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Short Communications

Long-term infective complications of deep brain stimulation in Parkinson's disease: A 22-year follow-up

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ABSTRACT

Introduction: Deep brain stimulation (DBS) is an established treatment for Parkinson's disease (PD), but infections remain a significant concern. This study evaluated infection rates and their impact in PD patients who underwent subthalamic nucleus (STN)-DBS over a 23-year period.

Methods: A total of 172 PD patients who underwent bilateral STN-DBS between 2000 and 2023 were included in this retrospective study. Patients were followed up for periods ranging from 5 to 22 years, with regular assessments conducted to monitor both clinical outcomes and the occurrence of infections. The study analyzed the timing of infections onset, clinical features, microbiological data, management and outcomes.

Results: The overall infection rate was 8.7 % over the follow-up period (15/172). Most of the infections (63.6 %) involved the implantable pulse generator (IPG) subcutaneous pocket, developed after a median of 22 months and were related to the number of substitutions with a notable peak in incidence after the third replacement (3.3 ± 1.5). All the infected devices were non-rechargeable and Staphylococcus epidermidis was the isolated pathogen in all cases except by one. Surgical revision of the IPG pocket was necessary in 46.2 % of cases while all the others were treated by antibiotics. Factors that significantly correlated with infections were the years elapsed since DBS implantation, BMI decrease, and the number of IPG replacements.

Conclusions: While STN-DBS remains effective for PD, infection risk rises with time, particularly during IPG replacements. Long-term follow-up and timely management are vital for sustaining therapeutic benefits.

1. Introduction

Deep brain stimulation (DBS) is a widely used neurosurgical treatment for Parkinson's disease (PD), but it carries infection risks associated with implanted hardware [1]. Infections affecting components like the implantable pulse generator (IPG), leads, or extension cables can compromise treatment, increase patient morbidity, and burden healthcare systems. Preventing such infections is a key focus for neurosurgeons. Infection rates vary widely (1 %–50 %) due to inconsistent definitions and methodologies, with an estimated prevalence around 5 % [2]. Risks arise during hardware implantation or IPG replacements, particularly with non-rechargeable devices requiring frequent surgeries for battery depletion [3]. The IPG pocket is the most common infection site [4]. Management of DBS infections remains contentious. Mild cases may respond to antibiotics and surgical debridement, but severe or resistant infections often require hardware removal [5]. Approaches differ across institutions; some favor immediate removal to avoid complications, while others prefer localized treatment initially [6]. We report our long-term experience managing infective complications following DBS surgery, their impact on PD patient outcomes, and

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providing insights into potential risk factors and optimal management practices.

2. Methods

2.1. Subjects and clinical evaluations

This retrospective study involved 172 PD patients who underwent bilateral DBS of the subthalamic nucleus between 2000 and 2023. For each patient we collected demographic and disease-specific information such as age at PD diagnosis, disease duration before DBS, and age at the time of DBS surgery. We assessed pre-operatively and post-operatively at every follow-up visit (at least once a year) the following variables: body mass index (BMI), daily L-DOPA dosage (LEDD), Hoehn and Yahr stage, L-DOPA response, Parkinson's Disease Questionnaire (PDQ39), Minimal Mental State Examination (MMSE), Frontal Assessment Battery (FAB), Unified Parkinson's Disease Rating Scale (UPDRS) I, UPDRS II (as an indirect index of patient's self-caring ability), IV and motor symptoms, which were evaluated using UPDRS part III in all the possible combination of stimulation On/Off and medication On/Off. The L-DOPA response was calculated as: [(UPDRS $III_{off\ med}$ − UPDRS $III_{on\ med}$)/ UPDRS $III_{off\ med}$]*100, where UPDRS III scores are those pre-DBS. For each patient, an estimate of the variation over time of UPDRS I, II, III and IV scores was derived from the calculation of the coefficient of the linear regression function (mUPDRS).

2.2. Surgeries

DBS surgeries were carried out in two stages on the same day. The first stage consisted of DBS electrode implantation on awakened patients while the second one in the subcutaneous implantation of the IPG in the left subclavicle area (Percept PC, Medtronic) under general anesthesia (see supplementary materials). IPG exchanges were scheduled before battery depletion and performed under local anesthesia. Skin preparation included chlorhexidine or povidone-iodine solutions, and patients received antibiotics (2 g cefazolin or 1 g vancomycin) preoperatively. Implants were opened immediately before insertion, and wounds were closed in layers to minimize dead space, with irrigation using gentamycin or rifampicin.

2.3. Infection detection and treatment

Our definition of DBS-related infection included at least one of the following: (a) purulent drainage around the generator, extension, or generator site, with or without laboratory confirmation; (b) organisms identified from an aseptically obtained culture of fluid or tissue from the affected site; or (c) at least one of the following infection signs or symptoms: pain, tenderness, localized swelling, redness, or warmth. Data collected included the infected device (IPG, lead, or extension), complete blood count, erythrocyte sedimentation rate, C-reactive protein, procalcitonin, liver and kidney function tests, wound swab culture results, time from IPG implantation to infection, and interventions such as systemic or topical antibiotics, and partial or total removal of the device.

2.4. Statistical analysis

Categorical and continuous data were expressed as percentages or mean ± SD. Risk factors for infection were analyzed using Chi-square or Fisher tests, followed by linear regression for significant relationships. Continuous variables were compared using t-tests or Mann-Whitney U-tests, while categorical variables used Chi-square or Fisher's exact tests. Kaplan–Meier curves were used to determine infection occurrence during patients' follow up and log-rank (Cox–Mantel) tests were employed to determine factors affecting infection development. Significance was set at $p < 0.05$, with analysis conducted in SPSS (ver. 22.0).

3. Results

3.1. Patient demographics and characteristics

A total of 172 PD patients who had undergone DBS implantation between January 2000 and December 2023 were included in the study (344 electrodes and 172 IPG). The follow-up time varied from a minimum of 5 to a maximum of 22 years, and a total of 15 (8.7 %) patients developed an infection of the DBS system. No statistically significant correlations were observed between infection and sex, the presence of hypertension, heart disease, dyslipidemia, and DMII (Table 1). All patients were nonsmokers. We did not find any statistically significant differences between infected and non-infected patients in terms of age at PD onset, age at the time of DBS surgery, or time interval between PD diagnosis and DBS (Table 1). Infected patients showed a slightly more severe PD profile given the higher score in the Hoehn and Yahr scale and all UPDRS registered right before DBS surgery (Table 1). However, the only statistically significant difference was registered in the UPDRS II score (18.92 ± 4.56 infected vs 15.09 ± 5.96 non-infected). We calculated the variation of UPDRS scores over time using regression coefficients, observing a higher positive coefficient for UPDRS II and III Off Med/On stim scales in the infected group, indicating a steeper worsening over time (Table 1). The average duration of DBS surgery was

Table 1
Summary of the statistics on demographic characteristic and PD-related features measured at the pre-DBS visit of infected and not-infected patients.

	Infected (15)	Not infected (157)	*p value*
Sex:			
- Male, *n (%)*	7 *(47)*	84 *(53.5)*	*0.43*
- Female, *n (%)*	8 *(53)*	73 *(46.5)*	
Comorbidities:			
- Hypertension, *n (%)*	7 *(47)*	38 *(24.2)*	*0.08*
- Heart disease, *n (%)*	1 *(6.7)*	9 *(5.7)*	*0.91*
- Dyslipidemia, *n (%)*	1 *(6.7)*	4 *(2.5)*	*0.65*
- DM II, *n (%)*	1 *(6.7)*	2 *(1.3)*	*0.31*
- Others systemic diseases, *n (%)*	1 *(6.7)*	19 *(12)*	*0.19*
Age at PD onset, *mean ± SD*	45.6 ± 8.5	47.6 ± 8.9	*0.44*
Age at DBS, *mean ± SD*	58.9 ± 5.8	59.5 ± 8.2	*0.88*
Δt (years) between PD onset and DBS, *mean ± SD*	13 ± 4.9	11.5 ± 4.9	*0.30*
Hoehn and Yahr stage (off), *mean ± SD*	3.83 ± 0.39	3.77 ± 0.76	*0.78*
Levodopa response, *mean ± SD*	73.7 ± 13.5	69.6 ± 20.3	*0.47*
UPDRS I, *mean ± SD*	24.00 ± 13.53	20.31 ± 14.55	*0.98*
UPDRS II, *mean ± SD*	** 18.92 ± 4.56	15.09 ± 5.96	*0.009*
UPDRS III (Off Med/On Stim), *mean ± SD*	40.83 ± 11.51	33.49 ± 12.26	*0.09*
UPDRS IV, *mean ± SD*	1.89 ± 0.60	1.6 ± 0.84	*0.38*
LEDD, *mean ± SD*	935.5 ± 433.1	1056.9 ± 411.8	*0.36*
mUPDRS I, *mean ± SD*	0.54 ± 0.45	0.36 ± 0.89	*0.47*
mUPDRS II, *mean ± SD*	* 1.45 ± 0.58	0.65 ± 1.29	*0.03*
mUPDRS III (Off Med/On Stim), *mean ± SD*	* 2.59 ± 2.46	1.04 ± 1.83	*0.02*
mUPDRS IV, *mean ± SD*	0.05 ± 0.59	−0.21 ± 1.17	*0.64*
PDQ39, *mean ± SD*	46.06 ± 20.04	37.09 ± 14.58	*0.16*
MMSE, *mean ± SD*	24.99 ± 7.54	27.25 ± 3.1	*0.10*
FAB, *mean ± SD*	15.5 ± 2.76	13.7 ± 3.18	*0.14*
Δ% of BMI reduction, *mean ± SD*	* −13.6 ± 7.8	−1.91 ± 2.5	*0.01*
Surgical time DBS implant (min), *mean ± SD*	290.6 ± 61.1	292.9 ± 68.9	*0.46*

DMII: diabetes mellitus II; PD: Parkinson's Disease; DBS: deep brain stimulation; UPDRS: Unified Parkinson's Disease Rating Scale; LEDD: daily L-dopa dosage; mUPDRS: coefficient of the linear regression of the UPDRS; PDQ39: Parkinson's Disease Questionnaire; MMSE: Minimal Mental State Examination; FAB: Frontal Assessment Battery; BMI: body mass index. * $p < 0.05$, ** $p < 0.01$.

slightly shorter for infected patients (290.6 ± 61.1 min) than for non-infected patients (292.9 ± 68.9 min) but without statistical significance (p = 0.46). We analyzed BMI changes by comparing values before DBS surgery to those at the last follow-up and observed a greater BMI reduction (−13.6 ± 7.8 vs −1.91 ± 2.5) in infected patients. Regression analysis revealed a slightly positive BMI trend for non-infected patients (m = 0.043) and a negative trend for infected ones (m = -0.52).

3.2. Incidence, timing and characteristics of infections

Among the 15 infections, 11 occurred in the subcutaneous pocket containing the IPG, 1 in the frontal inlets of the DBS electrode (6.7 %) and 3 along the course of the extensions, in the retroauricular and fronto-temporal sites (20 %) (Table 2). On average, patients developed a DBS hardware infection 117 ± 59.1 (range 0.25–216) months after DBS surgery and 21.3 ± 22.9 (range 0.25–60) months after the last IPG replacement surgery (Table 2). Staphylococcus epidermidis was identified in 13 cases, Staphylococcus Aureus and Morganella Morganii in the remaining 2 (Table 2).

A total of 191 IPG replacements were performed, 145 in the not infected group and 45 in the infected one. All infected patients underwent IPG substitution while in the not-infected group only 59/157 (37.6 %). The mean number of IPG substitutions for infected patients was 3.2 ± 1.7, significantly higher than non-infected ones. All IPG infections occurred after at least one replacement, involving only non-rechargeable devices such as 7 Activa PC® (Medtronic) IPG and 8 Kinetra® (Medtronic) (Table 2). Decubitus of a DBS system component was found in 9 cases (60 %) in the infected group, 6 over the IPG, and in only 1 case in the not-infected group, involving extensions in the retroauricular portion (Table 3). Additionally, stratified survival analysis revealed that decubitus significantly impacted infection probability over time (p < 0.0001) (Fig. 1). The mean duration of each IPG device progressively decreased over substitutions, with the infected group showing shorter IPG duration at each interval compared to the not-infected group. Statistical significance was reached for the duration of the fourth IPG implanted.

Table 3
Statistics related to IPG management and characteristics.

	Infected	Not infected	*p value*
Cases of IPG substitution, *n (%)*	** 15 (100)	59 (37.6)	*0.005*
Number of IPG substitutions, *mean ± SD (median)*	** 3.2 ± 1.7 (4)	1.67 ± 1.64 (1)	*0.0013*
Decubitus (at least 1 DBS component), *n (%)*	** 9 (60)	1 (0.6)	*0.001*
- IPG decubitus	6	0	
- Others	3	1	
Duration IPGs (months):			
- Device nr. 1, *mean ± SD*	58.86 ± 22.08	63.72 ± 25.15	*0.55*
- Device nr. 2, *mean ± SD*	43.64 ± 10.84	52.46 ± 16.73	*0.25*
- Device nr. 3, *mean ± SD*	35.78 ± 10.81	37.07 ± 17.48	*0.03*
- Device nr. 4, *mean ± SD*	* 22.71 ± 12.41	34.82 ± 8.4	*0.13*
- Device nr. 5, *mean ± SD*	22.75 ± 2.5	28 ± 7.48	*0.57*

* p < 0.05, ** p < 0.01.

3.3. Management and outcomes of infections

Infection management depended on severity and timing. All patients with signs of infection were hospitalized and treated with intravenous antibiotics based on pathogen sensibility. The antibiotics most used were Linezolid (600 mg BID), Vancomycin (20 mg/kg BID) and Daptomicin (10 mg/kg once daily). Of 15 infected patients, 5 were managed successfully with antibiotics alone without requiring hardware removal. If decubitus caused wound dehiscence, surgical wound revision was required. Patients continued oral antibiotics (usually Linezolid 600 mg BID, Rifampin 300–600 mg BID or 15–20 mg/kg Trimethoprim-Sulfamethoxazole 160/800 mg BID) for at least 4 weeks post-discharge. Hardware removal was necessary in severe cases or when antibiotics failed. It was performed in 10/15 (66.7 %) patients, including those with infections at DBS electrode inlets (2), along extension courses, or IPG

Table 2
Clinical characteristics of infections after deep brain stimulation surgery in patients with Parkinson disease.

Patient	IPG model	Nr. of substitutions	Infection Localization	Decubitus (1 = yes, 0 = no)	Δt DBS-infection (months)	Δt infection −last surgery (months)	Pathogen	Removal (1 = yes, 0 = no)
Patient 1	Activa PC®	1	Electrodes (frontal access)	1	144	60	St. aureus	1
Patient 2	Kinetra®	3	IPG	1	156	12	St. epidermidis	0
Patient 3	Kinetra®	2	IPG	0	48	2	St. epidermidis	1
Patient 4	Kinetra®	4	IPG	1	92	22	Morganella morganii	0
Patient 5	Activa PC®	2	Extensions (cranial)	1	157	4	St. epidermidis	0
Patient 6	Kinetra®	5	IPG	0	168	84	St. epidermidis	1
Patient 7	Activa PC®	5	IPG	0	168	3	St. epidermidis	1
Patient 8	Activa PC®	5	IPG	0	48	24	St. epidermidis	0
Patient 9	Kinetra®	1	Extensions (cranial)	1	60	18	St. epidermidis	1
Patient 10	Kinetra®	4	IPG	1	144	36	St. epidermidis	1
Patient 11	Activa PC®	3	IPG	0	168	4	St. epidermidis	1
Patient 12	Activa PC®	5	IPG	1	216	24	St. epidermidis	0
Patient 13	Activa PC®	4	Extensions (chest)	1	120	2	St. epidermidis	1
Patient 14	Kinetra®	4	IPG	1	60	24	St. epidermidis	1
Patient 15	Kinetra®	0	IPG	0	0,5	0,5	St. epidermidis	1
Mean ± SD		**3.2 ± 1.7**		**9/15 (60 %)**	**117 ± 59.1**	**21.3 ± 22.9**		**10/15 (66.7 %)**

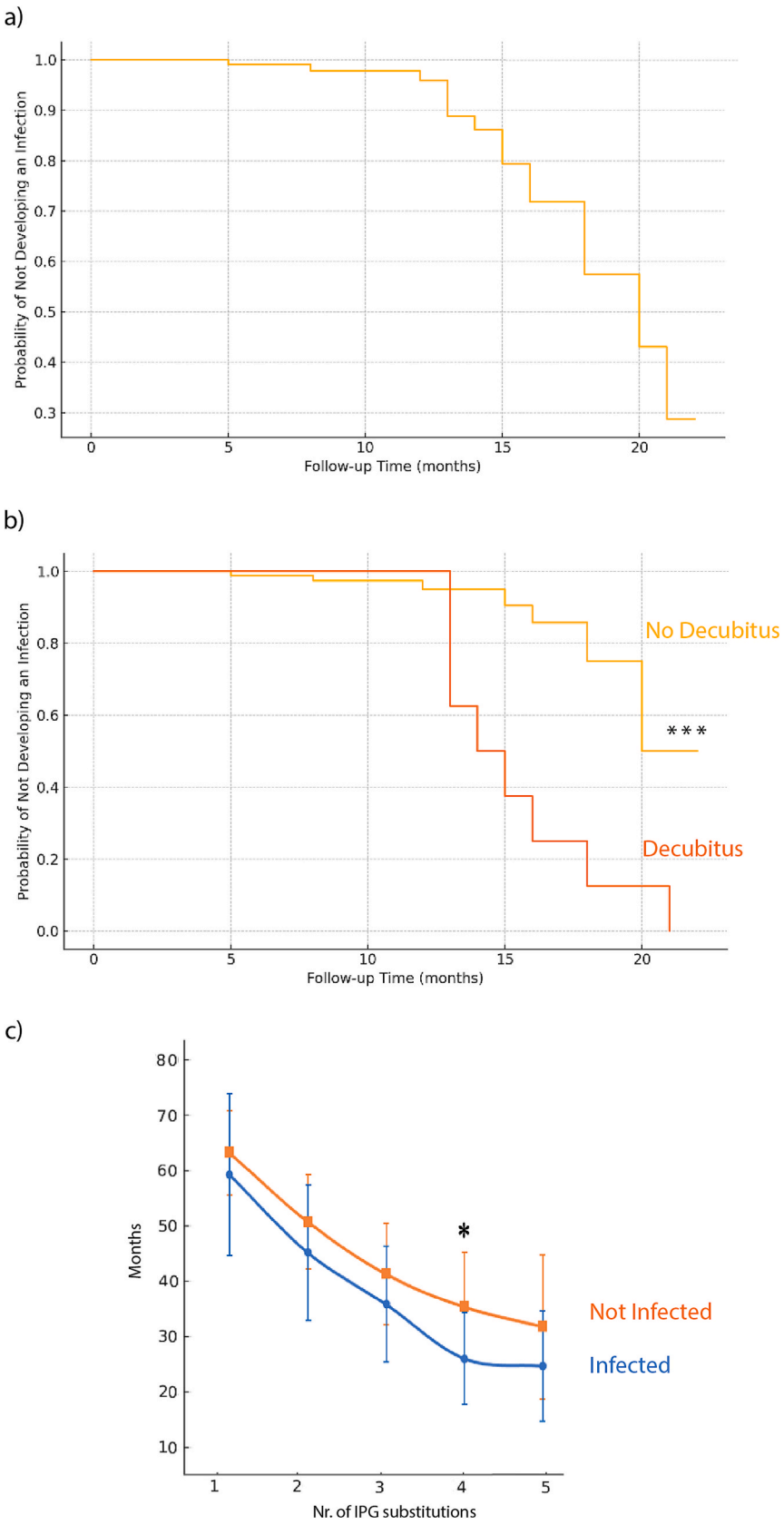

Fig. 1. Kaplan-Meier analysis. Kaplan-Meier analysis of infection occurence over time during the available follow up periods (a) and comparing infection probsability between those with decubitus and not (b). (c) Comparison of mean IPG duration (months) after each substitution in infected and not infected patients. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

infections. Decubitus was present in 5/10 cases. One infection occurred 2 weeks post-surgery at the IPG pocket, leading to full DBS removal due to higher risk of system compromission (Table 2). Reimplantation occurred in 5 patients after infection resolution (median 9 months), while others did not undergo reimplantation due to comorbidities or advanced age. Infection-related mortality was 0 %, but infections negatively affected quality of life, as reflected in PDQ-39 scores, even after reimplantation.

4. Discussion

DBS is an effective therapy for neurological conditions like PD, but infections remain a significant complication, especially with increasing DBS implants. In our study, the infection rate was 8.7 %, slightly higher than the 5.2 % in a recent *meta*-analysis [2] likely due to longer follow-up. No link was found between infections and common risk factors like smoking or diabetes, the IPG pocket was the main infection site and Staphylococci the prevalent pathogen. According to the definition given by the National Surgical Quality Improvement Program, DBS-related infection is defined as occurring within 6 months post-surgery [7,8]. Thus, with a median of 18 months after last surgery, we did not strictly encounter DBS-related infections but delayed-onset ones occurring either after one IPG replacement for IPG cases, or due to the development of decubitus and wound dehiscence for other DBS system components (extensions and electrodes inlets). The only exception is the patient who developed an early-onset infection of the IPG pocket with no decubitus-related issues or wound dehiscence.

As in several studies, we showed that an increasing number of IPG replacements increases the risk of developing an infection of the IPG pocket [9]. Rechargeable IPGs may reduce replacements and infection risks, though long-term performance and suitability for certain patient populations are yet to be fully understood [4]. Closed-loop systems, adapting stimulation to needs, could also reduce battery consumption [10,11]. Battery lifetime can vary according to PD phenotype and severity. In our sample, we did not encounter any difference in this regard between infected and not-infected patients. Unfortunately, we could not calculate the total electrical energy delivered (TEED) to estimate battery consumption.

In this study infected patients showed greater BMI reduction, which could be linked to a worse PD profile that led to greater battery consumption and more IPG substitutions. This is partially supported by the more significant PD worsening in terms of UPDRS II and III scores in the infected group, as UPDRS II serves as a good marker of disease progression [12]. The observed infections occurred on average 124.9 ± 54.1 months after DBS surgery, in a more advanced PD condition typically related to low BMI, which promotes decubitus and poor healing that facilitates infections [4]. Not by chance, the most encountered pathogen are skin commensal bacteria, and wound dehiscence and poor healing represents an important predisposing factor. We thus suggest that patient education and nutritional counseling become critical aspects of infection prevention.

Our approach to managing infections involved using local wound care and antibiotic treatment for cases with moderate clinical symptoms, such as no signs of systemic inflammation or minor wound dehiscence without hardware exposure. However, if the hardware became affected or the infection failed to resolve within four weeks of starting treatment, partial removal of the system was performed. More severe cases were treated with direct hardware removal and antibiotic therapy for a total of 10/15 (66.7 %). We preferred direct removal of the DBS system in the patient who developed early-onset infection of the IPG pocket 2 weeks after DBS surgery to prevent the spread of infection and reduce the risk of sepsis.

5. Conclusion

DBS remains an effective therapy for PD, but infections, particularly at the IPG pocket, remain a concern. Our study found an 8.7 % infection rate, with repeated IPG replacements significantly increasing infection risk. Patients with infections showed greater BMI reduction, likely reflecting advanced PD, which predisposes them to wound dehiscence and poor healing. Rechargeable IPGs and closed-loop systems may help reduce replacement frequency and associated infections. Infection management required a stepwise approach, with hardware removal in severe cases. Our findings highlight the need for patient and caregivers' education, nutritional support, and strategies to minimize repeated IPG interventions.

6. Ethics

Ethical review and approval were waived for this study due to the retrospective nature of the study.

CRediT authorship contribution statement

Riccardo Antonio Ricciuti: Writing – review & editing, Project administration, Data curation, Conceptualization. **Matteo Maria Ottaviani:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fabrizio Mancini:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Valentina Liverotti:** Writing – review & editing, Investigation, Data curation. **Daniele Marruzzo:** Writing – review & editing, Investigation. **Massimo Marano:** Writing – review & editing, Conceptualization. **Francesca Barbieri:** Writing – review & editing, Investigation. **Riccardo Paracino:** Writing – review & editing. **Serena Pagano:** Writing – review & editing, Investigation. **Vincenzo Di Lazzaro:** Writing – review & editing, Validation, Supervision. **Mauro Dobran:** Writing – review & editing, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

DBS surgery: Two types of DBS surgery were performed: frame-based and frameless with bone fiducials. All patients underwent pre-operative brain MRI and CT head scan for STN targeting and trajectory planning. Patients undergoing frameless DBS were CT-scanned the day before surgery after fixation of seven noncoplanar bone fiducial markers on the skull. The CT study was then computationally fused to the pre-operative MRI with StealthMerge (Medtronic). For patients undergoing frame-based DBS, the CRW stereotactic frame® (Radionics, Burling- ton, MA, USA) was fixed to patients' skull on the day of surgery and a CT scan was performed and fused with pre-operative MRI and CT scans using Origin server and Brainlab neuronavigation system (Brainlab).

In both cases, systemic antibiotic prophylaxis was administered for all surgeries and involved second-generation cephalosporin (cefazolin 2 g intravenously) or vancomycin (1 g intravenously), given 30 min to one hour before surgery, followed by 1 g every six hours thereafter. Under local anesthesia, two frontal burr holes were drilled, and the dura mater opened on the left side to proceed with the intraoperative recording procedure. After evaluating the selected channels by macro-test stimulation, the one with the largest therapeutic window was chosen for permanent electrode implantation. The electrode lead was then anchored to the skull with a lead anchoring device and the dura was

closed by fibrin glue to prevent cerebrospinal fluid leak or pneumocephalus. The same procedures were then repeated on the right side. In the second surgical stage, DBS leads were capped and tunneled under the parietal galea to the left retroauricular area, while the connector wires were tunneled to the subcutaneous infraclavicular IPG pocket.

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