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RESEARCH ARTICLE

# Correlation between programmed stimulation parameters and their efficacy after deep brain electrode implantation for Parkinson's disease

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## KEYWORDS

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## ABSTRACT

**Purpose:** Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an indispensable and effective surgery for patients with primary Parkinson's disease (PD). Nonetheless, its postoperative effects can be decided by many factors including the optimal programmed stimulation parameters. In this study, we analyzed the correlation between different postoperative programmed stimulation parameters and their efficacy after STN-DBS electrode implantation in patients with PD.

**Methods:** A total of 87 patients underwent electrode implantation and completed at least one year follow-up. Then, various combinations of stimulation parameters, including stimulus intensity, frequency, and pulse width, were examined for their effects on the clinical improvement of the patients. Improvements in motor and nonmotor symptoms were analyzed using Mini-Mental State Examination, Parkinson's Disease Quality of Life Questionnaire-39, and Unified Parkinson's Disease Rating Scale (UPDRS) scores before and after surgery.

**Results:** We found significantly improved UPDRS scores, quality of life, and neuropsychiatric symptoms postoperatively considering the findings of the aforementioned stimulation parameters compared with those observed preoperatively.

**Conclusion:** This study provides a better understanding on how programmed stimulation parameters help relieve PD symptoms and improve quality of life in patients with PD undergoing STN-DBS.

## 1 Introduction

Parkinson's disease (PD), the second largest degenerative disease of the central nervous system in China, is common among elderly individuals. Its main clinical manifestations include resting

tremors, muscle stiffness, motor retardation, and postural instability [1, 2]. Deep brain stimulation (DBS) has been widely accepted as an efficient surgical approach since its first application in China approximately 20 years ago [3, 4]. Its minimally invasive, reversible, and adjustable

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characteristics make it an indispensable option.

Several clinical and experimental studies have demonstrated that DBS of the subthalamic nucleus (STN) can effectively control resting tremors, muscle stiffness, bradykinesia, and dyskinesia in individuals with PD [5]. However, its curative effects have been associated with alternative programmed stimulus intensity, frequency, and pulse width. Therefore, we examined various combinations of altering stimulation parameters to determine the correlation between programmed stimulation parameters and their efficacy after DBS electrode implantation for PD.

## 2 Methods

### 2.1 Patients

We recruited a total of 87 patients with PD based on Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's Disease, including 61 males (average age, 61 years; 70%) and 26 females (average age, 64 years; 30%), who underwent electrode implantation by our neurosurgical functional group at the First Affiliated Hospital of Xinjiang Medical University from 2012 to 2018 (Table 1). All patients were preoperatively informed about the benefits and risks of the surgery. All patients signed an informed consent form, and all procedures were approved by the institutional ethics committee.

The selection criteria were as follows: (1) diagnosis of PD, (2) fit for STN-DBS, (3) responsive

to Madopar, (4) course of illness > 4 years, and (5) age  $\leq$  75 years.

The exclusion criteria were as follows: (1) severe cognitive dysfunction due to mental illness, (2) other comorbidities that significantly increase mortality risk, (3) any neuro comorbidities that may interfere with symptoms.

### 2.2 Surgical procedure

All the patients were preoperatively examined using computed tomography (CT) and magnetic resonance imaging (MRI). Then, the patients underwent stereotactic frame installation under local anesthesia during head CT. By fusing CT and MRI images, we determined the precise functional localization of the target coordinates and nucleus using a microelectrode recording system. The positioning of the final implant electrode was determined according to the data acquired for the electrodischarge characteristics of the neurons and needle length. A temporary pulse generator was used for prestimulation. Postoperative CT was used to confirm whether the electrodes were located at both sides of STN.

### 2.3 Study design

All included patients were followed up for 12 months. To explore the effects of different combinations of stimulation parameters on the main motor symptoms of PD, we altered frequency, voltage/current, pulse width, and amplitude during follow-up, after which patients' symptoms

**Table 1** Baseline demographic and clinical characteristics of the included patients with Parkinson's disease ( $n = 87$ ).

Baseline characteristics	Description or mean ( $\pm$ standard deviation)
Age (years)	62 ( $\pm$ 9.6)
Sex	61 males, 21 females
Cardinal symptom	Resting tremors, muscle stiffness, and bradykinesia
Duration of deep brain stimulation (years)	5 ( $\pm$ 2.3)
L-dopa-equivalent daily dose (mg)	540 ( $\pm$ 257)
Course of illness (years)	4 ( $\pm$ 3.2)

including resting tremors, muscle stiffness, and motor retardation were assessed. Accordingly, one parameter was used as a variable, whereas the other two parameters were kept constant. All programmed procedures performed on a patient lasted for  $\leq 4$  h in the morning. All preoperative and postoperative assessments were performed using objective scales.

## 2.4 Statistical analysis

Descriptive statistics were used to describe the patients' general information as well as preoperative and postoperative indices. All data were quantitative, and statistical significance was set at  $p < 0.05$ . During follow-up, scores were analyzed using variance analysis and compared using a randomized group design. Statistical analysis was performed using SPSS (version 23.0).

## 3 Results

Pulse width and frequency were uniformly set at 60–120  $\mu$ s and 130–185 Hz, respectively. Postoperative stimulation voltage was set at  $1.0 \pm 1.0$  V in 38 cases,  $2.5 \pm 1.0$  V in 32 cases at postoperative 6 months, and at  $3.0 \pm 1.0$  V in 17 cases at postoperative 24 months (Table 2). Until December, 2018, stimulation was performed in 48 cases involving single negative contact, whereas 20 cases involving total negative stimulation which also included cases of double negative

stimulation. The remaining cases included cross-electric pulse, frequency conversion stimulation, and inter-frequency stimulation. No severe surgical complications such as intracranial hematoma and electrode fracture were observed in any of the cases. Moreover, 2 patients exhibited improvement in short-term nonmotor symptoms owing to voltage lowering and stimulation site adjustment [6]. Four patients had obvious dyskinesia preoperatively, whereas single negative stimulation did not significantly improve their symptoms after the operation. However, dyskinesia was clearly controlled after double negative stimulation and voltage lowering. Three patients had difficulty in blinking following electrode implantation. After adjusting the stimulation parameters, all patients were followed up through telephone, E-mail, or clinic visitation, with one patient having been lost to follow-up at postoperative 6 months (Table 3).

## 4 Discussion

PD is a common occult neurodegenerative disorder characterized by resting tremors, muscle stiffness, or bradykinesia, which remains incurable to date. Although L-dopa can improve the symptoms of PD, its use is limited by patients' responsiveness to the drug and the length of the "honeymoon" period, which limits its long-term use [7]. Since the 1980s, DBS and other related

**Table 2** Deep brain stimulation parameters.

DBS parameters		Start-up	6 months	12 months
Right STN	Voltage (V)	$1.0 \pm 0.90$	$2.6 \pm 0.90$	$3.0 \pm 0.90$
	Pulse width ( $\mu$ s)	60	$60 \pm 15.50$	$90 \pm 15.0$
	Frequency (Hz)	$125 \pm 27.50$	$138 \pm 27.50$	$140 \pm 27.50$
Left STN	Voltage (V)	$1.0 \pm 1.1$	$2.5 \pm 1.1$	$3.0 \pm 1.1$
	Pulse width ( $\mu$ s)	60	$60 \pm 16.60$	$90 \pm 16.60$
	Frequency (Hz)	$125 \pm 28.50$	$140 \pm 28.50$	$150 \pm 28.50$

DBS, deep brain stimulation; STN, subthalamic nucleus.

**Table 3** Efficacy scores after deep brain stimulation.

	Preoperative	After booting	Postoperative 6 months	Postoperative 12 months
MMSE	23.0 ± 2.39	22.1 ± 2.36	21.2 ± 3.10	23.0 ± 2.50
UPDRS-I	3.25 ± 3.53	2.37 ± 3.07	2.10 ± 2.30	2.21 ± 3.02
UPDRS-II	20.5 ± 10.2	8.75 ± 11.0*	7.20 ± 12.3*	7.0 ± 11.5*
UPDRS-III	47.12 ± 9.0	23.7 ± 10.4*	18.6 ± 10.7*	20.7 ± 11.4
PDQ-39	90.5 ± 3.0	58.0 ± 7.50*	55.0 ± 7.0*	54.2 ± 7.8*

\*,  $p < 0.05$  compared with the preoperative scores, respectively. MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, Parkinson's Disease Questionnaire.

technologies have been developed vigorously, among which STN-DBS has been used most widely. Compared with other approaches, STN-DBS has the advantage of including a clear target, which can directly stimulate STN and block abnormal neural circuits. The mechanism by which STN-DBS exerts curative effects remains unclear. Nonetheless, the key factors in DBS treatment have been accurately implanting stimulus electrodes and obtaining the optimal curative effect with minimum voltage [8]. The optimal clinical efficacy can be obtained by stimulating the conductive fibers present around STN with minimum electricity. STN-DBS can improve the quality of life of patients with PD while reducing the use of L-dopa [9].

In this study, all 87 patients were followed up through long-term programmed control. Among them, 5 patients underwent electrode implantation at a voltage of  $> 5$  V and 1 at a voltage of  $< 2$  V. We observed improvement in motor symptoms in the patients who underwent electrode implantation within a certain range of voltage as well as at the same site, frequency, and pulse width. At a voltage of  $> 4$  V, resting tremors and muscle stiffness could still be improved with increasing voltage; however, the side effects of high voltage became more apparent than its benefits. Ultimately, the effects of programmed control were considered unsatisfactory. Studies showed that a number of patients suffered from

axial symptoms and freezing of gait (FOG), which significantly affected their quality of life [10]. Accordingly, these symptoms could be improved by adjusting other stimulation parameters. The present study included 1 case wherein the use of high-voltage implantation proved inappropriate. Although the results of multiple programmed control were unsatisfactory, continuous current stimulation was used to improve limb stiffness after measuring impedance. Although many studies showed no statistical difference in varied voltage or current for PD improvement [11], continuous current stimulation may be a better choice for patients with high impedance.

Overall, the present studies showed that low frequency was helpful in improving FOG and axial impairment [12–14]. During our follow-up, 10 patients exhibited acute FOG symptoms. Among them, 4 patients showed improvement after choosing a site at the back of the STN as the contact position, lowering frequency, and increasing voltage, whereas 3 showed improvement after setting multiple stimulation. Although lowering the frequency of stimulation (from 130 to 60 Hz) significantly improved FOG in 1 patient, the effect of programmed control rapidly decreased after only 24 h. Thus, this step may not be appropriate for patients with postoperative FOG given that it could lead to the reappearance of resting tremors and muscle stiffness.

In programmed control, pulse width had rarely

been adjusted and often remained between 60 and 90  $\mu$ s. Although recent studies have shown that a narrow pulse width could reduce side effects within the effective treatment window [15–17], our examination showed no obvious difference in effect between a pulse width of > 90 and < 60  $\mu$ s. Accordingly, despite using a narrow pulse width and low voltage in 2 patients, no effective symptom improvement was observed, unlike when a specific pulse width was used. Thus, more evidence-based research may be needed for the selection of a narrow pulse width.

DBS, which is characterized as minimally invasive, reversible, and adjustable, has been a well-accepted surgical treatment for dyskinesia, with postoperative programmed control being an indispensable part [1, 3, 18]. Electrode implantation was initiated at postoperative 1 month to reduce injury and stabilize electrode impedance, during which the patients' condition can be considered good. The initiation of programmed control should be performed at the off medication state to accurately observe the stimulation effect. Most initial parameters used herein were set to be a pulse width of 60  $\mu$ s and frequency of 130 Hz. Further, voltage was adjusted according to the patient's reaction. In theory, motor symptoms could be better improved when voltage is set at 2–3 V, and the therapeutic effect was gradually strengthened by increasing it. Nonetheless, no obvious difference was observed in efficacy between voltage of 2 and 3 V. In addition, stimulation frequency ranging from 130 to 180 Hz was found to improve FOG. Although increasing the stimulation pulse width could improve symptoms, changes in pulse width were not as beneficial as those in voltage and frequency.

Several problems could be resolved immediately when a patient seeks programmed control again. However, gait dysfunction and FOG as well as

other issues need to be programmed repeatedly. With a prolonged course of illness, patients would also need programmed control due to nonmotor symptoms. For example, dyskinesia, an adverse reaction that often occurs after SNT–DBS, can be ameliorated by reducing voltage, dopamine use, and setting double negative stimulation. Moreover, autism involved uncontrollable blinking, a form of dystonia, can be improved by increasing the amount of dopamine, reducing the frequency of voltage regulation and pulse width, and changing the backside contact position.

Given that postoperative programmed control is a long-term and cumbersome dynamic process, this prospective study included patients who underwent bilateral STN–DBS from 2012 to 2018. Accordingly, we found that a single increase in voltage during programmed control does not effectively improve motor symptoms but may often cause stimulation-related complications such as dysarthria. STN–DBS has generally been considered a safe and effective treatment for PD; further, it reduces the dosage and side effects of the drugs used. Moreover, postoperative programmed control is an integral part of DBS.

### Conflict of interests

All contributing authors have no conflict of interests related to this work.

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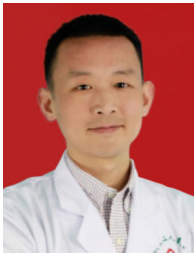
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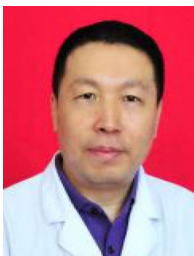
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