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Original Article

Evaluation of preoperative efficacy of levodopa in subthalamic deep brain stimulation

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Abstract: Objective: Withdrawal of levodopa (L-dopa) the night before subthalamic nucleus-deep brain stimulation (STN-DBS) procedures have been a standard practice, although some patients experienced severe withdrawal symptoms. In this cohort study, we investigated the effects of continuing preoperative L-dopa therapy on intraoperative microelectrode recording (MER), intraoperative cooperation and the clinical outcome for deep brain stimulation (DBS) which was performed under local anesthesia. Methods: The study included 99 patients with Parkinson's disease who were treated with bilateral STN-DBS between October 2014 and August 2018. The patients were followed for 12 months postoperatively and divided into "on-medication" and "off-medication" groups. The length of MER recordings, the number of microelectrode tracks, intraoperation cooperation, operation duration, and clinical outcomes were compared between the two groups. Results: The length of MER recording was longer in the "on-medication" group in both the left and right subthalamic nucleus (STN; P<0.001 and P=0.007, respectively). The unified Parkinson's disease rating scale (UPDRS) motor score indicated better improvement in the "on-medication" group at postoperative one month, six months and twelve months (P=0.045, P=0.034 and P=0.001 respectively). Patients in "on-medication" group could cooperate better with a shorter operation duration (177.9 vs. 195 min, P=0.038). Reduction in L-dopa equivalent dose (LED) and improvement of Hoehn-Yahr scale were comparable between the two groups during the follow-up period. Conclusion: The continuation of L-dopa therapy prior to DBS procedures had no impediment on MER and can contribute to reducing the duration of operation, and benefit the electrode insertion, as well as the clinical outcomes.

Keywords: Deep brain stimulation, microelectrode recording, levodopa, subthalamic nucleus

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease in middle-aged and elderly people. The motor symptoms of PD include static tremors, bradykinesia, rigidity and impaired balance. Treatment options for PD include several anti-Parkinson medications and surgical procedures. For advanced PD patients, deep brain stimulation (DBS) has become an important surgical treatment. DBS can improve the patient's quality of life and reduce drug-induced side effects significantly [1, 2]. Traditionally, surgical procedures require patients to discontinue the use of levodopa (L-dopa) and other anti-Parkinson medications before surgery, so as to assess the effect of intraoperative stimulation [3]. However, some patients experienced severe withdrawal symptoms that can potentially lead to the failure of the operation. Thus, from April 2017, we enrolled patients who continued levodopa therapy before DBS surgery. In this cohort study, we collected the information of operation time, levels of intraoperative neurophysiology markers, unified Parkinson's disease rating scale (UPDRS) motor score (Part III) and L-dopa equivalent dose (LED) to analyze the effects of continuing dopaminergic therapy on intraoperative cooperation, microelectrode recording (MER) and the clinical outcome of DBS performed under local anesthesia.

Patients and methods

Patients

The study included 99 patients with Parkinson's disease who were treated with bilateral subthalamic nucleus-deep brain stimulation

(STN-DBS) in Zhongnan Hospital of Wuhan University from October 2014 to August 2018. L-dopa therapy was applied to all the patients preoperatively from April 2017 to August 2018 (the on-medication group), Also, we retrospectively collected patient data from October 2014 to March 2017, in which the patients were asked to stop using L-dopa one night before operation (off drug group). Of the 99 patients, 37 were in the on-medication group and 62 were in the off-drug group. Informed consent was obtained from each patient and their family members before the operation. This study was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University, and the ethics approval number was 2017081.

Inclusion criteria: (1) Patients who met the diagnostic criteria of primary PD; (2) Patients who were treated with bilateral STN-DBS; (3) Patients who experienced a decrease in anti-Parkinson medication efficacy or drugs-induced serious side effects; (4) Patients with an improvement rate of at least 30% in the L-dopa challenge test according to UPDRS motor score [4]. Exclusion criteria: (1) Patients with severe cognitive impairment, anxiety, depression which impacted patients' daily living ability; (2) Patients with Parkinsonism-plus syndrome or various forms of secondary Parkinson syndromes; (3) Patients with obvious medical comorbidities that affected surgery or survival, or other chronic diseases with an expected survival rate of less than one year.

Surgical procedures

Preoperative evaluation and preparation were consistent with the standard practice and remained the same for the on-medication and off-medication groups. The only difference between them was that on the day of the procedure, the patients in on-medication group took L-dopa (200 mg, Sigma, Lot No. 21104002) according to the patient's daily drug dosage before the stereotactic frame (Leksell G type, Sweden) was installed, while the patients in off-medication group didn't take the drug.

The MRI of patients was taken, and the special sequences were obtained by a 3.0T MR scanner (Trio, SIMENS), and FrameLink surgical planning system (Medtronic, USA) was used to calculate target coordinates, burr hole and the best trajectory. It took about 3 hours from the L-dopa taking to the beginning of MER. The MER record was obtained in all patients under local anesthesia using a single-track microelectrode recording (AlphaOmega, Israel). The micro-electrode was inserted through the center hole of a five-hole array along planned trajectory to the STN, and the recording was started from 10 mm above the target so that we can detect the border of STN. In all the patients, the signal recorded in STN was longer than 4 mm, otherwise another record would be taken while the micro-electrode was placed 2 mm apart from the first track. The neurophysiological identification of the STN was mainly based on increased background activity (neuronal noise) and the irregular firing pattern. The therapeutic electrodes were implanted after obtaining a satisfactory recording and macrostimulation with the recording electrode, and then another test stimulation was given to confirm the efficacy and side effects. After the electrodes were fixed in place, the implantable pulse generator was implanted. Finally, the pulse generator was started, and parameters were set one month postoperatively.

Clinical assessments

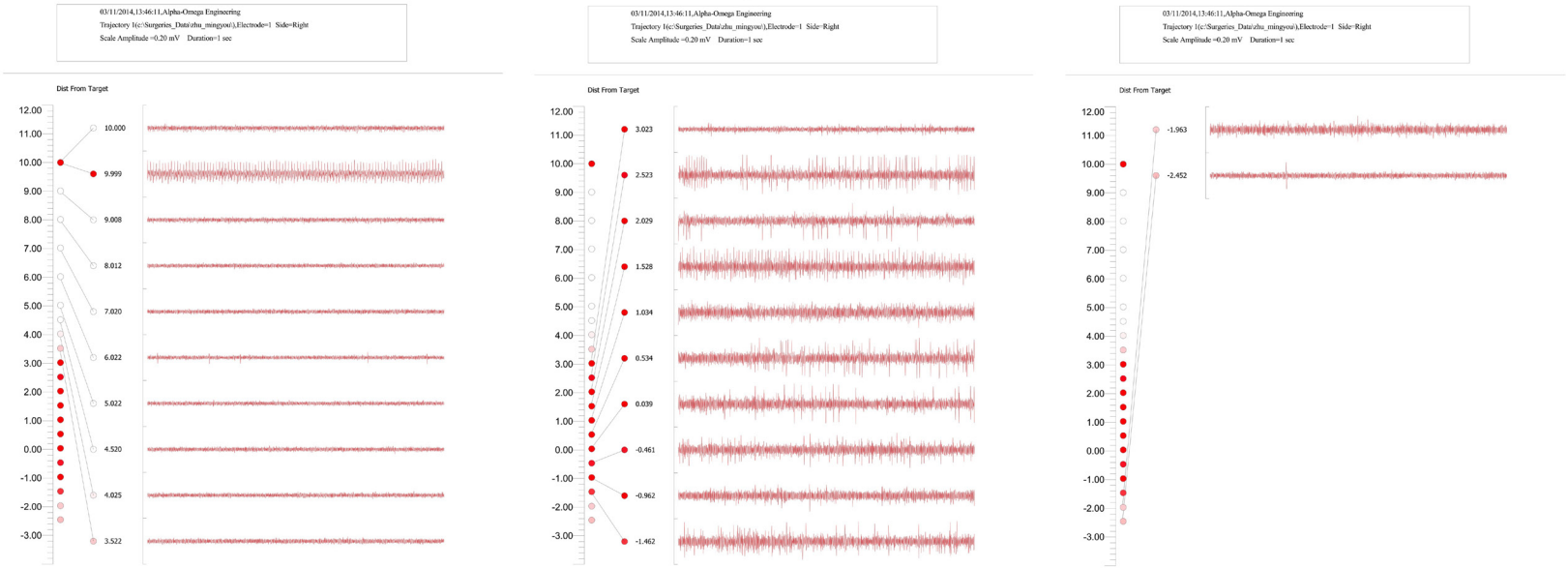
In this study, microelectrode tracks and recordings were used to evaluate the effects of L-dopa on intraoperative neurophysiological recording. The withdrawal symptoms and operation duration were recorded to assess the intraoperative cooperation. The UPDRS motor score was measured in the "off" state with the pulse generator turned on. The reduction of L-dopa equivalent dose and improvement on the UPDRS motor score and Hoehn-Yahr scale were used to evaluate the clinical outcome of DBS during the follow up. The length of MER recordings, the number of microelectrode tracks, intraoperation cooperation, operation duration, and clinical outcomes were compared between the two groups (**Figure 1**).

Statistical analyses

All analyses were performed using SPSS 22.0. All continuous variables were expressed as mean ± standard deviation ($\bar{x}$±sd), and t-test was used for comparison. Count variables were expressed as rate (%), and χ^2 test was used for comparison. For the discontinuous variables, dichotomous variables were transformed into numbers and percentages and compared using

Patient 1

Right side



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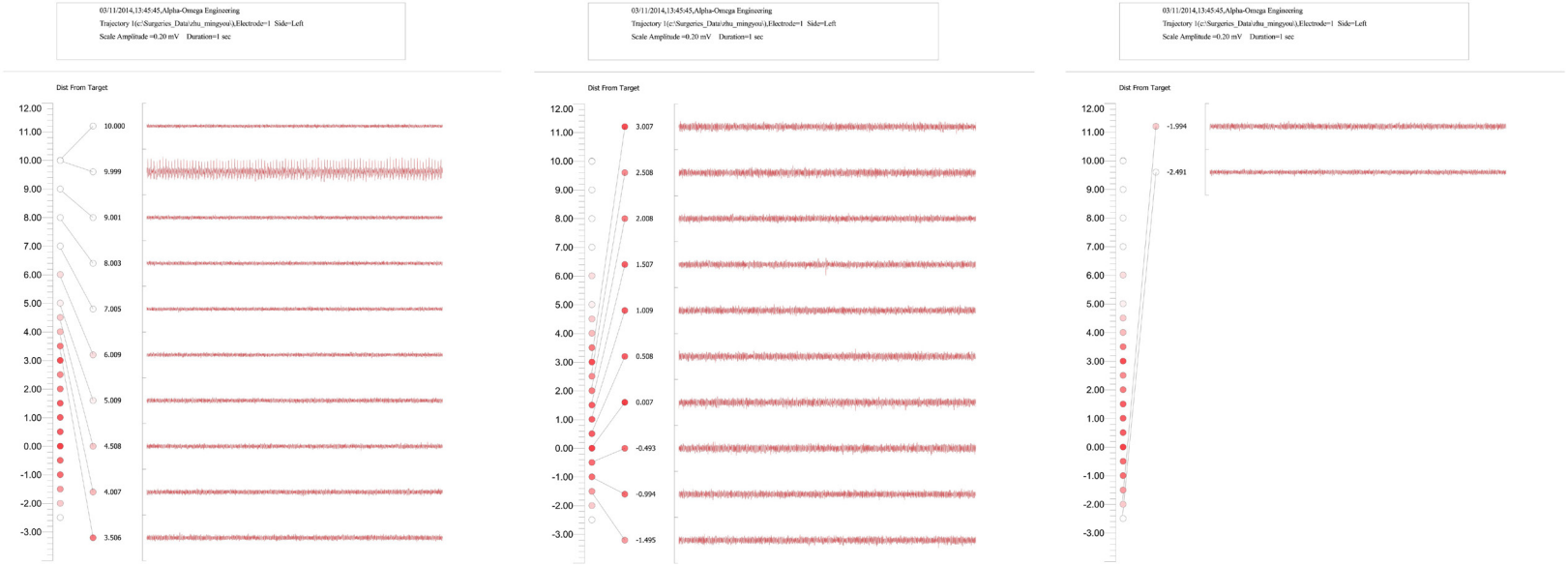

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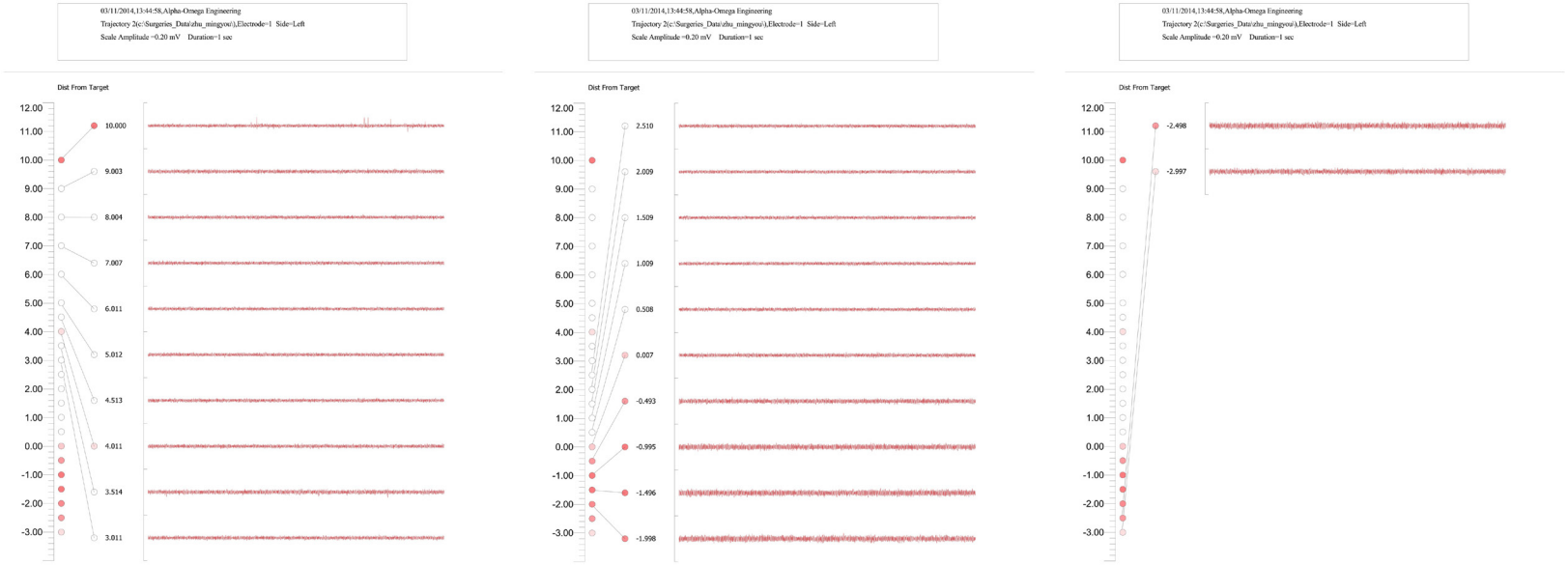

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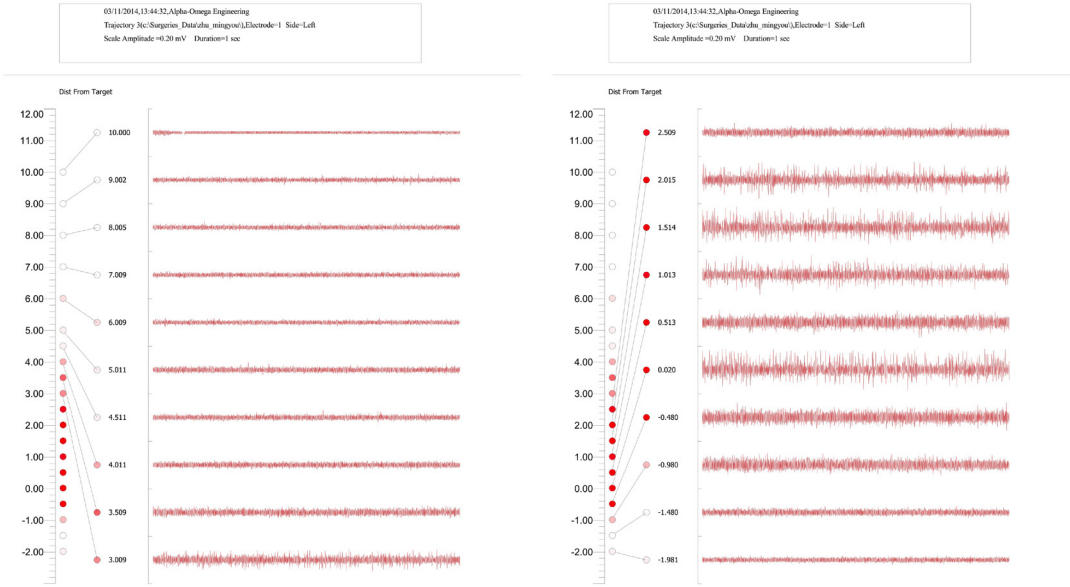
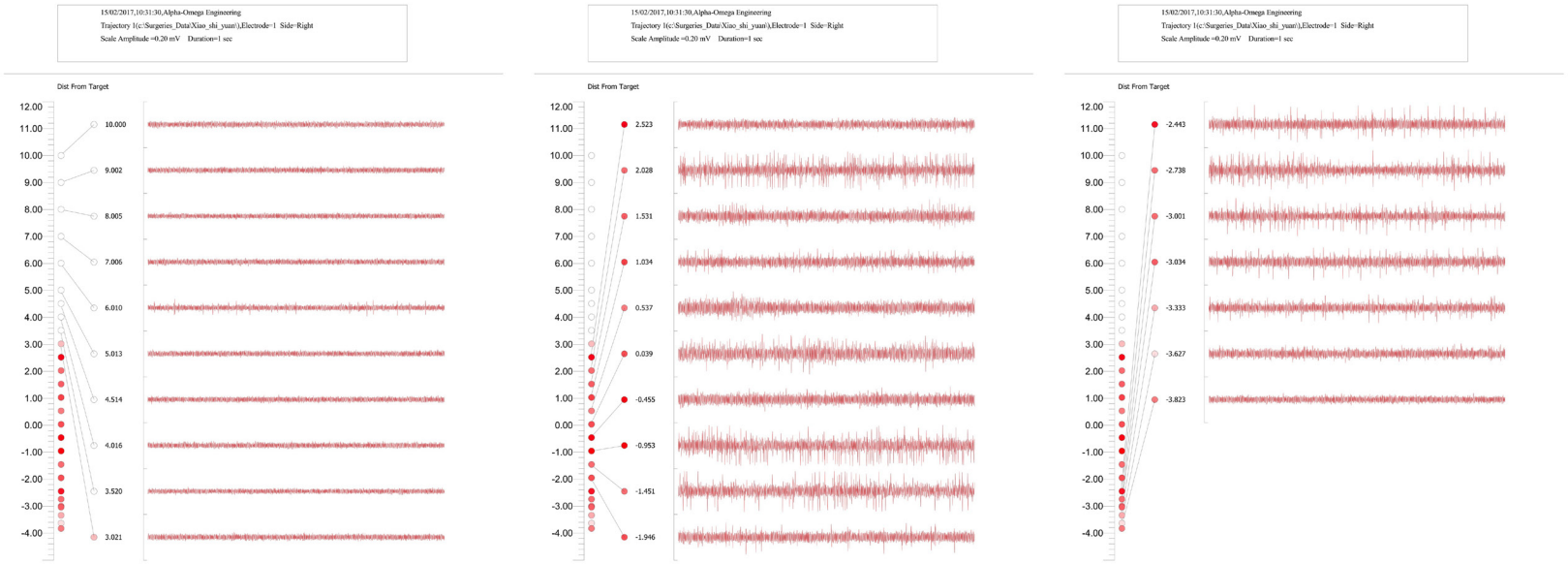


Patient 2

Right side



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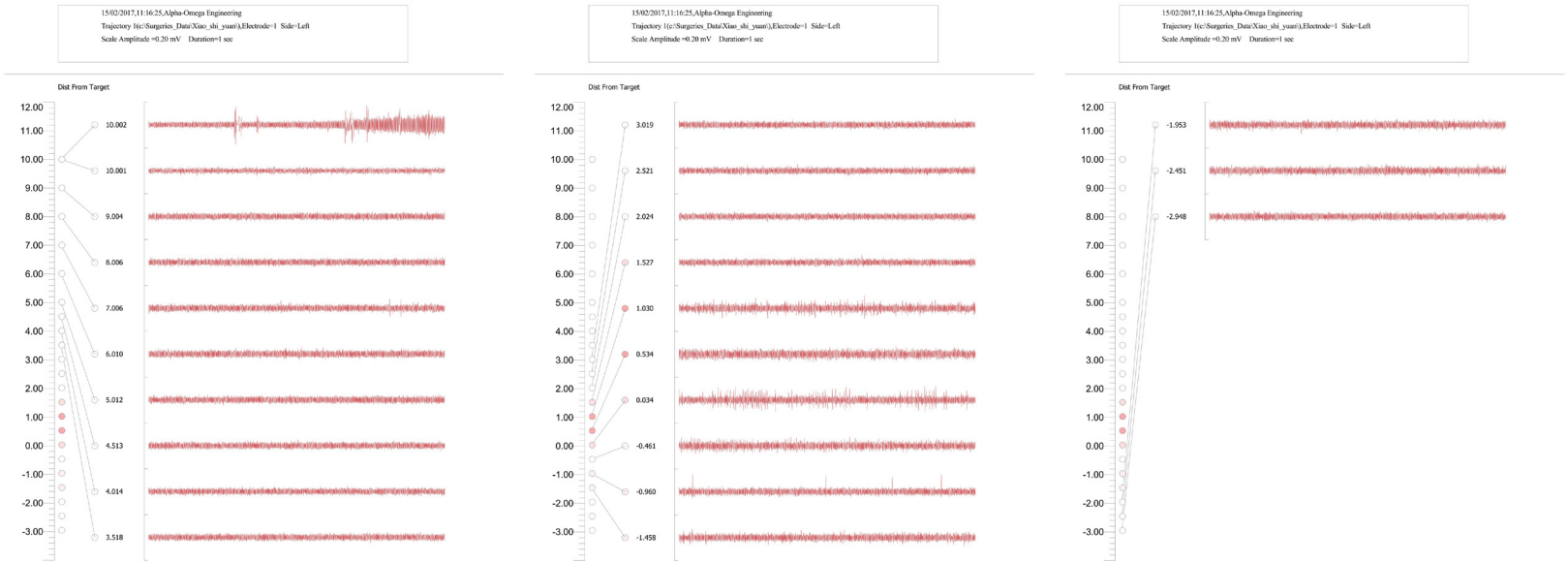

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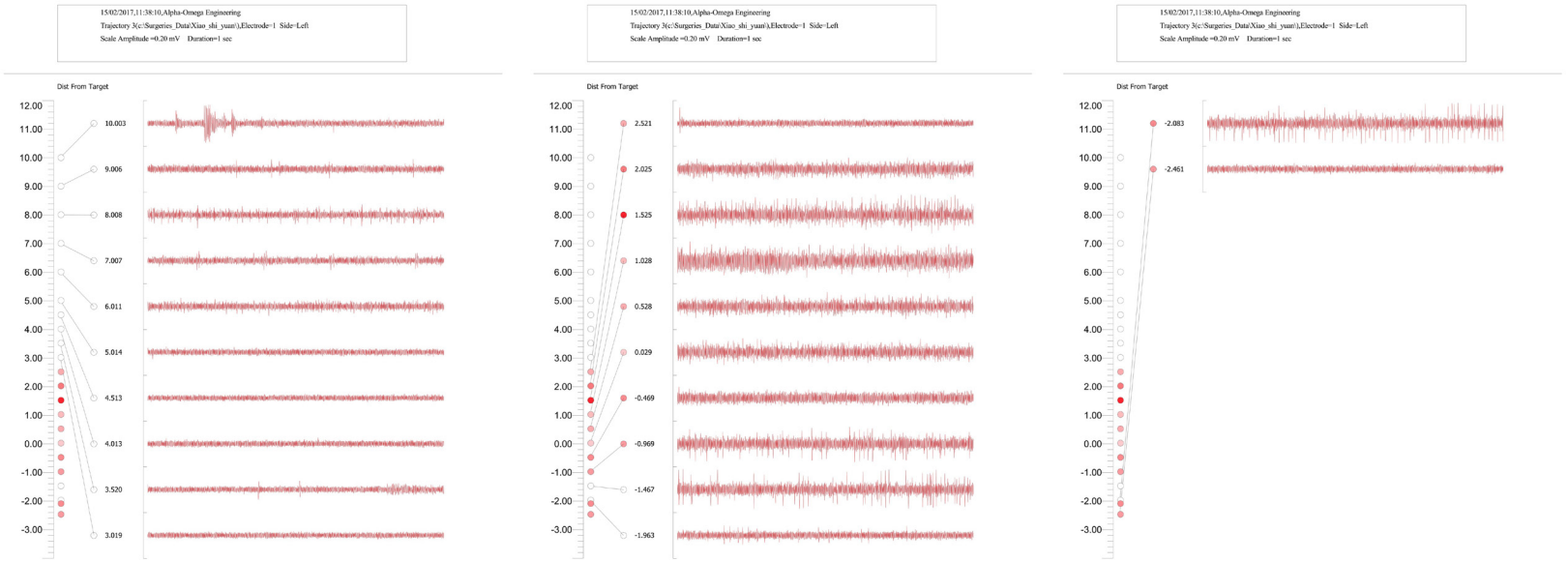

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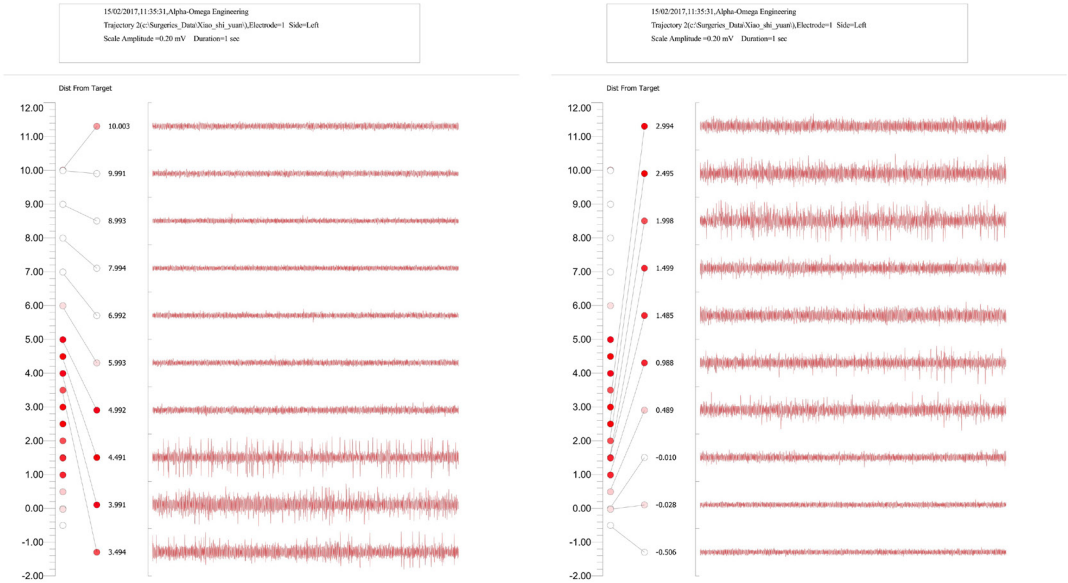
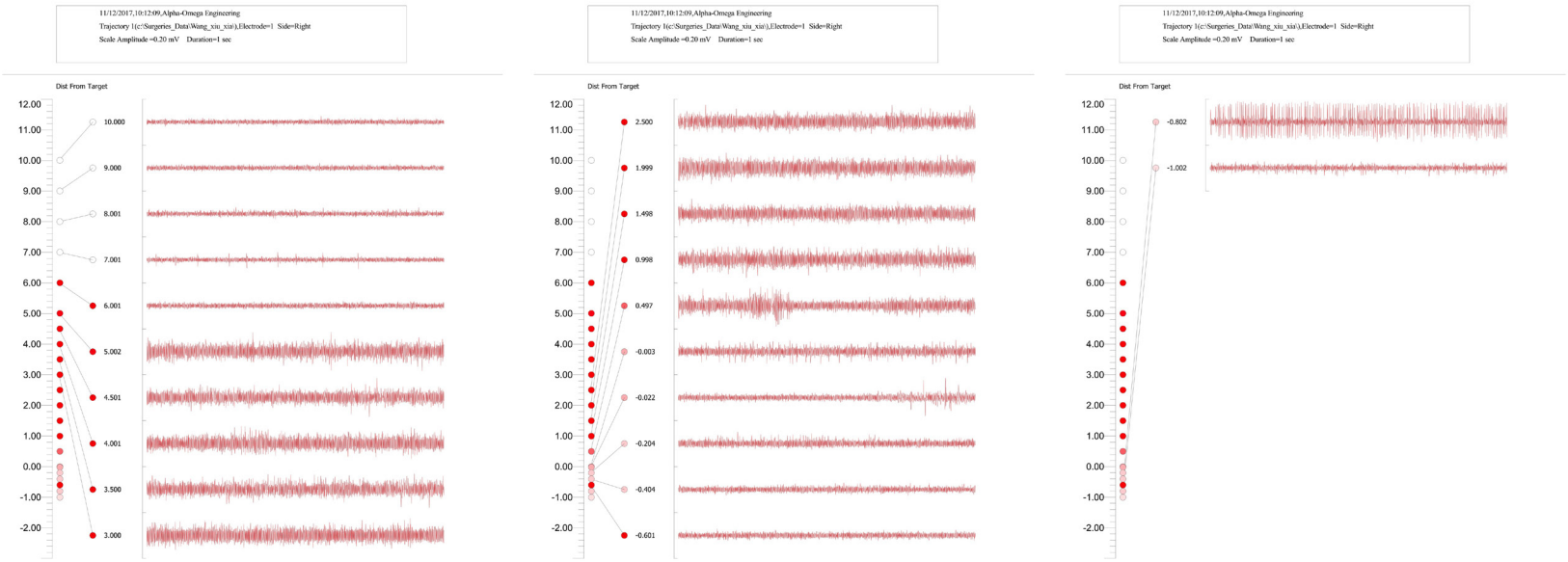


Patient 3

Right side



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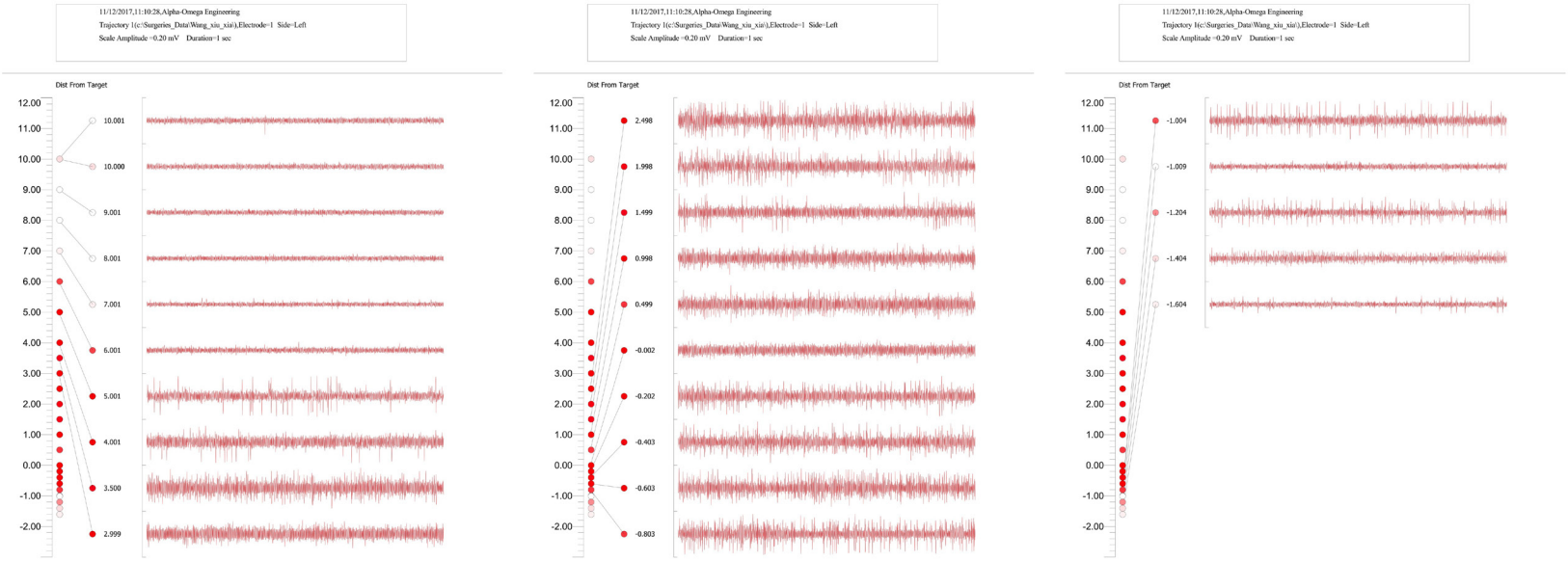

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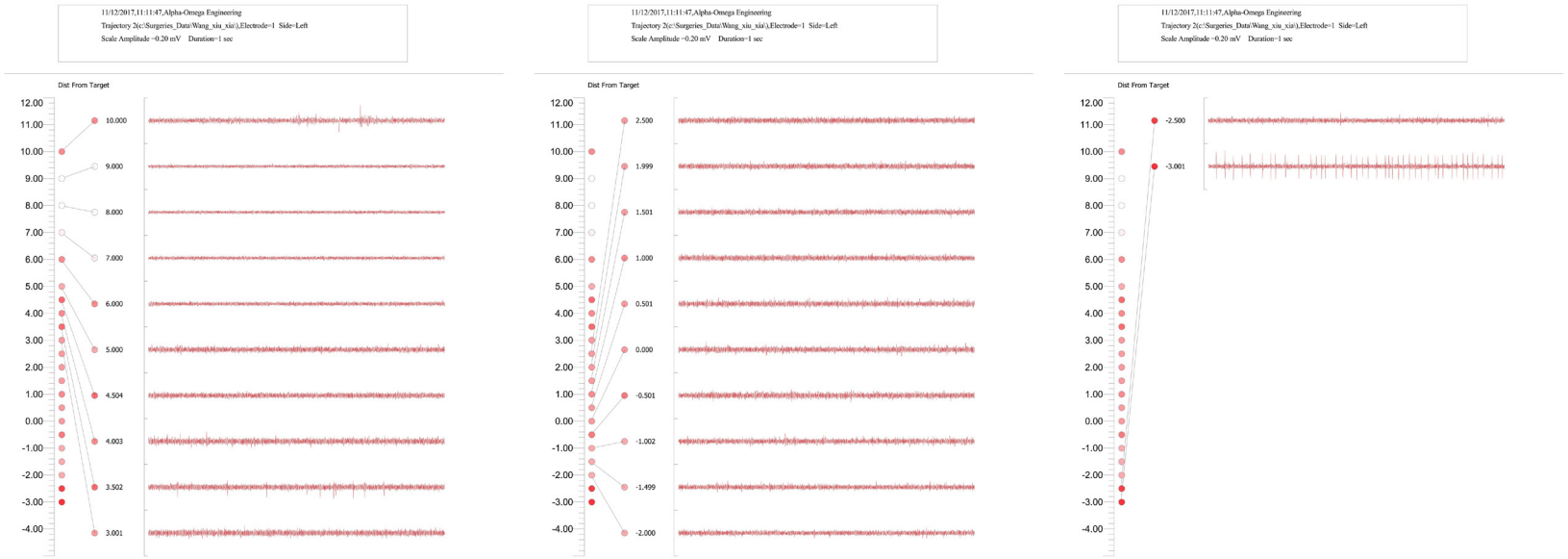

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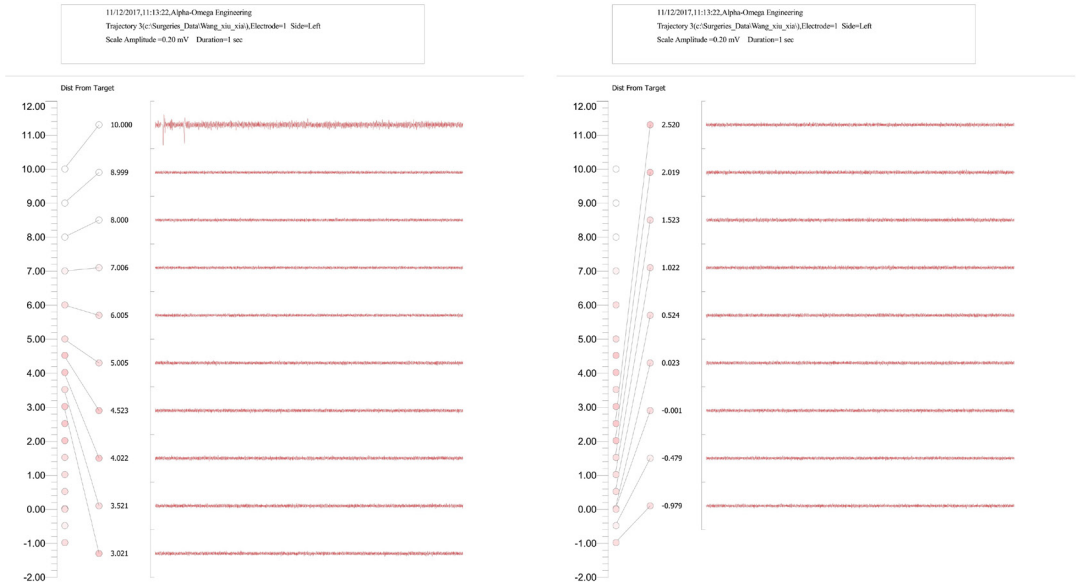

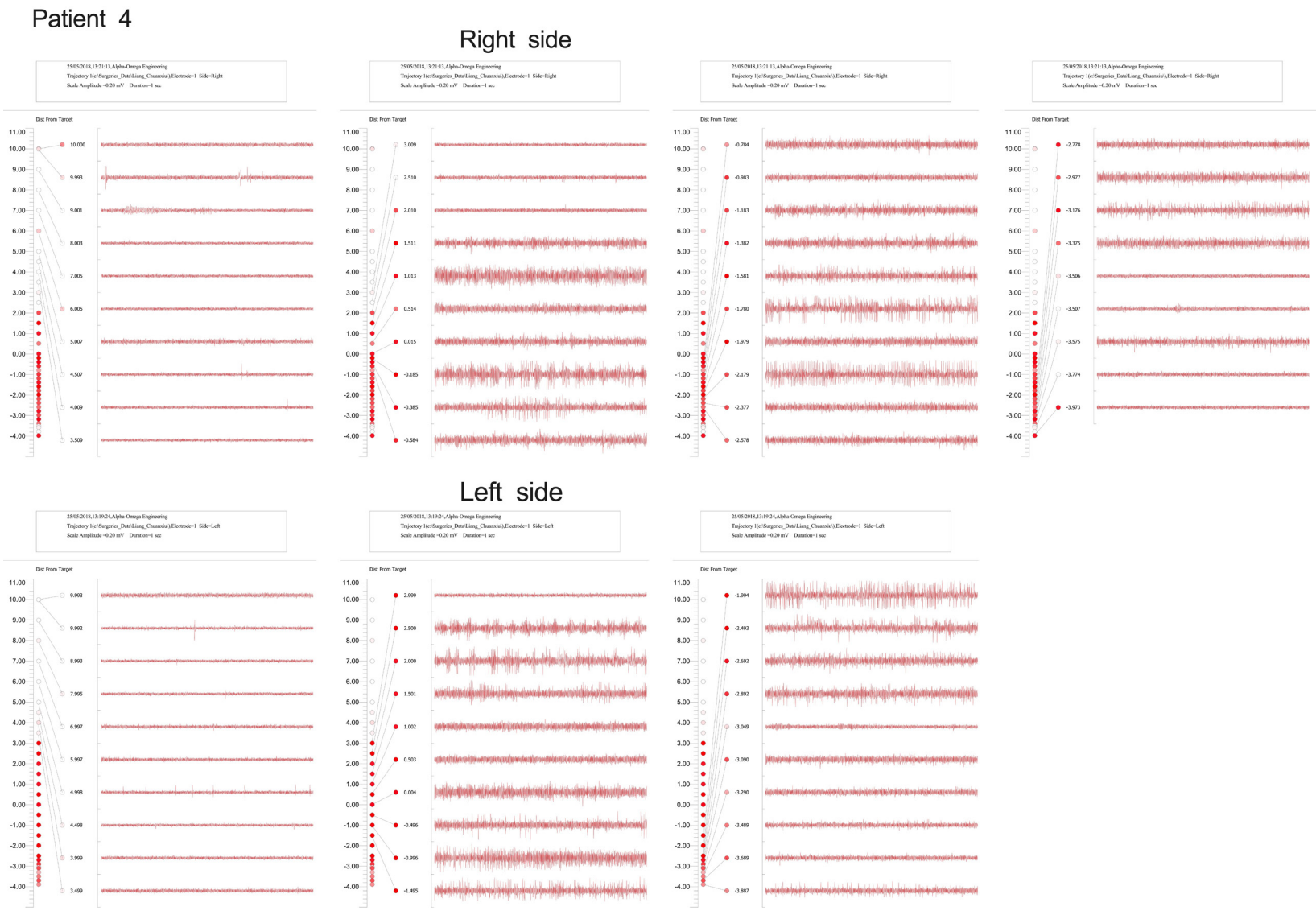

Figure 1. Typical figures of intraoperative neurophysiological recording.

Table 1. Patients' baseline characteristics

	On-medication (n=37)	Off-medication (n=62)	T	P
Age (Y)	60.2±7.0	62.1±7.2	18.524	0.193
Gender (male)	22 (59.5%)	29 (46.8%)	14.211	0.222
Duration of PD (years)	9.1±4.5	9.2±3.6	4.587	0.918
LED (mg)	975.2±462.5	879.5±327.8	13.698	0.233
UPDRS III	41.9±15.1	43.4±14.4	9.253	0.621

Table 2. Hoehn-Yahr scale (preoperative)

Hoehn-Yahr scale	2	2.5	3	4	5	χ^2	P
On-medication (n=37)	2	8	12	11	4	9.563	0.635
Off-medication (n=62)	2	16	15	19	10		

Fisher's exact tests, and ordinal variables were denoted by M (QL, QU) and compared using the Mann-Whitney test. The sample size was estimated according to the binomial enumeration method. Values of $P<0.05$ were considered statistically significant.

Results

Baseline characteristics

A total of 99 patients were enrolled in this study, among them 37 were in the on-medication group and 62 were in the off-medication group. We analyzed age, gender, duration of PD, LED (MG) and UPDRS III for different groups. There were no significant differences in the baseline characteristics between the two groups, P>0.05 (**Table 1**). In addition, we also compared the Hoehn-YahR scale results (preoperative) between the two groups, which showed no statistically significant difference between the two groups, P>0.05 (**Table 2**).

The effects on MER

The number of MER tracks was compared between the on-medication and off-medication groups. The mean length of recording (left) of the two groups was 5.5±0.5 mm and 5.0±0.7 mm, respectively (P<0.05). The mean length of recording (right) of the two groups was 5.4±0.7 mm and 4.9±0.8 mm, respectively (P<0.05). The mean length of MER recording of the on-medication group was longer than that of the off-medication group on either side of brain (**Table 3**). Single track (left) of the two groups was 81.1% and 69.4%, while single track (right) was 86.5% and 82.3%, respectively, showing no statistical significance (all P>0.05). Thus, preoperative L-dopa therapy had no negative impact on microelectrode recording.

The effects on clinical outcomes

No significant differences were detected in the improvement of postoperative H-Y scale between the on-medication and off-medication groups (**Table 4**). There were also no significant differences in the postoperative reduction of L-dopa equivalent dose (LED) [5]. However, during the 12 months follow-up period, the improvement of the UPDRS motor score was higher in the on-medication group compared to that in the off-medication group (**Table 5**).

Intraoperative cooperation and emergence delirium

While no patients in the on-medication group experienced difficulty in intraoperative cooperation (0/37, 0.0%), 7 patients in the off-medication group experienced difficulty during operation (7/62, 11.3%), who had extreme anxiety, sweating, dysphoria, and/or cognitive disorder, perhaps due to severe withdrawal symptoms, and they could not cooperate well with surgeons during the procedure, which led to increasing of operation time. Analysis suggested that the operation duration of on-medication group was shorter than that of off-medication group (**Table 6**). In addition, in the early time after anesthesia recovery, 1 patient from the on-medication group developed delirium tremens (1/37, 2.7%), while 11 patients from the off-medication group experienced emergence delirium (11/62, 17.7%). Both intraoperative cooperation and emergence delirium had a significant difference between on-medication and off medication groups.

Discussion

DBS is a reliable and widely accepted method for the treatment of advanced Parkinson's disease. Generally speaking, the most effective treatment is to require patients to stop using

Table 3. Length of recording and number of single track

	On-medication (n=37)	Off-medication (n=62)	T/χ^2	P
Length of recording (mm) (left)	5.5±0.5	5.0±0.7	90.527	<0.001
Length of recording (mm) (right)	5.4±0.7	4.9±0.8	42.574	0.007
Single track (left)	30 (81.1%)	43 (69.4%)	13.584	0.200
Single track (right)	32 (86.5%)	51 (82.3%)	8.142	0.580

Table 4. Improvement of Hoehn-Yahr scale

Time	Group	Improvement of H-Y scale								χ^2	P
		0.5	1	1.5	2	2.5	3	3.5	4		
12 months	On-medication (n=37)	0	3	9	12	5	6	0	2	8.574	0.509
	Off-medication (n=62)	1	10	14	14	11	9	2	1		

Table 5. Improvement of UPDRS III and reduction of LED

	Group	1 months	P	6 months	P	12 months	T	P
Improvement of UPDRS III	On-medication (n=37)	69.4%±8.4%	P=0.045	70.4%±8.4%	P=0.034	71.4%±9.0%	50.352	0.001
	Off-medication (n=62)	65.5%±9.8%		66.5%±9.0%		64.0%±10.9%		
Reduction of LED	On-medication (n=37)	30.3%±26.0%	P=0.919	36.6%±24.5%	P=0.734	37.8%±25.9%	21.639	0.371
	Off-medication (n=62)	29.8%±18.5%		35.0%±21.9%		32.5%±28.9%		

Table 6. Cooperation rate and operation duration

	On-medication (n=37)	Off-medication (n=62)	T	P
Number of cooperative patients (%)	37 (100%)	55 (88.7%)	30.525	0.043
Operation duration (min)	177.9±36.5	195.0±40.5	37.857	0.038

anti Parkinson drugs before surgery. There are mainly two reasons [3]. The first reason is relevant to patient assessment in the course of the intraoperative stimulation. The second argument supporting the cessation of L-dopa therapy is the potential of interference on MER.

According to clinical research reports, L-dopa can control the symptoms and signs of PD patients only when it reaches the lowest effective concentration [6]. L-dopa has a relatively short half-life of less than 2 hours [7]. When combined with benserazide and carbidopa, the half-life of L-dopa is less than 3 hours [6]. In our practice, on the day of the DBS procedure, patients usually took their dopaminergic medication (Madopa) at 7:00 am, and the microelectrode insertion occurred at approximately 10 am. By that time, most of the L-dopa would have been cleared from the plasma and the amount of L-dopa in the plasma would be below the minimal threshold of concentration. In other words, that would lead to dose failure which was used to describe “off” states [8]. Therefore, the level of L-dopa at that time would not affect the assessment of intraoperative macro-stimulation.

Quite a few technologies have been used in locating the target nucleus, and MER is considered to be reliable [9]. The length of MER record refers to the distance between the boundary of ventral STN and dorsal STN, which provides functional location information. Nevertheless, the length of the MER record is reported as the most useful criterion to select a trajectory [10]. Brain movement is related to the number of microelectrode tracks that needed to pick enough MER signal. If the brain is shifted, we need two or more MER tracks to find the most optimal target. That is to say that the higher rate of single track, the less brain shift, which facilitates precise implantation of electrodes [11].

According to reports by some surgeons, dopaminergic drugs may affect the frequency and synchronization of STN low-frequency oscilla-

tions [12-14]. Our findings had illustrated that there was no significant difference in the number of microelectrode tracks between the on-medication and off-medication groups. However, the length of MER recording in the on-medication group was longer than that in the off-medication group. This consequence suggested that preoperative medication did not prevent the acquisition of electrical signals. These findings also verified that L-dopa did not completely inhibit the electrical activity of the STN [15]. Our results confirmed that it was not necessary to routinely discontinue dopaminergic medications preoperatively. Kocabicak et al. also found that L-dopa did not completely inhibit the electrical activity of the STN, which was consistent with the result of this study [16].

The acute withdrawal of L-dopa may result in the dopaminergic malignant syndrome, intractable dystonia or terrible "off" state [16]. DBS entails many complicated and lengthy surgical procedures. Some patients are unable to tolerate the surgical procedures due to medication withdrawal symptoms. As a consequence, some medical teams had attempted DBS under general anesthesia [17, 18]. Nevertheless, those patients would still have to endure the symptoms associated with withdrawing from anti-Parkinson medications. Recently, Asha et al. reported that inadvertent continuation of medications did not affect the physiological localization of the STN or the clinical effectiveness of DBS under general anesthesia, and the continuation of dopamine therapy was likely to improve the perioperative experience for PD patients [19, 20]. The fundamental purpose for using general anesthesia is to avoid the extreme anxiety and painful dystonia experienced by some patients who are unable to tolerate electrode insertion under local anesthesia [21]. In our study, none of the patients in the on-medication group had difficulty during the course of operation, while 7 patients in the off-medication group experienced difficulty in cooperating. The difference in cooperation between groups was significant. In addition, compared with local anesthesia, general anesthesia has its limitations: the therapeutic effect of intraoperative stimulation and possible side effects cannot be easily judged, which may affect the accuracy of electrode insertion [21]. Thus, we prefer local anesthesia over general anesthesia for DBS. We believed that by continuing L-dopa preoperatively, the use of general anesthesia became unnecessary.

The accurate implantation of electrodes is a determinant factor in maximizing the clinical efficacy of DBS [22-24]. The dorsal part of the STN (i.e., the sensorimotor part) is the target area for electrode localization, and deviation from this area may lead to a decrease in clinical benefit or adverse reactions [25]. The brain shift performs a crucial function in the exact implantation of electrodes in the STN, and the brain shift increases as the duration of craniotomy lasts longer [11]. Compared to traditional practice in which L-dopa was withdrawn prior to the DBS procedures, patients who continued their medications were more surgically tolerant and cooperative in our study, which helped the operation to progress more smoothly. The study of Ivan et al. [11] showed that by allowing patients to continue taking medication before DBS, the operation time was shortened, the leakage of cerebrospinal fluid and brain shift were reduced, thereby ensuring more precise insertion of electrodes, which is consistent with our results. The implantation of electrodes usually started from the right side and the brain did not shift at the beginning, therefore, there were no significant differences between the two groups for the rate of single tracks of right side. On the left side, the on-medication group has shorter surgery duration so that it had the trend to have more single track than the off-medication group. The significant difference may be masked by the limited cohort size.

Even though interesting and rational, there are some limitations in this study. One of them is the study design. A randomized and controlled trial might be more reliable, and a larger cohort size and a longer follow-up duration are required to confirm the findings of this cohort study.

In conclusion, preoperative L-dopa therapy can relieve patients from the adverse withdrawal effects and reduce the operation duration, while having no interference on MER, which would promote the accurate implantation of electrodes and enhance the therapeutic efficiency of the procedure. Thus, preoperative L-dopa therapy offers an alternative option for PD patients undergoing DBS and unable to tolerate the withdrawal symptoms.

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Disclosure of conflict of interest

None.

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