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ORIGINAL ARTICLE

Effects of subthalamic nucleus deep brain stimulation using different frequency programming paradigms on axial symptoms in advanced Parkinson's disease

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Abstract

Background In advanced Parkinson's disease (PD), axial symptoms are common and can be debilitating. Although deep brain stimulation (DBS) significantly improves motor symptoms, conventional high-frequency stimulation (HFS) has limited effectiveness in improving axial symptoms. In this study, we investigated the effects on multiple axial symptoms after DBS surgery with three different frequency programming paradigms comprising HFS, low-frequency stimulation (LFS), and variable-frequency stimulation (VFS).

Methods This study involved PD patients who had significant preoperative axial symptoms and underwent bilateral subthalamic nucleus (STN) DBS. Axial symptoms, motor symptoms, medications, and quality of life were evaluated preoperatively (baseline). One month after surgery, HFS was applied. At 6 months post-surgery, HFS assessments were performed, and HFS was switched to LFS. A further month later, we conducted LFS assessments and switched LFS to VFS. At 8 months after surgery, VFS assessments were performed.

Results Of the 21 PD patients initially enrolled, 16 patients were ultimately included in this study. Regarding HFS, all axial symptoms except for the Berg Balance Scale ($p < 0.0001$) did not improve compared with the baseline (all $p > 0.05$). As for LFS and VFS, all axial symptoms improved significantly compared with both the baseline and HFS (all $p < 0.05$). Moreover, motor symptoms and medications were significantly better than the baseline (all $p < 0.05$) after using LFS and VFS. Additionally, the quality of life of the PD patients after receiving LFS and VFS was significantly better than at the baseline and with HFS (all $p < 0.0001$).

Conclusion Our findings indicate that HFS is ineffective at improving the majority of axial symptoms in advanced PD. However, both the LFS and VFS programming paradigms exhibit significant improvements in various axial symptoms.

Keywords Deep brain stimulation · Parkinson's disease · Axial symptoms · Programming · Low-frequency stimulation · Variable-frequency stimulation

Abbreviations

PD	Parkinson's disease
DBS	Deep brain stimulation
HFS	High-frequency stimulation
LFS	Low-frequency stimulation
VFS	Variable-frequency stimulation
STN	Subthalamic nucleus
LEDD	Levodopa equivalent daily dose
PDQ-39	Parkinson's Disease Questionnaire-39
UPDRS	Unified Parkinson's Disease Rating Scale
PIGD	Postural instability and gait difficulty
BBS	Berg Balance Scale
TUGT	Timed Up and Go Test
FOGQ	Freezing of Gait Questionnaire
VHI	Voice Handicap Index

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Introduction

Deep brain stimulation (DBS) is a minimally invasive and adjustable treatment for Parkinson's disease (PD) that significantly improves motor symptoms such as tremors, rigidity, and bradykinesia [12]. However, in advanced PD patients, axial symptoms are also common and can be debilitating. These symptoms mainly include postural instability and gait difficulty (PIGD), balance disturbances, speech disorders, and dysphagia [4, 13]. Axial symptoms such as freezing of gait (FOG) significantly reduce the motor performance of PD patients. This condition intermittently hinders the ability of sufferers to walk in a forward direction [23]. Additionally, axial symptoms exert a significant impact on the quality of life of PD patients because of reduced mobility, loss of independence, and recurrent falls and consequent injuries, all of which result in increased mortality [5]. Equally disabling axial symptoms include speech disorders such as stuttering and dysarthria. Axial symptoms impose a significant burden on both patients and their caregivers, and they represent the most complex clinical challenges in advanced PD [36]. Although the benefits of DBS surgery for motor symptoms are widely recognized, the effect on axial symptoms is difficult to predict. Postoperatively, axial symptoms improve in some patients, remain unchanged in others, and sometimes even worsen [10].

The DBS stimulation frequency may exert an influence on the axial symptoms after surgery in PD patients [17, 32, 34, 38]. Currently, there are no specific criteria for programming frequency classification after DBS surgery [21]. Regarding frequency ranges, some studies define the high-frequency range as being above 100 Hz and the low-frequency range as being below 100 Hz [33, 34, 38]. Other studies set the high-frequency range as 130–185 Hz and the low-frequency range as 60–90 Hz [10, 18, 28], which is the classification criteria we follow in this study.

The high-frequency stimulation (HFS) paradigm is generally applied after DBS surgery and provides long-term benefits for motor symptoms. However, the effect of HFS on axial symptoms is uncertain, and it may even aggravate symptoms [7, 25, 31]. Previous studies have reported that the application of low-frequency stimulation (LFS) or variable-frequency stimulation (VFS), which alternates between high and low frequencies, may alleviate certain axial symptoms [17, 32, 34, 38]. However, a definitive relationship between stimulation frequency and axial symptoms remains unclear. To our knowledge, it has not yet been reported whether multiple axial symptoms in PD patients can be effectively treated by applying the three different programming paradigms of HFS, LFS, and VFS consecutively. Additionally, the effects of motor symptoms, medications, and the quality of life with different stimulation frequencies have also not been thoroughly investigated. In this study, to determine the optimal programming strategy for this challenging problem, we explored the effects of multiple axial symptoms, motor symptoms, medications, and the quality of life in PD patients with the different frequency programming paradigms of HFS, LFS, and VFS.

Materials and methods

Patient selection

In this prospective study, we enrolled PD patients who exhibited preoperative axial symptoms and underwent bilateral subthalamic nucleus (STN) DBS surgery between January 2020 and June 2022 at Huanhu Hospital in Tianjin, China. The inclusion criteria were: (1) Advanced PD patients diagnosed according to the UK Parkinson's Disease Society Brain Bank diagnostic criteria [2]; (2) All PD patients had severe preoperative axial symptoms that seriously affected their quality of life. The exclusion criteria were: (1) Severe cognitive impairment; (2) Severe mental illness; (3) Prior neurosurgery for PD; (4) Other major contraindications to DBS surgery. During the study period, a total of 58 PD patients underwent STN-DBS surgery. Among them, 21 patients presented axial symptoms, while the remaining 37 patients did not exhibit any axial symptoms. Ultimately, 21 PD patients (12 male and 9 female) were enrolled in the study. All participants were required to sign a form providing informed consent. The study was approved by the Ethics Committee of Huanhu Hospital (JH-2020-80).

Study design

All PD patients were initially assessed 1 week before DBS surgery (baseline). The implantable pulse generator (IPG) was switched on, and the HFS paradigm was performed for programming 1 month after surgery. Subsequently, the patients were assessed at 6 months, 7 months, and 8 months post-surgery with different frequency programming paradigms (HFS, LFS, and VFS) in the ON-stimulation/OFF-medication condition.

Surgical procedure

On the morning of DBS surgery, we first installed a Leksell G Frame (Elekta Instruments AB, Sweden) under local anesthesia. After an intraoperative CT scan, the pre-scanned MRI and CT images were combined using the surgical planning system (StealthStation, Medtronic, USA or SinoPlan,

Sinovation, China). Subsequently, the coordinates and entry paths for the target sites were set. The target sites were all located in the dorsolateral STN (sensorimotor area). The STN coordinates were initially set 11 ~ 13 mm from the midline of the anterior commissure-posterior commissure (AC-PC), 2 mm behind the midpoint, and 2 ~ 4 mm below the plane. Next, the target position was refined and adjusted according to the surrounding structure of the STN nuclear mass. The STN target was measured from the midpoint of the upper edge of the red nucleus to about 7 mm in the axial view, and from the outer edge of the inner capsule to at least 5 mm in the crown view. During DBS surgery, microelectrode recording (MER) was employed to perform electrophysiological recording 10 mm from the target site. The final target location was determined according to the specific electrophysiological performance generated by the STN. Four-contact macroelectrodes (L301, PINS Medical, China) were implanted on both sides of the target to test the clinical effects as well as the side effects. A postoperative CT scan of the head was performed to verify the location of the target by merging the surgical navigation system with the preoperative plan. This step also prevented complications such as intracranial hemorrhage. Finally, an IPG was implanted in the chest under general anesthesia.

Clinical evaluation

In this study, we evaluated axial symptoms, motor symptoms, medications, and PD patient quality of life before and after DBS surgery. All assessments were conducted by the same specialist neurologist. One week before DBS surgery, numerous types of assessments without any medication were performed to obtain baseline level data. The PD patients were required to be free of any dopaminergic medications for at least 12 h. At 6 months, 7 months, and 8 months after surgery, various assessments were performed independently regarding the three different programming paradigms (HFS, LFS, VFS) under ON-stimulation/OFF-medication conditions. Axial symptom assessments included the Unified Parkinson's Disease Rating Scale PIGD sub-score (UPDRS-PIGD), Timed Up and Go Test (TUGT), Berg Balance Scale (BBS), Freezing of Gait Questionnaire (FOGQ), and Voice Handicap Index (VHI). The UPDRS-PIGD score is calculated using UPDRS II items 13–15 and UPDRS III items 27–30, with a score of 0–28 points [24]. The TUGT includes the total time to complete the test (TUGT time) as well as the number of FOG spells (TUGT FOG spells). The FOGQ reflects the perception of walking difficulty for PD patients, with higher scores signifying a higher FOG burden (0–24 points). The BBS test is used to assess functional balance, and higher scores indicate better balance (0–56 points). The VHI describes the subjective perception of laryngeal discomfort and impairment regarding voice use in daily life for PD patients. Here, higher total scores signify a more severe subjective self-assessment of speech disorders (0–120 points). Overall motor symptoms were evaluated using total UPDRS III items (UPDRS III-total; 0–108 points). Core motor symptoms included tremors, rigidity, and bradykinesia. Tremor evaluation was performed using the tremor sub-scores of UPDRS III (UPDRS III-tremor), which were calculated using UPDRS III items 20–21 (0–28 points). The rigidity evaluation utilized the rigidity sub-scores of UPDRS III (UPDRS III-rigidity), which were calculated using items 22 from UPDRS III (0–20 points). Bradykinesia evaluation was carried out using the UPDRS III bradykinesia subscores (UPDRS III-bradykinesia), which were determined using UPDRS III items 23–26, 31 (0–36 points). Parkinsonian medications were evaluated using the Levodopa equivalent daily dose (LEDD) calculator, which was based on the findings of Tomlinson et al. [26]. Finally, PD patient quality of life was assessed using the Parkinson's Disease Questionnaire-39 (PDQ-39), which was originally devised by Peto et al. [22].

Postoperative programming

One month after surgery, the IPG was turned on, and the conventional HFS paradigm was performed for programming. The stimulation frequency was set from 130 to 185 Hz. The PD patients usually attended follow-ups at 1-month intervals for adjustments to the stimulation parameters. The HFS paradigm was programmed to adjust the stimulation parameters and improve the motor and axial symptoms of the patients to the greatest extent. Six months after surgery, optimized HFS assessments were performed. After HFS evaluation, the paradigm was switched to LFS, and the stimulation frequency was set from 60 to 90 Hz. In principle, the active contacts, voltage, and pulse width were not altered, while only the stimulation frequency could be changed. At 7 months post-operation, LFS assessments were conducted, then the LFS paradigm was switched to VFS. Similarly, the stimulation parameters other than frequency could not be changed. The frequencies alternated between the high and low-frequency ranges, and the durations of the high and low-frequency stimulation were the same, at 30 s. Eight months after surgery, VFS assessments were carried out.

Statistical analysis

Initially, we calculated the descriptive statistical data, including means and standard deviations (± SD). Subsequently, the Shapiro–Wilk test was applied for normally distributed variables. According to the normality of the data, the assessment outcomes were tested using the one-way repeated measures analysis of variance (rANOVA) or Friedman test

in the different conditions (baseline, HFS, LFS, VFS). The assessment outcomes comprised axial symptoms (UPDRS-PIGD, TUGT time, TUGT FOG spells, FOGQ, BBS, and VHI), motor symptoms (UPDRS III-total, UPDRS III-tremor, UPDRS III-rigidity, and UPDRS III-bradykinesia), medications (LEDD), and quality of life (PDQ-39). Multiple comparisons between the groups were performed using post hoc Bonferroni correction. All statistical data were analyzed using IBM SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). The significance level was set at $p < 0.05$.

Results

Study population

Of the 21 PD patients initially enrolled, five patients who failed to follow up due to incomplete data or tremor aggravation were excluded. Ultimately, 16 patients were included in this study (Fig. 1), of whom there were ten males and six females, with an average age of 64.9 ± 7.6 years and disease duration of 8.3 ± 1.7 years. Preoperatively, all the PD patients suffered from mixed axial symptoms such as gait impairment, postural instability, and speech disorders. All the patients received bilateral STN-DBS (32 electrodes), with 30 electrodes applying monopolar stimulation and two electrodes with double monopolar stimulation. From 1 to 6 months after surgery, all PD patients were given HFS therapy. At 6 months, the HFS paradigm was switched to LFS, and the stimulation parameters were adjusted as follows: left average voltage: 1.9 ± 0.5 V; right average voltage: 1.7 ± 0.4 V; left average pulse width: 65.6 ± 6.1 μs; right average pulse width: 64.4 ± 7.0 μs; bilateral average frequency setting: 147.5 ± 10.9 Hz. At 7 months post-surgery, when LFS was switched to VFS, the bilateral stimulation contacts, voltage, and pulse width remained unchanged, while the bilateral average frequency setting was switched to 72.5 ± 7.5 Hz. At 8 months, the bilateral stimulation contacts, voltage, and pulse width were not altered, but the average high-frequency setting was 153.8 ± 14.1 Hz and the low-frequency setting was 67.5 ± 6.6 Hz. The main clinical characteristics and parameters under the different programming modes are summarized in Table 1.

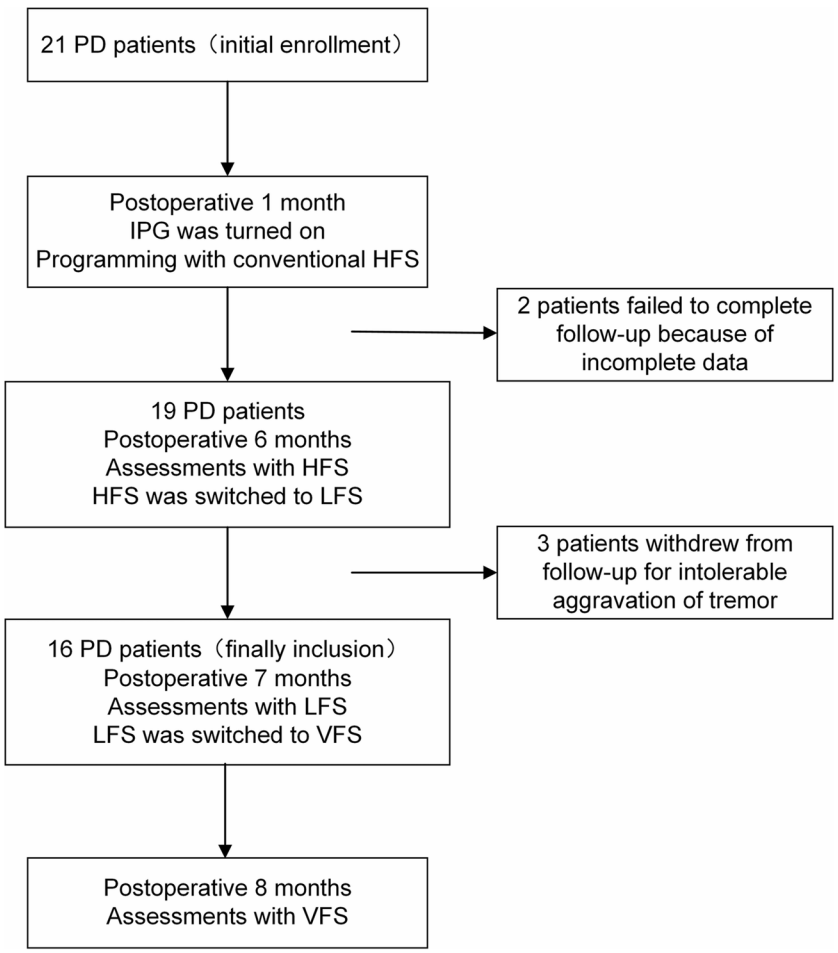

Fig. 1 Flowchart of the selection process for PD patients in this study

Table 1 The main clinical characteristics of PD patients and parameters with different frequency programming paradigms

Patient	Gender	Age	Disease duration (years)	Active contacts	Voltage (V) (HFS, LFS, VFS)	Pulse width (μs) (HFS, LFS, VFS)	Frequency (Hz)		
							HFS	LFS	VFS
PD1	M	72	10.6	L: C + 6-; R: C + 2-	L: 2.6 V; R: 1.7 V	L: 70 μs; R: 60 μs	140 Hz	80 Hz	140 Hz 30 s/70 Hz 30 s
PD2	M	61	7.5	L: C + 7-; R: C + 3-	L: 1.4 V; R: 1.9 V	L: 60 μs; R: 80 μs	150 Hz	70 Hz	160 Hz 30 s/60 Hz 30 s
PD3	F	57	7.2	L: C + 6-; R: C + 2-	L: 1.6 V; R: 1.4 V	L: 70 μs; R: 60 μs	160 Hz	70 Hz	170 Hz 30 s/60 Hz 30 s
PD4	M	72	10.5	L: C + 6-; R: C + 2-3-	L: 1.8 V; R: 2.1 V	L: 60 μs; R: 60 μs	150 Hz	80 Hz	160 Hz 30 s/70 Hz 30 s
PD5	M	68	8.5	L: C + 7-; R: C + 2-	L: 2.1 V; R: 2.7 V	L: 70 μs; R: 80 μs	160 Hz	80 Hz	160 Hz 30 s/80 Hz 30 s
PD6	M	60	5.8	L: C + 6-; R: C + 2-	L: 1.5 V; R: 1.3 V	L: 60 μs; R: 60 μs	130 Hz	70 Hz	130 Hz 30 s/70 Hz 30 s
PD7	F	52	6.7	L: C + 7-; R: C + 2-	L: 2.5 V; R: 1.7 V	L: 80 μs; R: 70 μs	150 Hz	80 Hz	170 Hz 30 s/70 Hz 30 s
PD8	M	62	8.5	L: C + 7-; R: C + 3-	L: 1.8 V; R: 1.2 V	L: 60 μs; R: 60 μs	130 Hz	60 Hz	130 Hz 30 s/60 Hz 30 s
PD9	M	53	7.6	L: C + 6-; R: C + 2-	L: 1.3 V; R: 1.5 V	L: 60 μs; R: 60 μs	130 Hz	60 Hz	130 Hz 30 s/70 Hz 30 s
PD10	M	71	9.5	L: C + 7-; R: C + 3-	L: 2.8 V; R: 1.4 V	L: 70 μs; R: 60 μs	160 Hz	80 Hz	170 Hz 30 s/80 Hz 30 s
PD11	F	66	7.2	L: C + 6-; R: C + 2-	L: 2.1 V; R: 2.1 V	L: 70 μs; R: 70 μs	160 Hz	70 Hz	160 Hz 30 s/70 Hz 30 s
PD12	M	76	10.5	L: C + 7-; R: C + 2-	L: 2.0 V; R: 1.8 V	L: 60 μs; R: 60 μs	160 Hz	80 Hz	170 Hz 30 s/60 Hz 30 s
PD13	F	75	11.5	L: C + 6-7-; R: C + 2-	L: 2.3 V; R: 1.7 V	L: 70 μs; R: 70 μs	150 Hz	70 Hz	150 Hz 30 s/70 Hz 30 s
PD14	F	60	7.5	L: C + 7-; R: C + 3-	L: 1.1 V; R: 1.3 V	L: 60 μs; R: 60 μs	140 Hz	80 Hz	150 Hz 30 s/60 Hz 30 s
PD15	F	60	6.5	L: C + 5-; R: C + 2-	L: 1.6 V; R: 1.4 V	L: 60 μs; R: 60 μs	140 Hz	70 Hz	160 Hz 30 s/70 Hz 30 s
PD16	M	74	7.5	L: C + 6-; R: C + 2-	L: 2.1 V; R: 1.7 V	L: 70 μs; R: 60 μs	150 Hz	60 Hz	150 Hz 30 s/60 Hz 30 s

Primary clinical outcomes

The assessment outcomes of the axial symptoms, including UPDRS-PIGD ($F = 42.42$, $p < 0.0001$), TUGT time ($F = 14.78$, $p < 0.0001$), TUGT FOG spells ($\chi^2 = 33.84$, $p < 0.0001$), FOGQ ($F = 27.10$, $p < 0.0001$), BBS ($F = 44.64$, $p < 0.0001$), and VHI ($F = 9.80$, $p < 0.0001$) exhibited significant differences among the baseline, HFS, LFS, and VFS paradigms under ON-stimulation/OFF-medication conditions using rANOVA or the Friedman test (Fig. 2). Compared with the baseline, HFS (20.6 ± 2.6 vs. 21.3 ± 3.0, $p = 0.133$) did not display a substantial change in UPDRS-PIGD scores, while LFS (14.6 ± 1.7 vs. 21.3 ± 3.0, $p < 0.0001$) and VFS (14.1 ± 1.7 vs. 21.3 ± 3.0, $p < 0.0001$) both demonstrated considerable improvements in UPDRS-PIGD scores using post hoc Bonferroni multiple comparisons. However, there was a statistically insignificant difference in UPDRS-PIGD scores between VFS and LFS ($p = 0.203$) (Fig. 2A). Similarly, with HFS, the TUGT time, TUGT FOG spells, FOG scores, and VHI scores were not significantly better than the baseline. In contrast, LFS and VFS exhibited substantial improvements, indicating the amelioration of gait and speech disorders. Additionally, there was a negligible difference in the TUGT time, TUGT FOG spells, FOG scores, and VHI scores between LFS and VFS (all $p > 0.05$) (Fig. 2B–E). Regarding PD balance disturbances, compared with the baseline, HFS (33.3 ± 7.2 vs. 30.6 ± 6.9, $p < 0.0001$), LFS (37.4 ± 7.9 vs. 30.6 ± 6.9, $p < 0.0001$), and VFS (38.2 ± 7.1 vs. 30.6 ± 6.9, $p < 0.0001$) all exhibited a significant improvement in the BBS scores. Moreover, the improvements gained using LFS (37.4 ± 7.9 vs. 33.3 ± 7.2, $p < 0.0001$) and VFS (38.2 ± 7.1 vs. 33.3 ± 7.2, $p < 0.0001$) were both noticeably better than HFS, according to post hoc Bonferroni multiple comparisons. Nevertheless, there was not a statistically significant difference in BBS scores between VFS and LFS ($p = 0.723$) (Fig. 2F).

Additional clinical outcomes

The overall and core motor symptoms, including UPDRS III-total ($F = 219.04$, $p < 0.0001$), UPDRS III-tremor ($\chi^2 = 40.41$, $p < 0.0001$), UPDRS III-rigidity ($\chi^2 = 35.35$, $p < 0.0001$), and UPDRS III-bradykinesia ($F = 89.08$, $p < 0.0001$), showed significant differences between the baseline and HFS, LFS, and VFS under ON-stimulation/OFF-medication conditions using the rANOVA or Friedman tests (Fig. 3). Furthermore, post hoc Bonferroni multiple comparisons indicated that HFS, LFS, and VFS all led to significant improvements over the baseline regarding the UPDRS III-total scores (HFS: 40.9 ± 3.0 vs. 54.8 ± 3.6, $p < 0.0001$; LFS: 40.5 ± 2.5 vs. 54.8 ± 3.6, $p < 0.0001$; VFS: 39.3 ± 2.5 vs. 54.8 ± 3.6, $p < 0.0001$), UPDRS III-tremor (HFS: 7.6 ± 1.2 vs. 13.4 ± 1.3, $p < 0.0001$; LFS: 9.2 ± 1.1 vs. 13.4 ± 1.3, $p = 0.0076$; VFS: 7.7 ± 1.0 vs. 13.4 ± 1.3, $p < 0.0001$), UPDRS III-rigidity (HFS: 6.4 ± 1.2 vs. 10.6 ± 1.9, $p < 0.0001$; LFS: 6.1 ± 0.9 vs. 10.6 ± 1.9, $p < 0.0001$; VFS: 6.2 ± 1.0 vs. 10.6 ± 1.9, $p < 0.0001$), and UPDRS III-bradykinesia (HFS: 12.3 ± 1.6 vs. 17.8 ± 1.8, $p < 0.0001$; LFS: 12.0 ± 1.7 vs. 17.8 ± 1.8, $p < 0.0001$; VFS: 12.2 ± 1.7 vs.

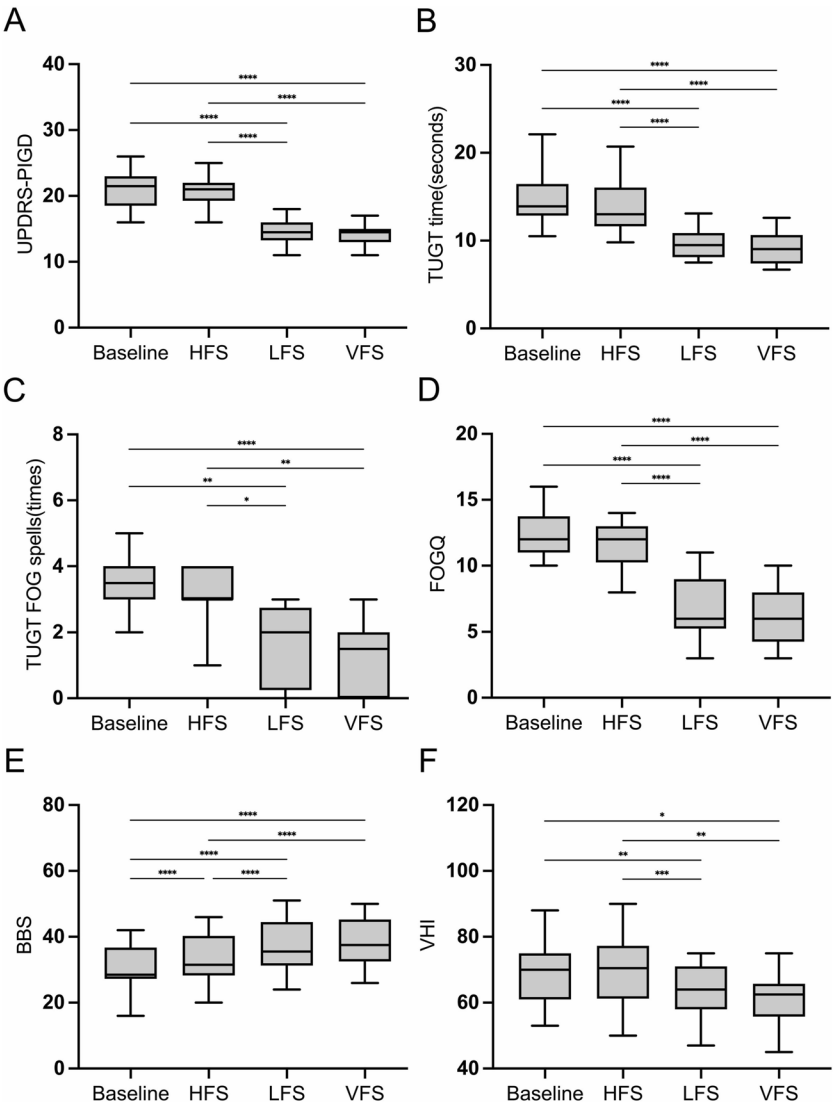

Fig. 2 Comparisons of assessment outcomes on axial symptoms including UPDRS-PIGD (**A**), TUGT time (**B**), TUGT FOG spells (**C**), FOGQ (**D**), BBS (**E**), and VHI (**F**) in the different conditions (baseline, HFS, LFS, VFS). Statistical significance notes: *$p<0.05$; **$p<0.01$; ***$p<0.001$; ****$p<0.0001$. All p values for comparisons not noted in the figure were not statistically significant. PIGD postural instability and gait difficulty, UPDRS-PIGD Unified Parkinson's Disease Rating Scale PIGD sub-score, TUGT Timed Up and Go Test, FOG freezing of gait, FOGQ Freezing of Gait Questionnaire, BBS Berg Balance Scale, VHI Voice Handicap Index, HFS high-frequency stimulation, LFS low-frequency stimulation, VFS variable-frequency stimulation

17.8 ± 1.8, $p<0.0001$) (Fig. 3A–D). However, there were no statistically significant differences among HFS, VFS, and LFS ($p>0.05$), except that tremor control with HFS (7.6 ± 1.2 vs. 9.2 ± 1.1, $p=0.0076$) and VFS (7.7 ± 1.0 vs. 9.2 ± 1.1, $p=0.0137$) was better than with LFS (Fig. 3B). Similarly, according to rANOVA, the LEDD ($F=43.08$, $p<0.0001$) and PDQ-39 scores ($F=52.70$, $p<0.0001$) exhibited significant differences between the baseline and HFS, LFS, and VFS. Additionally, post hoc Bonferroni multiple comparisons indicated that HFS, LFS, and VFS all presented a significant improvement over the baseline in the LEDD (all $p<0.0001$) and PDQ-39 scores (all $p<0.0001$). The LEDD of LFS was significantly higher than HFS (354.1 ± 79.4 vs. 328.8 ± 80.1, $p=0.0035$) and VFS (354.1 ± 79.4 vs. 327.2 ± 83.8, $p=0.0093$), while the PDQ-39 scores of LFS (34.9 ± 6.8 vs. 41.9 ± 5.2, $p<0.0001$) and VFS (33.7 ± 7.0 vs. 41.9 ± 5.2, $p<0.0001$) were considerably better than HFS (Fig. 3E–F).

Discussion

Adjustments to stimulation frequency may exert a significant impact on axial symptoms in patients with PD after DBS surgery. However, existing studies have mainly focused on comparing the effects of two frequency programming paradigms (e.g., HFS vs. LFS or HFS vs. VFS) on a limited selection of axial symptoms [17, 32, 34, 38]. To our knowledge, this is the first study to apply three distinct frequency programming paradigms (HFS, LFS, and VFS) and assess a full range of axial symptoms in a cohort of post-DBS surgery PD patients. We assessed multiple axial symptoms using composite measurements including UPDRS-PIGD, TUGT, BBS, FOGQ, and VHI. Additionally, we evaluated motor symptoms, medications, and quality of life of the PD patients. In summary, this study offers valuable insights into the application of programming paradigms using different frequencies.

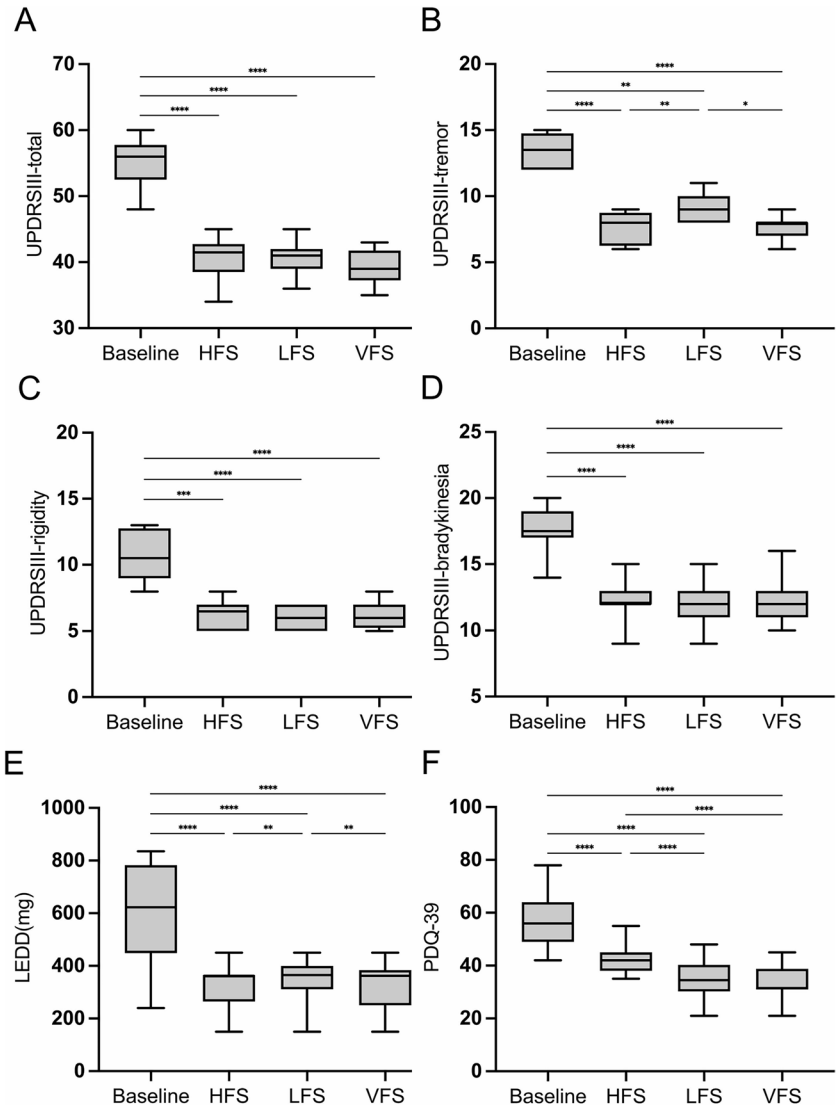

Fig. 3 Comparisons of assessment outcomes on motor symptoms, medications, and the quality of life in the different conditions (baseline, HFS, LFS, VFS). Motor symptoms: **A** UPDRS III-total, **B** UPDRS III-tremor, **C** UPDRS III-rigidity, **D** UPDRS III-bradykinesia; medications: **E** LEDD; the quality of life: **F** PDQ-39. Statistical significance notes: $*p<0.05$; $**p<0.01$; $***p<0.001$; $****p<0.0001$. All p values for comparisons not noted in the figure were not statistically significant. UPDRS Unified Parkinson's Disease Rating Scale, LEDD Levodopa equivalent daily dose, PDQ-39 Parkinson's Disease Questionnaire-39, HFS high-frequency stimulation, LFS low-frequency stimulation, VFS variable-frequency stimulation

Selection of stimulation frequency

In this study, we set the HFS frequency in the range of 130–185 Hz and the LFS frequency in the 60–90 Hz range. Similarly, for VFS, the high and low-frequency ranges were set to 130–185 Hz and 60–90 Hz, respectively. For each frequency programming paradigm, we set a rather wide range, due to the inconsistent changes in symptoms of PD patients at different frequencies. The stimulation frequencies of the specific HFS, LFS, and VFS programming paradigms could be adjusted within a certain range to improve the axial and motor symptoms to the greatest extent. For instance, some PD patients with obvious tremors required a higher frequency to alleviate their tremors, while others experienced more meaningful improvements in FOG at 60 Hz than at 80 Hz. Some previous studies used fixed frequency values for low-frequency or high-frequency stimulation [28, 32, 34]. However, to more closely study the effects of the specific frequency programming paradigms, the frequencies used in our study were within a fixed range. Moreover, using flexible frequency settings was more beneficial to the patients than the fixed frequency setting, thereby allowing participants to complete the study. Within a particular frequency range, the frequency was fine-tuned to determine the optimal stimulation frequency within the frequency programming paradigm.

Assessment outcomes of axial symptoms

We prospectively evaluated a cohort of advanced PD patients using the three frequency programming paradigms of HFS, LFS, and VFS. Most existing studies have reported changes in some aspects of axial symptoms using LFS or VFS, but the findings have been inconsistent [1, 7, 11, 25, 31]. Compared to the baseline, HFS did not lead to any improvements in axial symptoms except for BBS, while both LFS and VFS

produced significant improvements in all axial symptoms, including UPDRS-PIGD, TUGT time, TUGT FOG spells, FOGQ, and VHI. These results demonstrated that the three frequency programming paradigms could all improve PD balance disturbances. However, LFS and VFS were significantly better than HFS in terms of freezing of gait, postural instability, gait difficulties, and speech disorders. Additionally, there was a negligible difference between the effects of LFS and VFS.

The duration of the three frequency programming paradigms was not consistent. In our study, HFS lasted for 5 months, while LFS and VFS only lasted for 1 month each. The main reason for not applying LFS or VFS immediately after poor effects for axial symptoms at HFS was the necessity to make multiple adjustments to programming parameters and active contacts over several months following DBS surgery. One month after surgery we applied conventional HFS, then after a further 5 months, we changed the programming paradigm. We followed the principle of not changing the active contacts, voltage, or pulse width, but only the stimulation frequency. Our purpose was to study the effect of the frequency programming paradigm on axial symptoms and minimize interference from other factors as much as possible.

VFS is a novel stimulation paradigm that enables the alternation between high and low-frequency ranges. The PINS DBS system can cycle between these patterns at different intervals, whether they are transmitted to the same contact or two adjacent contacts [16]. VFS usually involves a cycle of high and low-frequency stimulation, while it can also apply only high or low-frequency stimulation [37]. Previous studies have reported that the number of freezing gait episodes and walking speed improved significantly after applying VFS [15]. In our study, we switched the DBS programming paradigm from LFS to VFS at 7 months post-surgery. After 1 month of applying VFS, similarly with LFS, assessment results revealed significant improvements over the baseline in the overall axial symptoms of PIGD, balance disturbances, and speech.

Additional assessment outcomes

Using LFS, there were significant improvements in motor symptoms, medication reduction, and quality of life in PD patients, compared to the baseline. Although LFS application led to a reduction in tremors, tremor control was significantly lower than with HFS. Notably, three patients withdrew from the study due to the exacerbation of tremors during the transition from HFS to LFS. Thus, for some PD patients with predominant tremors, the improvements in axial symptoms after applying LFS came with the cost of the tremor aggravation. However, we observed that PD patients with predominant tremors could effectively manage their tremors by increasing their medication dosage. Moreover, the overall quality of life using LFS was significantly better than with HFS.

Similar to LFS, VFS also improves the overall and core motor symptoms and reduces medications. Although the control of tremors and medications with LFS was better than the baseline, LFS was considerably worse than HFS and VFS. Ultimately, VFS exhibited superior tremor management and medication reduction than LFS and presented the optimal programming approach for PD patients with severe axial symptoms dominated by tremors.

TEED

To minimize the potential impacts of adjusting other parameters, we maintained the original active contacts, voltage, and pulse width, while modifying only the frequency. Previous studies have shown that maintaining the total electrical energy delivered (TEED) improves the specificity of adjacent structures while preserving beneficial motor effects [8, 29]. Conversely, another similar study did not correct the TEED and found no significant difference in benefits to the LFS paradigm with or without TEED correction [14, 32].

Mechanisms of action

The exact mechanisms of LFS and VFS on the axial symptoms in PD patients remain unclear. Previous studies have shown that the LFS mechanism may be related to the inhibition of pathological neuronal oscillations, enhancement of gamma-band activity, and improvement of freezing gait [6, 33]. Moreover, the amplification of alpha and low beta bands as well as the attenuating high beta power of LFS may affect the internal mapping of the articulates and their afferent feedback [3, 27]. Additionally, the underlying mechanism of LFS on axial symptoms may be related to the pedunculopontine nucleus (PPN), since LFS may affect neural activity in the PPN with the diffused current delivered by the implanted electrode [35]. Furthermore, the mechanisms of LFS and VFS on axial symptoms may be inconsistent. Some studies have suggested that various symptoms of PD may be linked to specific frequency bands [9, 19]. Low gamma oscillations are associated with tremors, beta oscillations are linked to bradykinesia and rigidity, and theta oscillations are related to certain axial symptoms [20, 30]. In contrast to regular pulse train delivery, VFS disrupts certain pathological oscillations by providing a temporal difference in the delivery of electrical stimulation pulses.

Study limitations

There are several limitations to this study. Firstly, there was a lack of blinding for both patients and assessing physicians,

and the performance of the different stimulation paradigms was not randomized. Additionally, the sample size in this study was small, with only 16 cases, and the follow-up time for the application of the LFS and VFS paradigms was short, lasting only 1 month. Therefore, the long-term effectiveness of LFS or VFS on axial symptoms requires further investigation. Finally, the criteria for classifying the frequency programming paradigms in this study must be further explored, and a more reasonable and standardized frequency division should be designed in detail. The VFS programming frequency can be administered across multiple frequency bands, and the stimulation duration can be adjusted for each frequency band. The relationship between different paradigm combinations and axial symptoms also requires further exploration.

Conclusion

In this study, we found that the conventional HFS paradigm was ineffective in relieving most of the axial symptoms in advanced PD. However, both the LFS and VFS paradigms significantly improved various axial symptoms including PIGD, balance disturbances, and speech disorders. At the same time, the LFS and VFS paradigms exerted obvious effects on ameliorating motor symptoms, reducing medications, and enhancing the quality of life of PD patients. In addition, we recommend applying the VFS paradigm for advanced PD patients with significant axial symptoms and simultaneous tremors.

Author contribution Yifeng Cheng, Keke Feng, and Shaoya Yin designed the study. Yifeng Cheng, Guangrui Zhao, Deqiu Cui, and Chunjuan Wang collected and analyzed the data. Deqiu Cui and Chunjuan Wang performed statistical analyses. Yifeng Cheng drafted the manuscript. Lei Chen and Shaoya Yin modified the manuscript. All authors approved the final manuscript.

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Data Availability Not applicable.

Code availability Not applicable.

Ethical approval All procedures performed in the study were approved by the Institutional Review Board of Tianjin Huanhu Hospital (protocol code JH-2020–80) and conducted in accordance with the Declaration of Helsinki.

Consent to participate All subjects signed written informed consent prior to any study activities.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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Comments

Interesting prospective study demonstrating how STN-DBS with LFS and especially VFS can provide relief of PD with dominant axial symptoms. Thus rather than considering STN-DBS less suited for these patients, one may focus on proper stimulation parameter selection to obtain the optimal relief of the individual PD patient symptoms.

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