 50 Hz and their harmonics (50 [SD 2] Hz). Finally, the energies in the LFP_{delta} (1–4 Hz), $LFP_{theta/alpha}$ (4–10 Hz), $LFP_{low\ beta}$ (10–20Hz), $LFP_{high\ beta}$ (20–35 Hz), $LFP_{low\ gamma}$ (35–80 Hz), and LFP_{HFO} (202–398 Hz) bands were estimated by summing the normalised values within the corresponding ranges.

Blood plasma sample collection, storage, and analysis

Arterial blood samples were collected to measure plasma dexmedetomidine levels during the LFP recordings in the awake state (Fig. 1). Ethylenediaminetetraacetic acid tubes (4 ml) were used to collect the blood, and each sample was stored on crushed ice and centrifuged at a maximum of 3000 × *g* for 10 min at 0–4°C within 30 min of sampling. The plasma obtained was stored at −80°C until the study was completed. The technique for analysing plasma concentration is described in Appendix A.

Statistical analysis

We calculated that a sample size of 12 patients would be sufficient to detect a standardised effect size of 0.95 with a power of 80%, considering a within-subject design, with a two-sided test, and assuming a 5% significance level and an expected dropout rate of 5%. Quantitative data were summarised using the means with their standard deviation or the median values with the minimum and maximum; categorical data were described using their frequencies and percentages. The Shapiro–Wilk test was used to check for normality of data. The repeated measures correlation coefficient (r_{rm}) was calculated to assess the association between dexmedetomidine doses and plasma dexmedetomidine levels, and the Friedman test was used to test differences between dexmedetomidine doses. Comparisons between the basal and subsequent levels were performed using paired *t*-tests or Wilcoxon matched-paired signed-rank tests. Two-tailed *P*-values <0.05 were considered statistically significant. Analyses were conducted using Stata 14 (StataCorp 2015 version 14; StataCorp, College Station, TX, USA) and R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Fourteen patients agreed to participate and underwent bilateral STN–DBS surgery for PD (Fig. 2 Consolidated Standards of

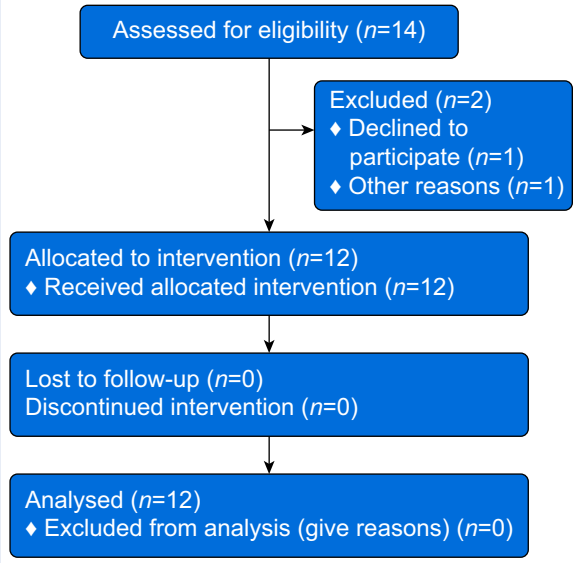

Fig 2. Consolidated Standards of Reporting Trials diagram detailing the selection process and analysis for patients. One patient retracted his authorisation because he felt too tired to cooperate after the first intervention, and another suffered a pulmonary thromboembolism during the perioperative period and was excluded from the study.

Table 1 Patient and clinical characteristics. DBS, deep brain stimulation; PD, Parkinson's disease; SD, standard deviation.

Characteristics	Overall, n=12
Mean age (SD) (yr)	61.1 (10.5)
Men/women, *n* (%)	6 (50)/6 (50)
Mean BMI (SD) (kg m^{-2})	28.5 (6.3)
Mean time from PD diagnosis (SD) (yr)	11.2 (10.0)
Main indication for DBS, *n* (%)	
End of dose 'wearing off'	6 (50)
Motor fluctuations	5 (41.7)
Gait disturbance	1 (8.3)
PD predominant clinical feature, *n* (%)	
Rigidity	7 (58.3)
Tremor	3 (25.0)
Dystonia	1 (8.3)
Bradykinesia	1 (8.3)
Medical history, *n* (%)	
Hypertension	5 (41.7)
Dyslipidaemia	1 (8.3)
Diabetes mellitus	1 (8.3)
Ischaemic cardiomyopathy	0 (0)
Kidney failure	0 (0)
Liver failure	0 (0)

Reporting Trials [CONSORT] diagram). Two patients did not complete the study; therefore, we analysed the data from 12 patients (24 nuclei) (Fig. 2 CONSORT diagram; Table 1 for patient characteristics).

Overall, the mean plasma dexmedetomidine levels showed statistically significant differences amongst the dexmedetomidine dose groups (P=0.011). A statistically significant positive correlation was observed between the administered dexmedetomidine dose and the mean plasma dexmedetomidine level (r_{rm}=0.504; P<0.001) (Table 2).

The BIS values showed statistically significant decreases on comparing the sedated and basal states at each of the administered doses (Supplementary Fig. 1). In the sedated state, the mean BIS values were <80 in all dose segments (Supplementary Fig. 1). Overall, the mean BIS values did not show statistically significant differences amongst the groups with increasing dexmedetomidine doses (P=0.14). All patients returned to the awake state over a median time of 1 (range: 0–9) min (Table 2). The mean BIS values in the awake and basal states were similar at the lower doses (0.2–0.4 μg kg^{-1} h^{-1}); however, the BIS values were lower at higher doses (0.5–0.6 μg kg^{-1} h^{-1}), and the decrease was statistically significant (Supplementary Fig. 1). No association was observed between the dexmedetomidine dose and the stimulus needed to verify the awake state (P=0.5) (Table 2; Supplementary Fig. 2).

The raw signals and power spectral estimates of LFP activity recorded in the basal, awake, and sedated states from a representative subject (Patient 5) are shown in Supplementary Fig 3. The power spectra of the oscillatory activity were recorded across the six different STN derivations (channels 0–1, 1–2, 2–3, 4–5, 5–6, and 6–7) with the patient in the basal and awake states under different dexmedetomidine doses (0.2–0.6 μg kg^{-1} h^{-1}) and the sedated state under the highest doses (0.5 or 0.6 μg kg^{-1} h^{-1}) (Fig. 3). In the basal state, all the patients displayed significant peaks in the beta range of the STN power spectrum, which is typical of patients with PD in the off-medication state, but not in all the bipolar channels analysed. A typical beta peak was observed only in six and five patients in the ventral channels (0–1 and 4–5, respectively). High-frequency oscillations (HFOs) observed in the basal ganglia of patients with PD were only present in the most dorsal (2–3 and 6–7) or intermediate (1–2 and 5–6) channels. Hence, the lower bipolar channels (0–1 and 4–5) might be recording activity outside the STN. Thus, the analysis of the effect of dexmedetomidine on STN activity was limited to the dorsal (2–3 and 6–7) and intermediate (1–2 and 5–6) bipolar subthalamic channels.

A quantitative comparison of STN activity in the different power bands was performed in channels 1–2, 2–3, 5–6, and 6–7 (Table 3). The STN activity in the awake state under dexmedetomidine doses between 0.2 and 0.6 μg kg^{-1} h^{-1} was not significantly different to that observed in the basal state in any channel or power band analysed (Table 3). However, significant differences in STN activity were found between the basal and sedated states (Table 3). In three of the four LFP channels analysed, a significant decrease in $LFP_{low\ beta}$, $LFP_{high\ beta}$, $LFP_{low\ gamma}$, and LFP_{HFO} power was evident (2–3: P=0.003, 0.006, 0.004, and 0.003, respectively; 5–6: P=0.04, 0.02, 0.01, and 0.01, respectively; and 6–7: P=0.01, 0.008, 0.03 and 0.006, respectively) (Table 3). In the other LFP channel analysed (1–2), a decrease was observed in $LFP_{low\ beta}$, $LFP_{high\ beta}$, and LFP_{HFO} power, but this was not statistically significant (P=0.06, 0.08, and 0.09, respectively) (Table 3).

Discussion

We evaluated and quantified the effects of increasing dexmedetomidine doses (from 0.2 to 0.6 μg kg^{-1} h^{-1}) on STN activity in patients with PD and STN–DBS electrodes. During dexmedetomidine infusion, patients achieved a sedated state, and a significant decrease in characteristic Parkinsonian STN

Table 2 Relationship between the increasing doses of dexmedetomidine, the plasma levels observed, and the external stimulus and time needed to verify the 'awake' state. *Mean (standard deviation); †median [minimum–maximum]; external stimulus in the following order: 0, calling their name loudly; 1, making a sharp sound near their ears; 2, tactile stimulation (touching or gently shaking of the patient's shoulder); and 3, painful stimulus (pressure on the nail bed).

Dexmedetomidine doses (μg kg^{-1} ml^{-1})	Dexmedetomidine plasma levels (ng ml^{-1})*	External stimulus necessary to achieve the 'awake' state†	Time from stimulus to 'awake' state (min)†
0.2	0.45 (0.10)	0 (0–2)	1 (0–7)
0.3	0.53 (0.17)	0 (0–1)	1 (0–9)
0.4	0.56 (0.14)	0 (0–2)	1 (0–3)
0.5	0.61 (0.17)	2 (0–3)	1 (0–9)
0.6	0.70 (0.31)	2 (0–2)	1 (0–2)

activity ($LFP_{low\ beta}$, $LFP_{high\ beta}$, and LFP_{HFO}) was observed at the doses analysed (0.5–0.6 μg kg^{-1} h^{-1}). At the end of each period of dexmedetomidine infusion, the awake status was verified within a median time of 1 min (range: 0–9 min) after the external stimulus, and STN activity did not show significant differences from the baseline in any of the channels or power bands analysed. The gradual increase in dexmedetomidine was closely related to changes in its plasma levels.

To obtain optimal results from STN–DBS electrodes and avoid adverse effects, determining the accurate location of the surgical target is crucial. High-definition real-time anatomical targeting under general anaesthesia can provide acceptable results,[6,8,9,27] but a combination of clinical testing (micro/macrostimulation), MERs, and direct neurological examination in a cooperative patient can be an invaluable tool for accurately defining the topography of the STN.[1,28–30] However, most anaesthetic drugs impact all of these elements. Moreover, a sedated patient might not cooperate properly, and Parkinsonian symptoms and MER signals may be affected. Accordingly, in many published studies, the patients were placed under monitored anaesthesia care, but propofol and remifentanil were still administered during certain parts of the procedure.[7,31,32] Patients with PD enter the OT in an off-medication state so their symptoms are likely maximal, as this facilitates testing and estimation. Nevertheless, this situation may be uncomfortable and even painful to many of them. The surgical position, prolonged surgery, unfamiliar environment, and general movement in the OT can also generate anxiety and pain. Therefore, some degree of sedation is considered desirable in many centres.

Depth of sedation

Dexmedetomidine has been widely used over the past decade.[15–21] Whilst some groups administer it throughout the procedure, others discontinue it during testing. Although concerns exist about the possible influence of dexmedetomidine on testing and MER recording,[15,16,20,21] sedation is advisable to overcome anxiety or other complications,[13,33] especially in cases of bilateral procedures.[10,29] Our patients achieved a sedated state (BIS <80 and closed eyes) during dexmedetomidine infusion, and all of them achieved the awake state after the external stimulus within a median time of 1 (range: 0–9) min. As the dexmedetomidine dose increased, no corresponding increase was noted in sedation depth or the intensity of the stimulus needed to bring the patient back into the awake state. Moreover, at higher dexmedetomidine doses, 75% of the patients responded to tactile stimuli, even though their mean BIS values were lower in the awake state.

Local field potentials and dexmedetomidine dose

LFPs are composite signals reflecting the aggregate electrical activity in an area of neural tissue. These are less affected by physiological fluctuations than are MERs, because they are not as sensitive to impedance or affected by the CSF and blood.[22] In the basal ganglia of patients with PD in the off-medication state at rest, LFP activity is dominated by prominent beta oscillations,[22–24] which are considered the most predictive electrophysiological marker of the motor benefits of STN–DBS.[34] The low beta range shows a more robust correlation with motor symptoms than does the high beta range.[35,36] The reduction in beta power observed in our patients with the highest beta peak does not limit the validity of our study, because it does not appear dose related. The beta peak was still observed despite the decrease in amplitude, and the activity profile matched that of a patient with PD in the off-medication state at all times. Nevertheless, the amplitude of beta activity fluctuates over time in the STN of patients with PD, and the dynamics of this phenomenon remain unclear.

In our series, no differences were observed in STN activity measured using LFPs (including $LFP_{low\ beta}$ and $LFP_{high\ beta}$) in the basal or awake state with increasing dexmedetomidine doses (0.2–0.6 μg kg^{-1} h^{-1}) in any of the channels or power bands analysed. Krishna and colleagues[19] obtained similar results when comparing STN activity in patients receiving continuous dexmedetomidine (between 0.1 and 0.7 μg kg^{-1} h^{-1}) during DBS implantation for PD to that in patients who received no anaesthetic. That study provided no evidence that dexmedetomidine altered either spike oscillations in the beta frequency band or LFP_{beta} power. The current study did not analyse the effect of a controlled, gradual increase in dexmedetomidine dose or plasma dexmedetomidine levels. In the sedated state (0.5–0.6 μg kg^{-1} h^{-1}), our patients showed a significant decrease in $LFP_{low\ beta}$, $LFP_{high\ beta}$, $LFP_{low\ gamma}$, and LFP_{HFO}, which could potentially complicate the identification of the target nucleus during the procedure. The sedated state induced by dexmedetomidine has a neurophysiological pattern similar to Stage 2 sleep,[37] which could justify our results, as previous studies have shown a significant decrease in characteristic Parkinsonian subthalamic beta activity during physiological Stage 2 sleep in PD.[38,39] In our case, a non-pharmacological external stimulus easily reversed this sedated state and its negative effect on STN activity. Therefore, patients requiring sedation during STN–DBS electrode implantation could probably receive dexmedetomidine up to 0.6 μg kg^{-1} h^{-1} without it interfering with STN activity during target localisation in an awake state.

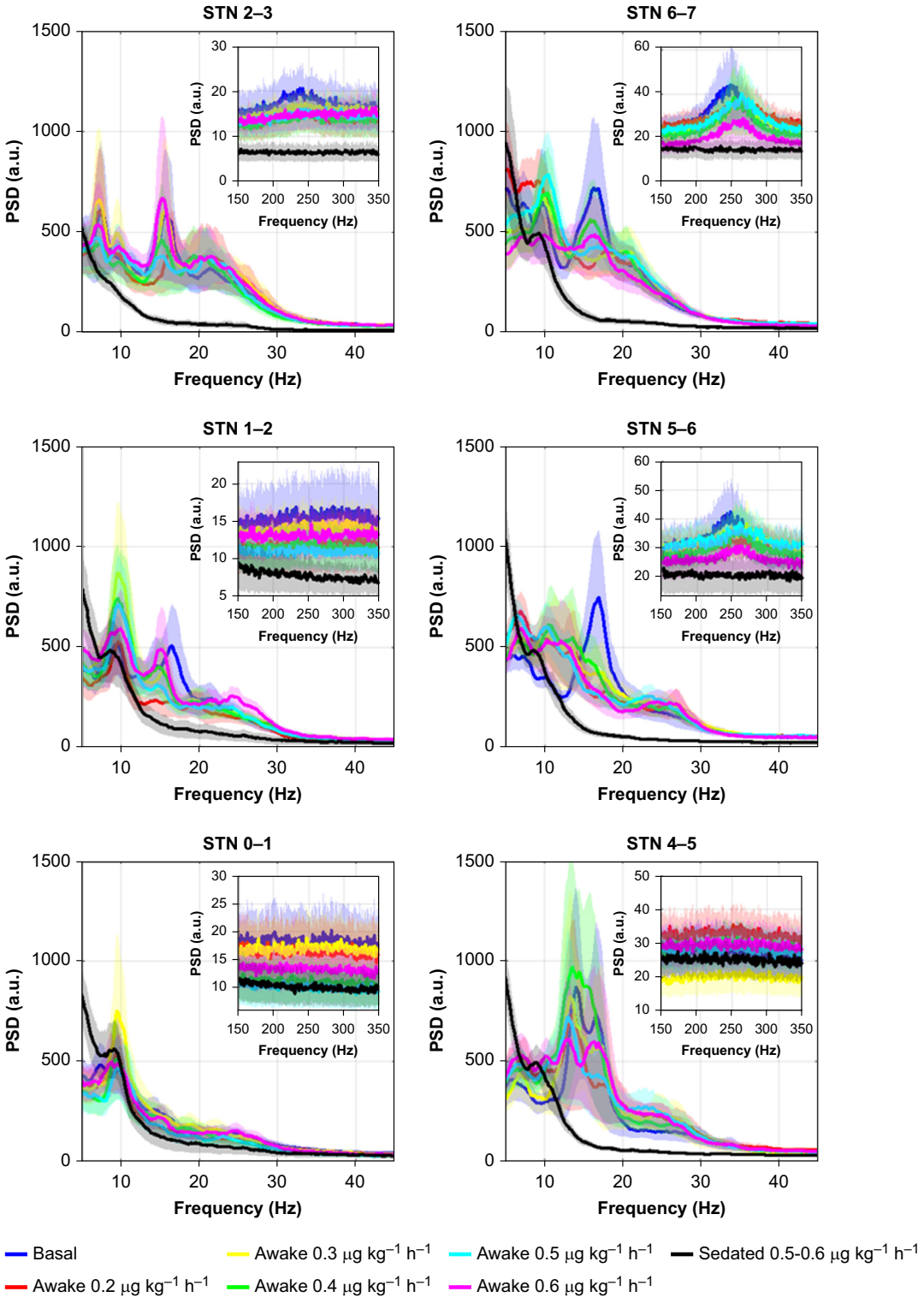

Fig 3. Subthalamic nucleus activity reflected as LFPs in the 'basal' and 'awake' states under different doses of dexmedetomidine, and in the 'sedated' state. Grand average of the power spectra estimates of the subthalamic LFP activity from the patients in the 'basal' state (before dexmedetomidine administration), in the 'awake' state under different doses of dexmedetomidine (0.2–0.6 μg kg^{-1} h^{-1}), and in the 'sedated' state under higher doses (0.5–0.6 μg kg^{-1} h^{-1}). The bipolar subthalamic channels are referred to as 0–1, 1–2, and 2–3 on the right-hand side, with 0 the most ventral contact and 3 the most dorsal one. On the left-hand side, 4 is the most ventral contact and 6 the most dorsal one. The main plots show the power estimate in the 5–45 Hz range. The insert displays the spectral estimate in the high-frequency oscillation range (150–350 Hz). The lines represent the mean value and the shaded areas the standard error of the mean. LFP, local field potential; STN, subthalamic nucleus.

Table 3 Activity in the subthalamic nucleus in the 'basal' and 'awake' states under different doses of dexmedetomidine, and in the 'sedated' state. HFO, high-frequency oscillation. Compared with basal levels: *P<0.05; **P<0.01; ***P<0.001. All values are expressed as mean (standard deviation).

Channel	Brain wave	Basal state	'Awake' state at different doses of dexmedetomidine (μg kg^{-1} h^{-1})					'Sedated' state
			0.2	0.3	0.4	0.5	0.6	
1–2	Delta	45 501.4 (19 157.3)	51 074.7 (19 760.8)	51 643.4 (14 168.8)	48 715.8 (15 795.2)	48 444.9 (17 673.7)	52 908.5 (12 318.7)	58 871.1 (16 316.8)
	Theta–alpha	17 007.4 (13 521.9)	16 037.9 (12 277.8)	21 788.4 (14 453.6)	20 127.4 (14 477.3)	19 621.2 (12 792.1)	21 008.3 (12 394.0)	23 904.4 (18 115.6)
	Low beta	24 686.4 (19 309.2)	16 229.3 (11 210.0)	24 184.0 (20 509.4)	23 476.7 (19 959.8)	20 857.1 (14 826.3)	23 780.2 (14 944.6)	10 519.8 (10 594.9)
	High beta	13 261.3 (10 665.3)	11 366.4 (7500.1)	13 044.7 (6206.0)	13 025.9 (7548.9)	12 900.1 (6987.2)	16 121.7 (9060.0)	5192.2 (8117.7)
	Low gamma	7289.4 (5424.8)	6053.4 (3807.7)	8003.4 (7166.4)	7480.9 (7836.8)	7350.4 (7354.1)	8107.7 (6859.9)	5160.7 (8322.6)
	HFO	18 467.0 (20 699.0)	14 074.9 (15 304.9)*	16 542.4 (12 722.2)	13 510.6 (11 507.6)	12 909.5 (10 665.7)	15 505.5 (12 808.9)	8809.6 (7940.5)
2–3	Delta	46 119.5 (22 381.1)	50 170.0 (23 504.8)	46 561.2 (19 430.6)	46 810.9 (24 169.6)	49 784.1 (23 178.9)	45 397.9 (23 306.9)	61 832.5 (29 373.3)
	Theta–alpha	18 512.1 (22 090.3)	17 994.2 (17 000.0)	20 280.6 (20 140.7)	16 134.9 (15 049.5)	17 127.7 (12 388.6)	18 567.7 (14 956.4)	15 024.8 (6940.1)
	Low beta	24 731.6 (22 231.8)	20 843.9 (20 452.6)	24 567.9 (24 132.3)	22 200.0 (22 585.2)	21 643.6 (17 889.5)	26 877.0 (26 879.2)	5170.3 (3612.3)**
	High beta	17 467.3 (14 666.0)	20 228.5 (21 926.4)	20 643.7 (16 618.5)	16 965.8 (14 764.5)	18 459.1 (14 967.3)	19 891.3 (15 528.5)	2623.9 (3063.0)**
	Low gamma	7776.4 (6552.0)	7182.8 (6094.7)	7373.9 (5482.4)	6681.1 (6719.6)	6922.0 (6457.0)	7337.4 (6213.6)	2542.1 (2288.7)**
	HFO	20 612.9 (19 664.9)	16 808.7 (15 348.9)*	18 956.1 (14 763.0)	16 723.4 (16 261.4)	17 760.3 (15 942.3)	18 020.2 (14 621.4)	7858.6 (7421.2)**
5–6	Delta	32 009.5 (17 498.1)	35 812.1 (16 863.2)	33 631.2 (15 134.7)	35 537.6 (17 908.9)	36 222.2 (19 797.3)	34 642.2 (19 113.7)	50 062.5 (22 842.6)*
	Theta–alpha	16 871.3 (6325.3)	23 666.1 (9151.8)*	20 698.7 (6671.3)	20 017.2 (7692.6)	23 389.0 (6731.1)*	20 829.5 (9788.7)	27 928.6 (14 459.7)
	Low beta	27 996.6 (27 093.9)	24 427.8 (19 638.4)	27 379.0 (25 687.3)	28 489.2 (26 431.9)	23 504.8 (14 292.2)	24 153.4 (24 051.2)	9291.0 (6440.0)*
	High beta	14 548.1 (13 812.6)	15 415.7 (10 978.9)	16 631.7 (10 542.6)	14 618.8 (9024.1)	16 045.2 (9600.5)	15 225.3 (13 046.3)	3741.6 (2557.7)*
	Low gamma	11 676.7 (7607.7)	12 452.4 (5558.7)	12 542.6 (6356.1)	11 712.0 (6695.6)	12 764.9 (6789.5)	11 338.1 (8340.9)	6736.0 (5746.7)*
	HFO	38 195.4 (29 666.7)	35 939.9 (20 849.6)	37 890.6 (26 050.0)	35 416.9 (23 841.0)	38 410.5 (25 254.8)	30 827.2 (24 336.4)	23 948.4 (23 634.2)*
6–7	Delta	39 602.7 (26 702.1)	34 448.8 (15 129.7)	30 637.0 (14 344.3)*	33 213.9 (25 571.8)*	34 786.4 (24 744.2)	33 973.8 (28 495.3)	50 028.4 (25 547.9)*
	Theta–alpha	25 733.4 (20 657.4)	30 171.2 (13 460.2)	21 966.1 (16 849.6)	20 794.9 (13 233.0)	24 434.6 (11 480.9)	18 144.3 (11 401.6)	26 864.0 (21 125.2)
	Low beta	32 555.7 (26 816.5)	27 326.6 (18 126.0)	27 913.2 (21 590.4)	31 783.0 (27 052.9)	31 278.4 (20 927.5)	27 697.9 (27 854.1)	9061.1 (6909.1)*
	High beta	15 533.1 (11 420.1)	15 890.8 (8728.4)	17 725.6 (14 140.1)	16 119.5 (11 544.1)	17 479.9 (10 227.1)	14 618.4 (11 984.4)	3591.0 (3153.7)**
	Low gamma	9127.1 (5730.8)	10 085.6 (5183.6)	8767.2 (5533.7)	9163.1 (4792.7)	9501.8 (4802.7)	7362.7 (5526.8)	5115.9 (4595.6)*
	HFO	34 852.6 (27 646.6)	35 208.1 (24 692.3)	31 744.5 (27 951.3)	30 321.4 (25 621.6)	33 655.1 (26 638.4)	24 500.6 (23 192.6)	17 310.4 (15 935.7)**

Action potential recording through MERs is the gold standard in intraoperative mapping of the STN. LFPs are considered to represent the grand average of the postsynaptic activity around the electrode, whilst action potentials recorded using MERs represent the output of the specific structure analysed. Hence, it is highly likely that any interference in the postsynaptic activity of a structure, in principle through the input to that structure, will change the output in terms of action potentials. A change in the LFPs should reflect changes in the MERs. Therefore, including LFP information (obtained through the same microelectrode or through the macroelectrode part of a mixed micro-/macro-electrode) when localising the dorsal sensorimotor area of the STN is an interesting prospect.

This study has some limitations. During dexmedetomidine infusion, the patients were considered to be in an awake state when their eyes were open and they responded adequately to verbal commands. These features ensure patient collaboration, but more specific neurological tests might have provided more precise information about the cognitive level at each point. Moreover, although the study was conducted in a non-OT setting, the results are likely similar to what would be recorded during the actual surgery. Furthermore, the size of the study was relatively small, but the *a priori* power analysis

showed that the selected population size had sufficient statistical power to yield meaningful clinical results.

In summary, although not all patients with PD need sedation throughout STN–DBS electrode implantation, those who require it can probably receive dexmedetomidine up to 0.6 μg kg^{-1} h^{-1} (0.70 ng ml^{-1}) without it interfering with STN activity during target localisation in an awake state. During dexmedetomidine infusion, the patients achieved a sedated state and showed a significant decrease in characteristic Parkinsonian STN activity at the doses analysed (0.5–0.6 μg kg^{-1} h^{-1}). The awake state can easily be achieved in less than 10 min with an external stimulus, and STN activity is not significantly different from that in the basal state.

Authors' contributions

Study conception/design: all authors
Data acquisition: AM-S, MV, EC-A, CH–C, OM, MA
Data analysis/interpretation: AM-S, MV, JMN-C, AA, MA
Drafting of paper: AM-S, MV, JMN-C, MA
Critical revision of paper with important intellectual contribution: EC-A, CH–C, OM, AA, AP, JG
Final approval: all authors

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Declarations of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.01.036.

Appendix A.

Plasma concentrations of dexmedetomidine were analysed by ultra-performance liquid chromatography (UPLC)/mass spectrometry (MS)/MS using an ACQUITY UPLC device with triple quadrupole MS from Waters Corporation (Cerdanyola del Vallès, Spain). Solid phase extraction was performed with Oasis® HLB cartridges (30 mg; Waters Corporation), and subsequently, the samples were washed with a water:methanol (80:20; v/v) solution. The column and pre-column used were ACQUITY BEH C18 1.7 μm 2.1 × 50 mm and MassTrak TDM C18 IVD 2.1 × 10 mm, respectively (Waters Corporation). The mobile phases used were formic acid 0.1% in water (Channel A1) and formic acid 0.1% in acetonitrile (Channel B1). Deuterium-labelled dexmedetomidine (Toronto Research Chemicals, Toronto, ON, Canada) was used as the internal standard, and the calibration points ranged from 0.1 to 10 ng ml^{-1}. Inter- and intra-assay precision (variation coefficient) and accuracy were less than 5%.

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