Clinical Neurophysiology 130 (2019) 1562–1569

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Brain impedance variation of directional leads implanted in subthalamic nuclei of Parkinsonian patients

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ARTICLE INFO

Article history:
Accepted 14 June 2019
Available online 22 June 2019

Keywords:
Deep brain stimulation
Electrodes
Electric impedance
Parkinson disease
Neurostimulation

HIGHLIGHTS

- Directional leads have significantly higher impedance than ring leads in deep brain stimulation (DBS).
- Stimulated contacts have lower impedance than non-stimulated contacts.
- Impedance of the directional leads is higher in the operating room, with a fast initial decrease 5 days post-DBS.

ABSTRACT

Objective: Conventional deep brain stimulation (DBS) systems with ring-shaped leads generate spherical electrical fields. In contrast, novel directional leads use segmented electrodes. Aim of this study was to quantify the impedance variations over time in subjects with the directional Cartesia-Boston® system.
Methods: Impedance records, programming settings, and clinical data of 11 consecutive Parkinsonian patients implanted with DBS directional leads in two Italian centers (Udine and Vicenza) were retrospectively evaluated. Data were collected before starting stimulation (in the operating room and at days 5 and 40) and after switching stimulation on at the successive follow-up visits (1, 6 and 12 months).
Results: Directional leads have significantly higher impedance than ring leads. Stimulated contacts had always lower impedance compared to non-stimulated contacts. Before DBS-on, all contacts had higher impedance in the operating room, with an initial decrease five days post-surgery and a subsequent increase at day 40, more evident for directional contacts. The impedance of directional leads increased post-implantation at 1 and 6 months with a plateau at 12 months.
Conclusions: There was a significant difference between the directional and ring leads at baseline (before activation of DBS) and during follow-up (chronic DBS).
Significance: Our study reveals new information about the impedance of segmented electrodes that is useful for patient management during the initial test period, as well as during long-term DBS follow-up.

1. Introduction

Deep brain stimulation (DBS) is a well-known and effective therapy for patients affected by Parkinson's disease (PD) and other movement disorders, even though a wide range of factors can influence the clinical outcome after surgery (Rehncrona et al., 2003; Rodriguez-Oroz et al., 2012; Moro et al., 2017). Voltage-controlled neurostimulators, which are traditionally used, provide

Abbreviations: AC-PC, anterior commissure-posterior commissure; CAPSIT-PD, Core Assessment Program for Surgical Interventions and Transplantation in Parkinson's Disease; DBS, deep brain stimulation; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; SD, standard deviation; VTA, volume of tissue activated.

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https://doi.org/10.1016/j.clinph.2019.06.001
1388-2457/

an unstable amount of stimulation current over time due to changes in system impedances (Lempka et al., 2010). Current-controlled neurostimulators, which have recently been introduced, supply a constant amount of stimulation that is independent of variations in impedance, ensuring a more predictable and steady therapeutic effect over time (Lempka et al., 2010, 2015).

The impedance that it can be measured in a DBS circuit are "therapy impedance" and "electrode impedance" (Butson et al., 2006; Montgomery, 2010; Lettieri et al., 2015). The former varies in relation to the DBS parameters used in the subject, while the latter is measured at standardized stimulation parameters and it is useful to monitor electrode dysfunction (Allert et al., 2011). In vivo, the impedance variations depend on several factors including the lead and extension connections to the neurostimulator, the surface area of the electrode, the tissue encapsulation surrounding the electrode and the neurostimulator and the tissue conductivity. High impedance values are often associated with circuit breakage or other mechanical failure, while very low impedance values with high current levels are associated with short circuits in the hardware. Furthermore, the interface impedance contributes to the distribution of current density on the electrode, which may influence neural excitation, tissue damage, and electrode corrosion during brain stimulation.

Since 1965, the use of instant impedance measurements during surgical procedures has been reported in several studies (Hemm et al., 2004; Lempka et al., 2009), however, these techniques measure acute impedance, which is significant different for electrode and pulse features, from chronic setting when a permanent electrode is implanted (Lempka et al., 2010; Hemm et al., 2004).

Following advances in technology, it is now possible to obtain impedance measurements after electrode implantation and during chronic DBS, where impedance has been shown to fluctuate immediately after implantation and during chronic stimulation (Hemm et al., 2004; Lempka et al., 2009). The electrical field around the electrode and the clinical outcome over time are requirements to understand the impedance values variation. *In vivo* measurements have shown that tissue impedances can vary up to 33.3% from patient-to-patient (Back and Alesch, 2003). Following retrospective collection of impedance and programming data from 128 electrodes in 84 patients with PD, essential tremor, or dystonia, impedance changes were examined after contact activation and deactivation (Satzer et al., 2014). It was demonstrated that impedance decreased by 73 Ω/year, with 72% of contacts following a downward trend. Compared to inactive contacts, chronically-activated contacts showed both lower impedance and slower impedance decline over the time.

Some studies suggest that tissue conductivity plays an important role in DBS and affects the size and shape of the volume of tissue activated (VTA) (Diersen and Marg, 1965; Laitinen et al., 1992; Butson et al., 2006). Conventional DBS systems use ring-shaped electrodes that generate a largely radial electric field. In these systems, programming of polarity and stimulation pulse parameters allow only limited control of the shape of the VTA (Deuschl et al., 2006). Directed stimulation using segmented electrodes has resulted in increased stimulation thresholds for side effects compared with standard radial electric field stimulation (Contarino et al., 2014; Pollo et al., 2014; Dembek et al., 2017). In addition, the side effects of stimulation may be minimized because multi-electrode leads allow the field to be steered towards the functional target and away from side effect structures (Abosch et al., 2012; Dembek et al., 2017).

Nevertheless, the smaller contact surface of segmented electrodes increases electrode impedance in comparison with ring electrodes, and a higher stimulation voltage is required to deliver the stimulation current (Lempka et al., 2010). Consequently, directional stimulation is likely to be less energy efficient than stimulation in ring mode, as decreasing the surface area of the active contact will result in increased impedance and therefore increased power consumption. To date, published data derived from the use of the commercially-available Vercise PC® (Boston Scientific, Valencia, CA, USA) has been limited to acute intraoperative settings, with only limited information about the impedance variation in a clinical and chronic postoperative setting.

The aim of our study is to quantify the relationship between electrode impedance and time in a population of PD patients by comparing the variations in impedance using the directional and ring modes of a directional lead (Vercise Cartesia™ Directional Lead, Boston Scientific, Valencia, CA, USA). In addition, we wanted to characterize the relationship between electrode activity and impedance. Based on the established evidence for the ring lead (Cheung et al., 2013), we hypothesized that also impedance in segmented (directional) leads could decrease more rapidly in active (therapeutic) contacts after activation when comparing to inactive contacts.

2. Material and methods

2.1. Population

We retrospectively evaluated clinical data and stimulation records of 11 consecutive patients with PD who underwent DBS bilateral surgery implantation in two Italian centers (S. Maria della Misericordia University Hospital of Udine and S. Bortolo Hospital of Vicenza) with a directional system (electrodes DB-2202 Cartesia™ Directional Lead connected to the Vercise PC® neurostimulator from Boston Scientific, Valencia, CA, USA) since December 2015 where the surgery was performing by one step implantation in each DBS centre. This novel directional DBS lead has four electrode levels; the two middle levels are split into three segments, spanning approximately 120° (used for directional stimulation), whereas the highest and lowest level consist of ring-shaped electrodes (for radial distribution of the current). All patients were clinically screened at baseline before surgery and one year after implantation (off-stimulation/off-drug and on-stimulation/off-drug), evaluated using the Core Assessment Program for Surgical Interventions and Transplantation in Parkinson's Disease (CAPSIT-PD) (Defer et al., 1999). A postoperative CT scan was done the day after surgery (24 h after OR) to evaluate the final lead position, to assess postoperative pneumocephalus, or to rule out asymptomatic hemorrhage. The postoperative CT slices were then merged to the preoperative CT and MRI images in the Medtronic Stealth Station (Framelink®; Medtronic, Minneapolis, MN) to blend the anterior commissure-posterior commissure (AC-PC) coordinates and angles of trajectory of the final DBS leads.

Each patient provided informed consent to surgery and to use of their clinical data. This observational, retrospective, non-profit study was approved by our local ethics committee (80/2013/Sper/CERU).

2.2. Data collection

Demographic data included age at DBS surgery, disease duration at surgery, levodopa-equivalent dose at baseline, 6 and 12 months after surgery. Clinical features at baseline and 12 months post-DBS were collected using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008) total score part I, II and III (in the off-drug state before surgery, in the off-drug/on-stimulation state after surgery) and part IV.

In the operating room (OR), DBS impedance measurements were made by a biomedical engineer (SG) and one of the

physicians (MM, SD, MP). We collected data before starting the stimulation in OR and after IPG placement (on days 5 and on days 40) always by using the electronic clinician programmer (model Asus Eee Slate B121 tablet, Neural Navigator software, Boston Scientific, Valencia, CA, USA); in these subjects the stimulator was never switched on before impedance checking. At the successive follow-up visits (at 1, 6 and 12 months), the impedance values were collected after activation of the DBS system.

At each control visit, impedance and current measurements were always performed with patient in supine position. During the chronic follow-up (over the course of 12 months), impedance and current values were measured by one of the physicians (EB, CL, SR, RE) at least once a day during hospital visit. Measurements were made for five different parameter configurations per electrode by a dedicated Boston neurostimulator® software (copyright of Boston Scientific, Valencia, CA, USA). This software uses different configurations to calculate the final impedance. Various rate and amplitude were applied to check the circuits. Impedances were tested as the electrical resistance of the circuit, comprised of the battery, leads and extensions, and were always collected retrospectively from the report obtained from the electronic clinician programmer (model Asus Eee Slate B121 tablet, Neural Navigator software, Boston Scientific, Valencia, CA, USA).

The entire programming visit was carried out using the best configuration and stimulation settings in terms of clinical outcomes. In each subject, data and analysis for electrodes implanted in each hemisphere were done independently, and included active contacts, stimulation set-up mode (unipolar or bipolar), duration, frequency, and amplitude of the delivered stimulus. Programming session data were collected to evaluate parameters of stimulation at 6 months and 1 year after implantation. Pulse width was measured in microseconds (μs), frequency in hertz (Hz), and amplitude of stimulation in milliampere (mA).

A therapeutic contact was considered active if it had been selected and did not change during the period of the study; if the contact was changed, the contact was not considered in the sample size for the statistical analysis. "Therapeutic" means a contact with stimulation-on (active contact) independently from the DBS parameters selected. The impedances were collected for contacts with directional distribution of the current and for those with radial distribution. Impedance values collected were separated into active contacts and inactive contacts in the stimulation configuration.

2.3. Statistical analysis

We used a combination of generalized linear mixed models (GLMM) for repeated measures and a repeated-measures analysis of variance has been applied to examine the impedance's effects over the time, comparing directional vs. ring and active vs. inactive contacts. p values of less than 0.05 were considered statistical significant. The Mixed model procedure in The SAS System Version 9.3 software (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA) was used for the analyses. Analysis was made considering the real impedance values and the calculated variations of impedance values collected over time for a single contact in the same patient. Comparison of means used the Mann-Whitney test assuming statistical significance as $p \leq 0.05$. Comparisons were also made between impedance values collected over time (baseline, 6 and 12 months) in the same contact and between contacts, for directional and ring contacts and for active and inactive contacts made by Wilcoxon test assuming a *P*-value significance level of 0.05. Confidence intervals (CI) for all tests used was 95%. Statistical analysis was made with the software SAS Version 9.5 (SAS Institute Inc.).

The means of the values obtained over the time were also compared for directional active vs. directional inactive contacts, and for directional (active or inactive) vs. ring (always inactive) contacts. All results are presented as mean ± standard deviation (SD). Comparison between parameters was made for settings of pulse width, frequency, and amplitude of stimulation for right and left STN and considering the different values at timing of evaluation using t-test, assuming an alpha of 0.05.

3. Results

Eleven patients (four females, seven males) were included in the study. The mean age at surgery was 61 ± 9 years, the mean duration of PD before surgery was 13.3 years ± 4.3, and the UPDRS III in the off-drug condition was 38.29 ± 11.87. Clinical features at surgery and after 12 months post-DBS implantation are reported in Table 1 (top), in which we detected an improvement in the MDS-UPDRS scale for all of the dimensions evaluated: 44.9% for non-motor aspects of experiences of daily living (Part I), 41.1% for motor aspects of experiences of daily living (Part II), 37.5% for motor examination (Part III) while DBS-ON and 73.3% for motor complications (Part IV).

Considering the levodopa equivalent daily dose and the best Hoehn and Yahr score, results at 1 year after surgery showed a 67.1% reduction in oral drugs and a 44.0% clinical improvement, respectively. Programming configurations at the 6- and 12-month evaluation are available for nine and seven patients, respectively and the different samples sizes of impedance values collected at 6 and 12 months was related to the drop-out of a few subjects that have missed the control visit. Increases or changes in stimulation programming between 6 months and 1 year were not statistically significant, considering the means of the whole population. Data are reported in Table 1 (bottom).

Impedance values were collected for 104 contacts in the operating room, for 78 contacts at day 5 and for 44 contacts at day 40 post-implantation – and always before turning the system on. For all subjects, impedance values were available at activation visit (baseline) and at the first monthly evaluation (134 contacts). Data concerning the evaluation at 6 and 12 months were available for 107 and 86 contacts, respectively.

Overall, we collected 463 measure impedances over 12 months of evaluation: 135 values for the ring contacts, 181 for inactive (non-therapeutic) directional contacts and 147 for active (therapeutic) directional contacts. After 6 and 12 months of follow-up,

Table 1
Clinical scores and stimulation parameters in the study population.

Clinical features			
	Baseline Mean (±SD)	12 months Mean ± SD	*p*
UPDRS I	8.71 (5.02)	4.8 (2.68)	*0.057*
UPDRS II	12.57 (6.55)	7.4 (2.30)	*0.045**
UPDRS III ON	11.29 (4.07)	7.0 (1.58)	*0.017**
UPDRS IV	6.86 (4.78)	1.8 (1.10)	*0.016**
LEDD	1160.43 (498.879)	381.4 (413.53)	*0.008**
Stimulation parameters			
	6 months Mean (±SD)	12 months Mean (±SD)	*p*
Pulse width (μs)	52.86 (9.14)	56.43 (7.45)	*0.134*
Frequency (Hz)	134.21 (11.48)	142.07 (21.43)	*0.119*
Amplitude (mA)	2.68 (0.56)	2.72 (0.84)	*0.437*

For clinical scores, p is the comparison (unpaired test) at baseline and 12 months; for stimulation parameters, p is the comparison between 6 and 12 months post-implantation (statistical significance ≤ 0.05); * = significant improvement between 12 months and baseline; LEDD = levodopa equivalent daily dose; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

the 98% of therapeutic active contacts were directional, respectively 47/48 and 28/29.

The GLMM controlled the within-subject nature of the 4 measures of impedances by including random effects from the subject, with an autoregression covariance structure and restricted maximum likelihood estimation (REML). The results that the impedance at the 1, 6, 12 months is statistical significant in comparison to the baseline (p values < 0.05). A statistical significance was also found in the directional active vs. directional inactive, directional active vs. ring inactive, and directional inactive vs. ring inactive, with a p value of 0.0463, <0.0001 and <0.0001 respectively.

Table 2 showed the results of the analysis of the impedances collected in the early phase, before DBS activation in the OR and after days 5 and 40 post-surgery. In the pre-activation phase, for all contacts (independent of the design) mean impedance values significantly decreased from OR to day 5, with a subsequent increase at day 40. When compared to the OR values, impedances at day 40 were similar in the ring contacts and significantly lower in directional contacts (Fig. 1).

The mean impedances collected over time in the ring contacts compared to directional active and inactive contacts are shown in Table 3. The mean impedance at baseline, before turning on the system, was 942 Ω for the ring (inactive) contacts, 2035 Ω for the directional inactive contacts, and 1870 Ω for the directional active contacts, with a significant difference between the ring and directional contacts ($p < 0.0002$). Comparison of mean values over time showed a significant increase in impedance during the first month, followed by a subsequent lasting stabilization of values; this was observed for all contacts, independent of design and activation. Furthermore, a comparison between ring and directional inactive contacts revealed a constant and significantly ($p < 0.0001$) lower impedance with the ring contacts over time. Similar results were observed between the ring (inactive) and directional active contacts. Finally, comparison between the directional inactive and active contacts demonstrated a persistent and significant difference in values, always lower for active directional contacts.

Table 4 shows the impedance values obtained in the same contact, for each patient over time. During the first month, the

Table 2
Early impedance values over time in the off-stimulation condition using the directional versus ring contacts.

	Directional contacts	Ring contacts
OR	*n = 78*	*n = 26*
Mean ± SD (min–max)	2539.70 ± 2518.78 (1121–13981)	1055.95 ± 757.49 (735–4409)
5 days	*n = 60*	*n = 16*
Mean ± SD (min–max)	1559.42 ± 381.90 (1011–2385)	771.67 ± 200.73 (479–1101)
40 days	*n = 31*	*n = 11*
Mean ± SD (min–max)	2386.03 ± 799.77 (1285–4546)	1049.00 ± 271.25 (646–1442)
p OR vs. 5 days	*0.0030**	*0.0523**
p 5 days vs. 40 days	*0.0006**	*0.0420**
p 40 days vs. OR	*0.0483**	*0.1433*

Impedance values before starting deep brain stimulation: in the operating room (OR) and at days 5 and 40 (paired test). Data reported in Ohms as mean, standard deviation (SD), minimum and maximum values. *p*-values are for Mann-Whitney test for comparison of mean values obtained (* significance ≤ 0.05).

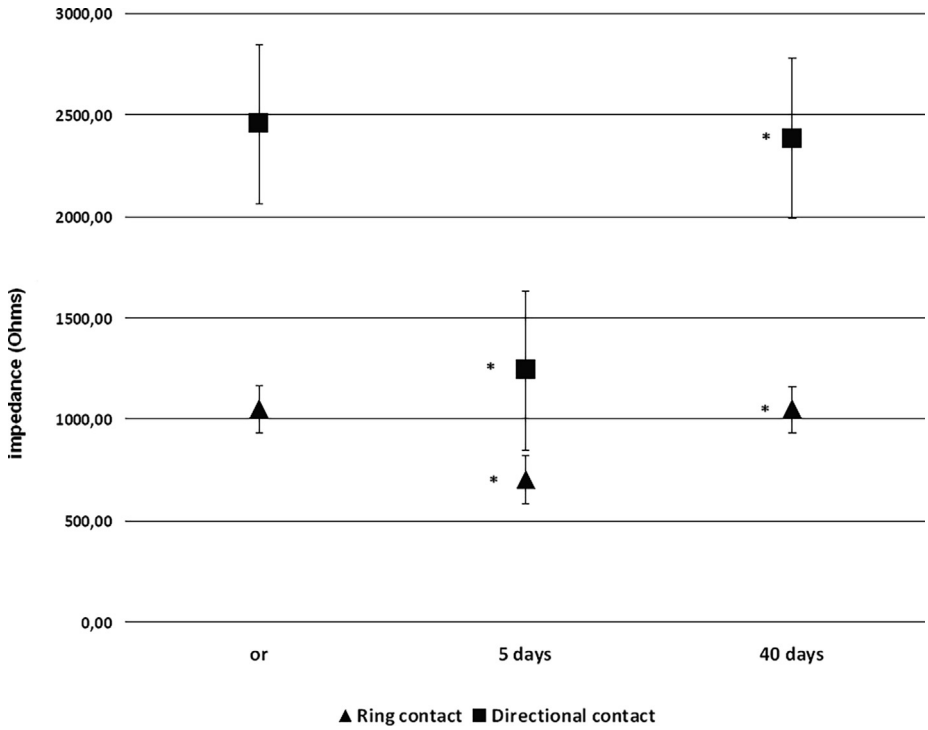

Fig. 1. Impedance trend values during the early postoperative phase. Figure showed the trend of impedances collected during implant phase, in the operatory room (OR), 5 and 40 days after surgery, before turning the stimulator on. * = Mann-Whitney test significance ≤ 0.05 for comparison of impedances mean values detected at the different times (5 days vs or; 40 days vs 5 days).

Table 3
Impedance values over time in the ring versus the directional contacts.

	Baseline		*p baseline vs 1 month*	1 month		*p 1 month vs 6 months*	6 months		*p 6 months vs 12 months*	12 months	
	Sample size	**mean** ± SD (min–max)		Sample size	**mean** ± SD (min–max)		Sample size	**mean** ± SD (min–max)		Sample size	**mean** ± SD (min–max)
Ring Inactive	n = 39	**942.28** ± 288.95 (479–1531)	*0.0005*[*]	n = 38	**1237.50** ± 272.30 (675–1827)	*0.4858*	n = 32	**1269.06** ± 252.35 (616–1773)	*0.4793*	n = 26	**1231.08** ± 239.90 (617–1653)
Directional Inactive	n = 56	**2035.95** ± 880.84 (916–4546)	*0.0005*[*]	n = 55	**2880.38** ± 810.41 (1419–4585)	*0.5173*	n = 38	**3033.84** ± 788.85 (1480–4370)	*0.4858*	n = 32	**2912.78** ± 842.00 (1439–4435)
Directional Active	*n = 41*	***1870.10*** *± 574.77 (882–3048)*	*0.0018*[*]	*n = 41*	***2337.15*** *± 473.38 (1081–3626)*	*0.1454*	*n = 37*	***2563.95*** *± 555.64 (1066–3683)*	*0.4793*	*n = 28*	***2434.57*** *± 530.76 (1064–3148)*
p[a]	*0.0002*[*]			*0.0002*[*]			*0.0002*[*]			*0.0002*[*]	
p[b]	*0.7926*			*0.0004*[*]			*0.0005*[*]			*0.0519*	
p[c]	*0.0002*[*]			*0.0002*[*]			*0.0002*[*]			*0.0002*[*]	

Mean impedance values from baseline to 12 months of follow-up, compared over time. Data reported in Ohms as mean, standard deviation (SD), minimum and maximum values. *p*-values are for comparison (unpaired test) of values detected over time for all populations.

[a] *p* = *p*-value for comparison between impedances of inactive ring and directional inactive contacts.

[b] *p* = *p*-value for comparison between impedances of inactive directional and active directional contacts.

[c] *p* = *p*-value for comparison between impedances of inactive ring and active directional contacts.

[*] Significance $p \leq 0.05$ (Mann-Whitney test). SD = standard deviation.

Table 4
Comparison of values detected in the same lead, for each patient, in the ring contacts compared with the directional contacts over time.

Leads	***Time***	**Mean** ± SD (min–max)	***Time***	**Mean** ± SD (min–max)	***Time***	**Mean** ± SD (min–max)	***Time***	**Mean** ± SD (min–max)	***Time***	**Mean** ± SD (min–max)	***Time***	**Mean** ± SD (min–max)
Ring Inactive	**Baseline**	**944.63** ± 292.45 (479–1531)	**Baseline**	**958.03** ± 278.23 (538–1531)	**Baseline**	**925.32** ± 278.52 (538–1531)	**1 month**	**1264.28** ± 241.18 (689–1827)	**6 months**	**1280.91** ± 228.03 (663–1717)	**1 month**	**1280.50** ± 240.72 (689–1827)
	n = 39		*n = 30*		*n = 23*		*n = 30*		*n = 23*		*n = 27*	
	1 month	**1237.50** ± 272.30 (675–1827)	**6 months**	**1255.24** ± 246.79 (616–1717)	**12 months**	**1211.68** ± 252.74 (617–1653)	**6 months**	**1255.24** ± 246.79 (616–1717)	**12 months**	**1211.68** ± 252.74 (617–1653)	**12 months**	**1231.08** ± 235.24 (617–1653)
p		*0.00012*[*]		*0.0021*[*]		*0.0072*[*]		*0.8157*		*0.4778*		*0.9494*
Directional Inactive	**Baseline**	**2016.78** ± 815.20 (916–3175)	**Baseline**	**2105.82** ± 788.68 (916–3715)	**Baseline**	**2015.32** ± 797.97 (916–3608)	**1 month**	**2890.15** ± 712.11 (1419–4287)	**6 months**	**3002.36** ± 699.40 (1480–3997)	**1 month**	**2867.97** ± 716.87 (1419–4287)
	n = 42		*n = 35*		*n = 26*		*n = 35*		*n = 26*		*n = 33*	
	1 month	**2854.76** ± 779.71 (1419–4457)	**6 months**	**3007.29** ± 822.30 (1480–4370)	**12 months**	**2846.84** ± 932.48 (1439–4435)	**6 months**	**3007.29** ± 822.30 (1480–4370)	**12 months**	**2846.84** ± 932.48 (1439–4435)	**12 months**	**2912.78** ± 828.74 (1439–4435)
p		*0.0009*[*]		*0.0009*[*]		*0.0153*[*]		*0.2455*		*0.2993*		*0.5905*
Directional Active	**Baseline**	**1870.10** ± 574.77 (882–3048)	**Baseline**	**1899.40** ± 624.75 (882–3048)	**Baseline**	**1812.65** ± 649.50 (882–3029)	**1 month**	**2377.63** ± 471.50 (1081–3626)	**6 months**	**2477.30** ± 503.10 (1066–3171)	**1 month**	**2368.43** ± 469.21 (1081–3626)
	n = 41		*n = 31*		*n = 24*		*n = 31*		*n = 24*		*n = 29*	
	1 month	**2337.15** ± 473.38 (1081–3626)	**6 months**	2466.00 ± 543.40 (1066–3522)	**12 months**	**2369.35** ± 550.15 (1064–3148)	**6 months**	**2466.00** ± 543.40 (1066–3522)	**12 months**	**2369.35** ± 550.15 (1064–3148)	**12 months**	**2434.57** ± 521.19 (1064–3148)
p		*0.0021*[*]		*0.0021*[*]		*0.0232*[*]		*0.5584*		*0.5005*		*0.5584*

Impedance values obtained in the same contact, for each patient over time are reported in Ohms as mean, standard deviation (SD), minimum and maximum values.

[*] *p*-value is for Wilcoxon test (significance ≤ 0.05) for paired samples test. *n* = sample size.

impedance increased independently of the design of the contact. This data is confirmed for all the populations evaluated, by comparing the value at baseline with 6-month and 12-months. Considering only data obtained with the system switched on, we compared the values at 1 month with those at 6 and 12 months, as well as between 6 months and 12 months, with no significant differences at any stage.

4. Discussion

There are only few data on brain impedance variations during chronic DBS in humans (Abosch et al., 2012; Cheung et al., 2013; Sillay et al., 2013). The resistance of the extension cable and the lead wire (about 120 Ω) are constant values in the DBS circuit. In contrast, the electrode-tissue interface changes are responsible for the most impedance variations in patients, depending on the environment of the electrode and the patient's condition (e.g.: fever, dehydration, etc.). Annual MRI control images do not reveal fibrosis or other tissue changes around the electrode, and after years of chronic neurostimulation there is an absence of progressive gliotic scar formation of the tissue and only minor changes compatible with post-traumatic tissue reactions (Haberler et al., 2000; Vayssiere et al., 2002).

For STN ring electrodes of PD subjects which underwent to DBS, a monitoring of the postoperative electrical properties of tissue and electrodes has been reported (Back and Alesch, 2003). The voltage declines between the four electrode contacts but specific tissue resistance could not be calculated because of a significant heterogeneity of the surrounding tissue.

In our study, we retrospectively evaluated PD patients implanted with directional leads in the STN during a follow-up period of one year. After this period, the clinical results (see Table 1) were comparable to those for classical ring contacts, confirming that the directional lead system can be considered a valid therapy. Moreover, the directional facility was used in 47 of the 48 contacts selected, suggesting that the ability to steer the direction of the electric field is useful in clinical practice.

The evaluation of the impedance variation during chronic STN stimulation revealed directional electrodes had higher impedance than the classical linear ring electrodes, in accordance with their smaller surface area (Contarino et al., 2014; Pollo et al., 2014). Moreover, there was a significant difference between the directional lead and the ring lead contacts at baseline (before activation of the neurostimulator) and during follow-up (active DBS). Similar to the classical ring electrodes, the impedance of the directional leads increased over time in a transient mode in the days post-surgery, comparable to the findings obtained by Lempka et al. (2010), but with stabilization of the impedance at six months. A plateau and a later impedance decrease over time was observed during the second part of the year (Fig. 2), although a greater impedance was always noted with the directional lead compared to the ring lead, analogous to experimental data published *in vivo* (Lempka et al., 2009). The impedance's variation is probably due to the chronic electrical stimulation that it causes a separation of proteins and cells from the electrode by the formation of an oxidative film surrounding the DBS lead (Johnson et al., 2005; Lempka et al., 2010). The decrease in impedance values during the last six months of DBS may suggest lower battery consumption, although this hypothesis has to be proved in a study with a larger population. A support in favor of this hypothesis was the absence of any significant parameter variations in our patients between 6 and 12 months.

Our study also confirms that the application of continuous DBS through the active therapeutic directional lead contact produced a decrease in the electrode impedance over time in comparison to the inactive directional lead contacts, with a significant statistical difference and the largest changes occurring within the first weeks of stimulation similarly at which previously reported for radial contact by Hemm et al. (2004).

Before starting DBS, we detected high impedance in the directional leads in the operating room with a rapid decrease five days post-surgery. This was followed by an increase in impedance at day 40, such that impedance was not significantly different to the previous operating room values (Fig. 2). This observation is important for the clinician because the high impedance of the

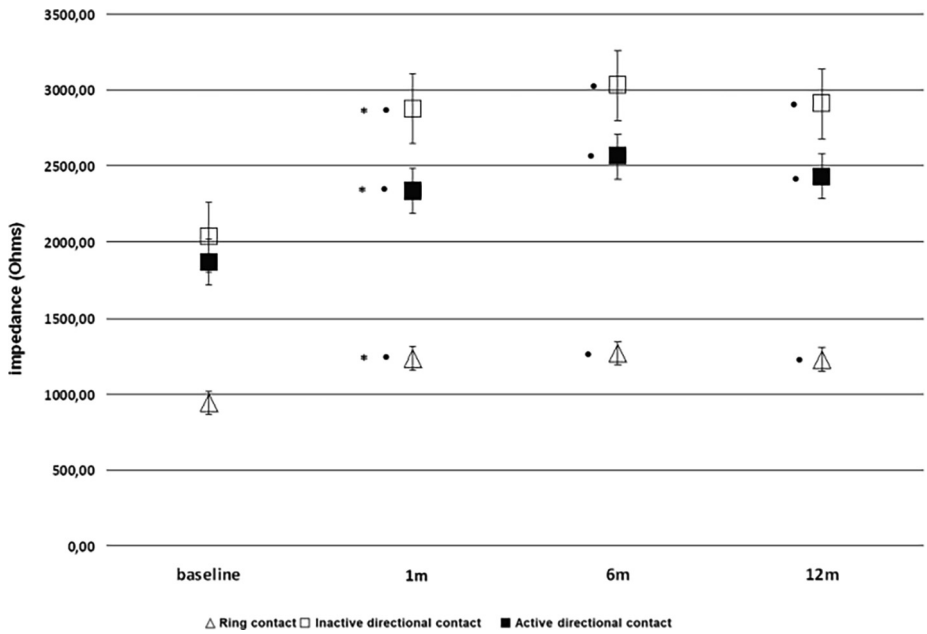

Fig. 2. Variations in impedance during chronic DBS follow-up. The Figure shows the trend of impedances collected at baseline (before turing stimulator on) and after 1, 6 and 12 months of continuous DBS. * = Wilcoxon test significance ≤ 0.05 for comparison of impedances mean values detected at the different times (baseline vs 1 m; 1 m vs 6 m; 6 m vs 12 m). ● = Wilcoxon test significance ≤ 0.05 for comparison of impedances mean values detected at each time (1, 6 and 12 months) in comparison to baseline.

directional leads in the operating room may be not related to a dysfunction of the circuit system, suggesting that it is necessary to evaluate these parameters in a later postoperative period. The reason for this dramatic decline in impedance during the early post-surgical phase could be the result of the transient edema surrounding the electrodes that usually disappears after 40 days.

Several studies have reported changes in impedance over hours to days. In active contacts, impedance has been found to drop after a few hours following acute stimulation (Johnson et al., 2005; Lempka et al., 2009). Rosa et al. found in DBS PD subjects an impedance falls over two days post-surgery, even if it returns to two-thirds of the initial value after one month (Rosa et al., 2010; Rosa et al., 2011). Hence, an impedance daily check of values could be proposed as a measure of cerebral edema variation over time, similar to the instantaneous impedance measurements done during neurosurgical procedures (Diersen and Marg, 1965; Laitinen et al., 1992).

Although greater impedance is observed with the smaller contacts on directional leads compared with the ring electrodes, this is not necessarily an issue as use of a current-controlled system rather than a voltage-controlled neurostimulator can help to maintain a stable VTA. This is because with a current-controlled system, the current delivered is always known and impedance is less of a factor. However, it should be noted that if multiple directional electrodes are utilized, use of a single-source current-controlled system may present some problems because the current will flow through the path of least resistance; thus, the amount of current being delivered to each electrode might change unexpectedly. As reported in Tables 2 and 3, at a specific time point the variability of impedances values of active contacts can be significantly high, with SD up to 574.77 within a range of 882–3048 Ω. A substantial difference is registered also in the same patient; for instance, one active contact was found to be higher than the adjacent active contact by 66%, 3% and 17% at baseline, 6 months and 12 months, respectively. This real example confirms how the role of impedance is relevant in DBS titration and how the selection of a proper DBS directional system is the key and this aspect has been recently discussed by Schüpbach et al. (2017). In particular, a single source system may not allow to have and maintain the most advantageous field, given an inhomogeneous arrangement of the impedances. Moreover, an unexpected fluctuation of the impedances may bring to VTA shift in a single source current control system, with a potential change in the therapy outcome due to side effect elicitation. A system where each electrode is independently controlled by a dedicated current source would allow a more constant VTA to be maintained, despite impedances. Considering a directional DBS system, some observations need to be reported about the edge effects within segmented contacts. As discussed in 2005 by Wei and Grill (2005), in segmented contacts the current density over their surface increases towards the edges of the electrode. In addition, multiple edges, like in directional contacts, increase the inhomogeneity of the current density. Given also a reduced area respect to the conventional cylindrical contacts, a more focal activation may be able to produce the same degree of neuronal activation in the specific target structures (with lower levels of activation outside the target areas) at a lower stimulation amplitude due to the fact that the charge density is more concentrated in a clinical preferred direction. In addition to it, charge density can only be properly controlled by a multiple independent current controlled system (Schüpbach et al., 2017). On the other hand, activating multiple segmented contacts in a single source current control system may be potentially critical in a clinical point of view. A system where each electrode is independently controlled by a dedicated current source (multiple independent current control) would allow a constant VTA to be maintained.

Our retrospective study had some limitations about the data interpretation, such as the "electrode impedance" rather than the "therapy impedance" values measured. However, the detection of electrode impedance is necessary to have a valid comparison between impedances collected from different patients, at different time points. Another criticism could be related to the low sample size (eleven subjects), but the directional leads surgical implantation in humans is a recent technique and a long follow-up of the segmented electrodes is missing in clinical practice. Therefore, the collections of 135 values for the ring contacts, 181 for inactive (non-therapeutic) directional contacts and 147 for active-therapeutic directional contacts represent an excellent first step for evaluating electrode impedances (sample size with alpha of 0.05). Moreover, in this study we do not calculate any correlation between segmented or ring lead's position and the anatomical border of STN because we do not use any dedicated software to estimate VTA or lead position into STN.

Finally, this study was restricted to electrodes associated with the new current-controlled neurostimulator that provides independent current sources for each electrode; thus, the effect of impedance changes on stimulation is minimal (Timmermann et al., 2015). Repeating this study using voltage-controlled or single-source current-controlled neurostimulators might generate different results in electrode impedance or clinical responses. Repetitive impedance measurements of the directional leads are useful to identify hardware issues because an isolated impedance detection in segmented directional contact more than 4000 Ω (our personal experience) cause a suspect of circuit failure in clinician that has only a previous experience in classical ring electrode DBS system.

5. Conclusions

Our study reveals new information about the evolution of brain impedance of segmented directional electrodes, and the results are useful for patient management during the initial test period as well as during the long-term DBS follow-up when high impedance's lead value could be confounding the physicians about a system failure. In fact, in operative room or in post-operative period a suspected circuit break could be thought when the clinician detects a contact with impedance value more than 4000 Ω. The acquisition of consecutive measurements when the system is operating properly appears also to be useful to monitor the relative changes, which can be compared to the clinical outcome and eventually used for troubleshooting. Moreover, a directional electrode combined with a neurostimulator that provides independent current sources for each electrode would be the optimal combination to compensate for any fluctuations in impedance and allow reliable current steering.

Acknowledgements

Sara Grisanti was involved in the data collection and statistical data analysis.

Declaration of Competing Interest

All the authors did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Funding

This research and all the authors did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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