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Subthalamic deep brain stimulation aggravates speech problems in Parkinson's disease: Objective and subjective analysis of the influence of stimulation frequency and electrode contact location

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ABSTRACT

Background: Speech disorders, including stuttering and hypophonia, have been reported in patients with Parkinson's disease (PD) after subthalamic deep brain stimulation (STN-DBS).
Objective: To evaluate the effect of stimulation frequency or electrode contact location on speech disorders in PD patients with STN-DBS.
Method: In this case-controlled study, we enrolled 50 PD patients with, and 100 PD patients without STN-DBS to compare their vocal intensities, measured by a sound pressure meter, and perceptual speech ratings, obtained from the speech sections of the United Parkinson's Disease Rating Scale (UPDRS) and subjective ratings regarding the impediment of functional communication by stuttering. For patients with STN-DBS, comparisons were made between high-frequency (HFS; 130 Hz), low-frequency (LFS; 80 Hz), and off-stimulation. We also evaluated the effect of electrode contact locations on speech function.
Results: Patients with STN-DBS had decreased vocal intensities and UPDRS scores compared to those without ($p < 0.05$). Vocal intensity was significantly lower during HFS than during LFS and off-stimulation (both, $p < 0.05$). Stuttering impeded STN-DBS patients' communication to greater extent than for those without ($p < 0.001$). Vocal intensity was lower when active contacts were in the dorsal zone compared to those in the ventral zone ($p < 0.05$). Only STN-DBS treatment was a predictive factor for low vocal intensity (OR = 9.53, $p = 0.04$).
Conclusion: High-frequency STN-DBS with dorsal zone contacts can aggravate certain speech problems in PD patients. Therefore, it is important to balance between motor control and speech impairments in these patients.

1. Introduction

Speech disorders can be a significant problem for patients with Parkinson's disease (PD). These disorders can arise at any stage of the disease and vary in severity, however patients at later stages tend to be more severely affected, which may cause a sharp decline in quality of life [1]. Speech production can be difficult, stress or rhythm of speech can be affected, and some patients may stutter [2]. Patients also often begin to lose the ability to form facial expressions or make other gestures that support communicate, leading to a decline in social skills and interactions that may worsen as the condition progresses [3].

Deep brain stimulation (DBS) is an advanced treatment for motor fluctuations and refractory tremors in PD patients, with the subthalamic nucleus (STN) or globus pallidus internus (GPi) as the main targets [4,5]. One advantage of STN-DBS is that medication can subsequently be used at a lower dose, whereas GPi-DBS is more typically used to treat severe levodopa-induced dyskinesia [4,5]. Although motor symptoms tend to improve over the course of treatment with DBS, speech disorders do not improve and may become worse as the disease progresses. While several studies have shown the benefit of DBS of the STN, GPi, and ventral intermediate nucleus of the thalamus (VIM) on motor symptoms in PD [6,7], studies on the effects of DBS on voice and speech are contradictory [8–11], and patients may experience other axial symptoms, such as freezing of gait (FOG), postural instability, and difficulties swallowing [5,12].

Dysarthria, a motor speech disorder, can appear at all PD stages and usually worsens with disease progression [13]. However, a number of studies have reported that DBS-related dysarthria often arises in PD

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patients who receive STN-DBS, but since these symptoms are not uncommon in PD, they cannot be clearly attributed to the adverse effects of STN-DBS rather than disease progression [14–16]. PD patients frequently exhibit patterns of distinct speech phenotypes, including stuttering and hypophonia [3,17,18]. Stuttering interferes with speech fluency and is observed in PD patients independent from DBS [17]. However, Toft and Dietrichs reported that stuttering is often exacerbated by DBS and that patients verbally communicate more easily when stimulation ceases [19]. Moreover, hypophonia, or reduced speech volume, is a common speech dysfunction in PD patients and usually presents as hypokinetic dysarthria, which is additionally characterised by monotonous and breathy speech [3,20]. Taken together, stuttering and hypophonia appear to be directly associated with PD and may be aggravated by STN-DBS [18].

During STN-DBS treatment, high-frequency stimulation (HFS), ranging from 130 to 185 Hz, has been shown to effectively improve motor problems, such as rigidity, bradykinesia, and tremor [21]. Despite these positive outcomes, speech impairment appears to increase directly with stimulation, and may also lead to a deterioration in axial symptoms, including FOG, postural instability, falls, and problems with swallowing [5,12]. Therefore, an alternative approach is required to prevent this exacerbation of axial symptoms following STN-DBS. Researchers have suggested that low-frequency stimulation (LFS; 60–80 Hz) may reduce the risk of these symptoms occurring [22,23]. To date, little research has been carried out to assess the impact of LFS on axial symptoms, and all studies were reported with small sample sizes [24–27].

While the pathophysiology is not fully apparent, previous studies have suggested that LFS is able to alleviate speech problems and other axial symptoms [28,29]. Evidence is still lacking, though, to support altering DBS settings to improve stuttering and hypophonic speech, therefore, the objective of this study was to determine the effects of stimulation frequency and electrode contact location on vocal intensity and perceptual speech rating in STN-DBS patients.

2. Methods

2.1. Study design & participants

This case-controlled study was performed at an outpatient clinic of the Chulalongkorn Center of Excellence for Parkinson's Disease and Related Disorders, King Chulalongkorn Memorial Hospital. The participants were classified into two groups: PD patients treated with DBS (PD-DBS) and PD patients treated with medications (PD-MED) who were consecutively enrolled into the study. Inclusion criteria included a PD diagnosis in accordance with the criteria established by the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria, and aged between 18 and 70 years. Exclusion criteria were a diagnosis of any other condition that may affect speech, including deafness, congenital stuttering, cognitive abnormalities, or psychiatric issues. The PD-DBS group included all PD patients who had undergone STN-DBS treatment at the center from 2008 to 2018 and were following regular clinic appointments. The PD-MED group included PD patients who had regular clinic appointments and continued to take their anti-PD medications on a regular basis. To increase statistical power, patients were recruited at a 2:1 ratio (PD-MED: PD-DBS) [30]. Overall, 100 PD-MED patients and 50 PD-DBS patients were enrolled. Neurostimulator systems were bilaterally implanted into the brains of PD-DBS patients using the model 3389 DBS™ lead (Medtronic, Minneapolis, MN, USA), and computed tomography with a slice thickness of 3 mm permitted the identification of the DBS locations in the STN (Fig. 1). The severity of PD was classified based on the Unified Parkinson's Disease Rating Scale (UPDRS), while the Hoehn and Yahr (HY) score was calculated during the 'on' period by movement disorder neurologists (OP and RB). We also collected demographic and patient characteristic data, including the levodopa equivalent dose (LED) and DBS locations and settings. The

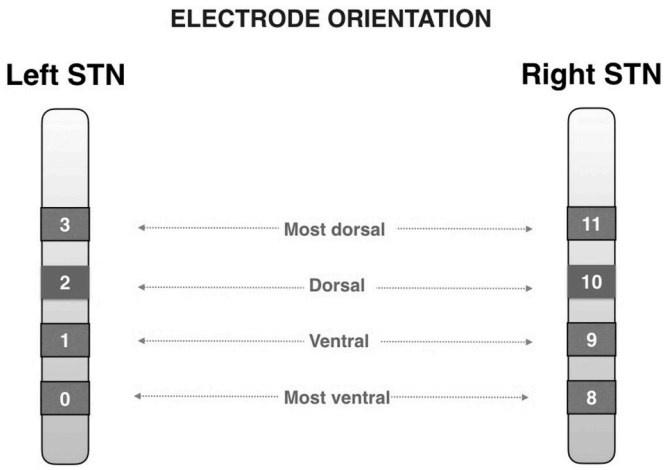

Fig. 1. Electrode orientation on each STN target. Each quadripolar electrode contained four 1.5 mm contacts separated by 0.5 mm. These contacts are traditionally numbered from ventral to dorsal zones as 0, 1, 2, 3 for the left hemisphere and 8, 9, 10, 11 for the right hemisphere. Each contact was further classified into two ventral zone contacts, "ventral" (number 1, number 9) and "most ventral" (number 0, number 8), and two dorsal zone contacts, "dorsal" (number 2, number 10) and "most dorsal" (number 3, number 11). The designations were made on the basis of their locations.

Human Subject Ethics Committee of the Faculty of Medicine, Chulalongkorn University approved this research. Furthermore, informed consent was obtained from all participants prior to participation, based on guidelines of the Declaration of Helsinki.

2.2. Speech assessment

Every patient underwent an assessment of speech and voice disorders. To ensure consistency in clinical interpretation in both parkinsonism and speech evaluation without significant interrater variability, a board-certified neurologist (OP) and a PD nurse specialist (KB) conducted all clinical assessments, and patient's and/or caregiver's concern of communication impediment recorded, to ensure clarity and agreement within the results. The assessments were performed in a soundproof venue during the on-state phase. The PD-DBS patients were evaluated using their regular optimal medication and regular STN-DBS settings, while PD-MED participants were evaluated using their regular optimal medication. According to ICD-10, dysarthria is characterised by poor articulation of phonemes due to problems associated with the muscles that help produce speech, thus making it very difficult to pronounce words. Similar to previous studies observing stuttering [31], participants, who were mainly elderly people with varying educational levels, were asked to read passages from primary school books to prevent any influence from educational differences. These passages were approved by the Ministry of Education of Thailand as a standard learning tool for Thai vowels and consonants. To determine any abnormalities in phonation patterns, participants were requested to carry out sustained phonations, making long and short vowel sounds. Stuttering was considered significant when patients or their caregivers reported it as an impediment to communication. Hypophonia was determined using a digital sound pressure meter (Benetech™, USA) that obtained vocal intensity or loudness, with the microphone situated 15 cm from the patient's mouth. Environmental noise levels during normal conversations are approximately 60 dB, and the vocal intensity of normal speech is approximately 70 dB at a distance of 1 ft. Therefore, a vocal intensity of less than 70 dB may lead to communication difficulties. Perceptual speech ratings were recorded by physicians and patients using recognised rating scales. Physicians assessed symptom severity using the speech sections of the UPDRS (UPDRS-2/item 5 and UPDRS-3/item 18), and patients completed the Voice Handicap Index

(VHI) to identify speech disorders and voice abnormalities in terms of physical, functional, and emotional dysfunction. Vocal intensities and perceptual speech ratings were measured in the PD-DBS group during HFS (130 Hz), LFS (80 Hz), and off-stimulation. The effects of electrode contact location on voice/speech were also analysed. The off-stimulation condition was assessed 30 min after stimulation cessation.

2.3. Statistical analysis

Independent t-tests, Mann-Whitney U tests, and Chi-square tests were used to compare the clinical backgrounds and voice/speech functions of patients in the PD-DBS and PD-MED groups. The comparisons of voice/speech functions between the three conditions (HFS, LFS, and off-stimulation) were made with a repeated-measures ANOVA. To identify predictors for low vocal intensity (less than 70 dB), we conducted a binary logistic regression using the prevalence of low vocal intensity as the dependent variable and participant-related parameters as independent variables. The logistic model was conducted using the enter method in order to select the most predictive variables of low vocal intensity, and the predictors are reported as odds ratios (ORs). All analyses were performed using SPSS Version 22 software (Chicago, IL, USA), and $p < 0.05$ was considered significant.

3. Results

3.1. Demographic data

Demographic data of all participants are shown in Table 1 and Supplementary Table 1. There were no significant differences between PD-DBS and PD-MED groups in demographic information, including gender, age, duration of disease, current LED, and HY scores ($p > 0.05$). However, the mean vocal intensity of PD-DBS patients was significantly lower than that of PD-MED patients ($p < 0.05$) and the VHI scores of PD-DBS patients were significantly higher than those of PD-MED patients ($p < 0.05$). The three subscale scores of the VHI (physical, emotional, and functional) were also significantly higher in the PD-DBS group than in the PD-MED group ($p < 0.05$ for all three sections). In addition, the speech sections of the UPDRS scores for daily living activities (UPDRS-2) and motor function (UPDRS-3) were significantly lower in the PD-DBS group than in the PD-MED group ($p < 0.001$). The percentage of patients whose stuttering impeded communication was higher in the PD-DBS group (36%) compared with the PD-MED group (8%, $p < 0.001$).

In the PD-DBS group, all patients received bilateral STN-DBS. Prior to surgery, the mean disease duration was 147.07 months (SD ± 54.55) and the mean duration since the surgical procedure was 45.78 months (SD ± 38.81). The mean pre-operative LED (1353.56 mg, SD ± 372.14) was significantly higher than the post-operative LED (867.30 mg, SD ± 463.87, $p < 0.05$). There were also no significant differences in the mean pre-operative UPDRS-3 score during the 'on' period of PD-DBS group and the 'on' period of PD-MED group with regards to the total UPDRS-3 scores (29.08 points, SD ± 11.02 vs. 27.78 points, SD 9.69), the speech sections of the UPDRS-2 scores (1.10 points, SD ± 0.65 vs. 1.04 points, SD ± 0.89), and the speech sections of the UPDRS-3 scores (1.00 points, SD ± 0.45 vs. 1.11 points, SD ± 0.91) ($p = 0.461$, $p = 0.675$, $p = 0.421$, respectively). Additionally, the mean pre-operative UPDRS-3 score during the 'on' period (29.08 points, SD ± 11.02) was numerically, but not significantly ($p > 0.05$), higher than the post-operative UPDRS score during the 'on' period (28.04, SD ± 12.97). The monopolar setting was the most widely applied and constituted 76% and 72% of the left- and right-sided STN lead positions, respectively. In left-sided STN, the ventral zone contacts were set as the active cathodes for 20 (40%) of the PD-DBS participants, while the remainder used dorsal zone contacts. In right-sided STN, 26 (52%) of the PD-DBS participants had active ventral zone contacts, while the remainder had dorsal zone contacts. During the experiments, PD-DBS participants were stimulated with a constant voltage. The mean amplitude in the right-sided STN and left-sided STN was 2.99 V (SD ± 1.14) and 3.01 V (SD ± 0.98), respectively. The mean pulse width in the left-sided STN and right-sided STN was 75.00 μs (SD ± 21.44) and 75.62 μs (SD ± 18.56), respectively. The mean frequency for all STNs was 127.81 Hz (SD ± 13.83). The percentage of patients in the PD-DBS group for whom the caregivers' assessment indicated that stuttering impeded communication were 36% during HFS, 12% during LFS, and 8% during the off-stimulation.

3.2. Differences between HFS, LFS, and off stimulation

In the evaluation process, all PD-DBS patients were stabilised at HFS settings. However, during LFS, two patients exhibited tremors and were unable to continue with the off-stimulation. Comparative data between HFS, LFS, and off-stimulation shows that vocal intensity was lowest during HFS ($p < 0.001$), followed by LFS ($p = 0.006$), and highest during off-stimulation (Table 2 and Supplementary Fig. 1). However,

Table 1
Comparison of demographic data of all 150 Parkinson's disease patients.

Item	PD-DBS (N = 50)	PD-MED (N = 100)	*p*-value
Age (years)	60.79 ± 9.46	63.37 ± 9.64	0.128$^{\beta}$
Male gender	34 (68%)	53 (53%)	χ^2 (1, *N = 150*) = 3.079, $p = 0.079^{\varphi}$
Disease duration (months)	149.27 ± 54.68	134.24 ± 43.59	0.122$^{\beta}$
Current LED (mg)	867.30 ± 463.88	889.13 ± 389.39	0.769$^{\beta*}$
Current HY score during the 'on' period (points)	3.16 ± 1.00	2.99 ± 1.13	0.371$^{\beta}$
Current total UPDRS-3 scores during the 'on' period (points)	28.04 ± 12.97	27.78 ± 9.69	0.891$^{\beta}$
The speech sections of the UPDRS-2 scores/item no.5 during the 'on' period (points)	2.44 ± 0.95	1.04 ± 0.89	< 0.001$^{\beta*}$
The speech sections of the UPDRS-3 scores/item no.18 during the 'on' period (points)	2.34 ± 0.96	1.11 ± 0.91	< 0.001$^{\beta}$
Vocal intensity during the 'on' period (dB)	68.87 ± 6.99	77.60 ± 7.07	< 0.001$^{\beta*}$
• PD-DBS: on medication and on stimulation			
• PD-MED: on medication			
VHI functional score (points)	23.12 ± 8.44	14.2 ± 9.42	< 0.001$^{\beta*}$
VHI physical score (points)	20.74 ± 8.48	14.44 ± 5.26	< 0.001$^{\beta*}$
VHI emotional score (points)	19.34 ± 9.58	10.45 ± 2.83	< 0.001$^{\beta*}$
Stuttering impeding conversation during the 'on' period	18 (36%)	8 (8%)	χ^2 (1, *N = 150*) = 1.405, $p = 0.236^{\varphi}$
• PD-DBS patients were assessed during HFS stimulation			
• PD-MED patients were assessed during on medication			

$^{\varphi}$: Chi-square test; $^{\beta}$: Independent t-test; *: Statistically significant; PD-DBS patients were assessed during HFS stimulation; Value in parentheses are shown as percentage; dB: decibel unit; PD-MED: Parkinson's disease patients treated with medications; PD-DBS: Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation; HFS: High frequency stimulation; LED: Levodopa equivalent dosage; HY: Hoehn & Yahr score; UPDRS: The Unified Parkinson's Disease Rating Scale; VHI: Voice Handicap Index.

Table 2
Comparison of speech parameters of 50 Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation (PD-DBS) in three conditions with High frequency stimulation (HFS), low frequency stimulation (LFS), and off-stimulation.

Item	HFS	LFS	Off-stimulation	*p*-value
Vocal intensities	68.87 ± 6.99	74.97 ± 6.72	76.94 ± 7.38	< 0.001[X*]
The speech sections of the UPDRS-2 scores/item no.5	2.44 ± 0.95	1.58 ± 0.70	1.60 ± 0.88	< 0.001[X*]
The speech sections of the UPDRS-3 scores/item no.18	2.34 ± 0.96	1.58 ± 0.64	1.70 ± 0.84	< 0.001[X*]

[X]: One-way Repeated-measured ANOVA; *: Statistically significant; UPDRS: The Unified Parkinson's Disease Rating Scale.

UPDRS speech sections scores were significantly higher during HFS compared to LFS and off-stimulation ($p < 0.001$ for both sections 2 and 3), but between LFS and off-stimulation no statistically significant difference was seen. The significant difference on vocal intensity, but not the UPDRS speech section scores, between LFS and off-stimulation may be related to better sensitivity of objective nature of vocal intensity measurement.

3.3. Association between speech abnormalities and active contact location

Table 3, Fig. 1 and Supplementary Fig. 1 demonstrate that speech disorders were influenced by the active contact location in PD-DBS patients. In the left STN, the vocal intensity was lower when active contacts were made in the dorsal zone rather than the ventral zone. Compared to active dorsal contacts, active ventral contacts were associated with higher intensity during HFS, LFS, and the off-stimulation ($p = 0.033$, $p = 0.002$, and $p = 0.008$, respectively). These findings were almost replicated in the right STN, with active ventral contacts showing significantly higher intensity during HFS and LFS ($p = 0.018$ and $p = 0.021$, respectively).

3.4. Determining the predictors for lower volume intensities

A logistic regression analysis was conducted to identify predictors for low vocal intensity (Table 4) using the following variables: PD-DBS group, age, female sex, disease duration, current HY score during the 'on' period, and current total UPDRS-3 scores during the 'on' period. Results from the logistic regression indicated that there was a moderate relationship (34.7%) between these predictors and low vocal intensity. The overall prediction success was 74.1%. The enter method criterion demonstrated that only STN-DBS (OR, 9.53) was a strong predictive factor for low vocal intensity ($p = 0.04$).

4. Discussion

The present study compared the influence of DBS frequency on stuttering, as the primary outcome, and vocal intensity as a secondary outcome. Our findings demonstrate that the PD-DBS group exhibited lower volume intensity values and increased stuttering compared to the PD-MED group. Moreover, they show that in comparison to LFS, HFS decreased vocal intensity and increased stuttering when measured subjectively using conversational communication and objectively using a sound pressure meter. These results provide evidence that HFS contributes to the deterioration of speech in PD patients. Future studies should evaluate if the vocal intensity is enhanced following a reduction in stimulation frequency.

Previous studies have demonstrated that DBS negatively affects speech functions, therefore, to further understand these side effects, we examined the differences in volume intensity and stuttering between PD patients undergoing DBS and those taking conventional medication. Our results suggest that STN-DBS contributes to speech problems and that PD patients treated with STN-DBS are 9.53 times more likely to have a lower vocal intensity than those who were not. Furthermore, our findings are consistent with those of a previous review suggesting that the causes of speech problems were the consequence of disease progression, STN-DBS, or medication reduction [32]. However, two previous meta-analyses did not find a relationship between medication reduction and verbal fluency decline following DBS [33,34].

The role of the STN, as part of the basal ganglia, is to control motor functions through the basal ganglia-thalamocortical motor circuit, which is active during the development of stuttering [35]. Similar to results from a previous study [19], our findings also show that stuttering might be improved by decreasing stimulation frequency. This suggests that stimulation of the STN or nearby structures may worsen stuttering [19]. Our findings are consistent with earlier reports that indicate that lesions of the basal ganglia-thalamocortical motor circuit play a role in the development of stuttering [19,36]. Moreover, our results support earlier findings that LFS in STN-DBS can improve a number of symptoms, including swallowing, axial symptoms, and FOG [23].

According to the literature, STN-DBS via ventral contacts enhances positive emotions in comparison to stimulation via dorsal contacts [37]. Moreover, when the active contact is positioned in the ventral zone of the STN, it is possible for the current to pass into the associative and limbic regions, resulting in a number of related psychological problems linked to cognition [37,38]. However, while dorsal contact stimulation enhances motor functions in PD-DBS patients better than ventral contact stimulation [37], our study revealed that though both active contact locations reduce the vocal intensity, this is especially marked when contacts are made in the dorsal zone, in agreement with a previous study [39]. This phenomenon may result from the stimulation spreading into the adjacent internal capsule, which contains corticobulbar fibres [39]. In addition, a previous study has demonstrated that the decline in both mental status and verbal learning scores, six months post-surgery, can be attributed to the dorsal location of electrodes in the left hemisphere [39]. In the right hemisphere, laterally positioned electrodes were associated with a decline in verbal short-term memory [39]. Additionally, STN-DBS is linked to more severe declines in swallowing and speech function, which can again be attributed to anatomical location, with stimulation effects spreading to the corticobulbar tracts adversely affecting swallowing and speech [40,41].

This study used a case-controlled approach to objectively assess speech outcomes under different DBS settings. In the PD-DBS group, participants were assessed under three DBS settings within a single day to eliminate variations over time and the assessments were consistently performed during the 'on' period. This study investigated clinical vocal/speech outcomes in PD patients undergoing bilateral STN-DBS using both objective measurements and perceptual rating scales. Our results demonstrate that objective tools may be more sensitive than subjective tools for clinical assessments [42]. While previous studies reported that subjective measurement may lead to inaccurate vocal intensity interpretations [31,42], our study provides evidence of better sensitivity with objective assessment. As speech problems can be linked to emotional symptoms such as social withdrawal, depression, and loss of confidence, the potential to detect speech problems amongst DBS patients earlier may help physicians to adjust medications and/or stimulation settings to improve a patient's quality of life before social and/or emotional problems occur [3,43,44].

This study has certain limitations. Firstly, we could not assess the effect of LFS on speech problems in patients with pre-existing oral

Table 3
Comparison of demographic data of 50 Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation (PD-DBS) with the active contact on each STN target.

Item	Left STN		Right STN		*p*-value	
	Ventral contact (N = 20)	Dorsal contact (N = 30)	Ventral contact (N = 26)	Dorsal contact (N = 24)		
Age (years)	60.68 ± 10.34	60.86 ± 9.03	60.42 ± 9.45	61.17 ± 9.67	P_A=0.924$^{\beta}$	P_B=0.718$^{\beta}$
Disease duration (months)	152.78 ± 63.89	142.96 ± 47.47	148.45 ± 57.09	145.62 ± 52.88	P_A=0.715$^{\beta}$	P_B=0.842$^{\beta}$
Current LED (mg)	877.83 ± 586.94	860.28 ± 372.53	931.21 ± 503.19	779.84 ± 400.45	P_A=0.711$^{\beta}$	P_B=0.364$^{\beta}$*
Current HY score during the 'on' period (points)	2.95 ± 0.96	3.30 ± 1.02	2.96 ± 0.97	3.37 ± 1.01	P_A=0.219$^{\beta}$	P_B=0.132$^{\beta}$
Current total UPDRS-3 scores during the 'on' period (points)	26.42 ± 14.06	29.10 ± 12.34	26.35 ± 13.26	30.04 ± 12.63	P_A=0.381$^{\beta}$	P_B=0.259$^{\beta}$
Vocal intensities during HFS stimulation (dB)	71.59 ± 6.17	67.05 ± 7.01	71.01 ± 5.78	66.54 ± 7.55	P_A=0.033$^{\beta}$*	P_B=0.018$^{\beta}$*
Vocal intensities during LFS stimulation (dB)	78.28 ± 6.35	72.76 ± 5.96	77.04 ± 6.32	72.72 ± 6.52	P_A=0.002$^{\beta}$*	P_B=0.021$^{\beta}$*
Vocal intensities during off-stimulation (dB)	80.22 ± 6.30	74.79 ± 7.34	77.92 ± 6.95	75.79 ± 7.86	P_A=0.008$^{\beta}$*	P_B=0.234$^{\beta}$*
The speech sections of the UPDRS-2 scores/item no.5 during HFS stimulation (point)	2.40 ± 0.82	2.47 ± 1.04	2.35 ± 0.98	2.54 ± 1.10	P_A=0.866$^{\beta}$	P_B=0.446$^{\beta}$
The speech sections of the UPDRS-2 scores/item no.5 during LFS stimulation (point)	1.65 ± 0.48	1.53 ± 0.82	1.46 ± 0.65	1.71 ± 0.75	P_A=0.568$^{\beta}$	P_B=0.272$^{\beta}$
The speech sections of the UPDRS-2 scores/item no.5 during off-stimulation (point)	1.65 ± 0.88	1.57 ± 0.89	1.35 ± 0.85	1.88 ± 0.85	P_A=0.941$^{\beta}$	P_B=0.071$^{\beta}$
The speech sections of the UPDRS-3 scores/item no.18 during HFS stimulation (point)	2.30 ± 0.98	2.37 ± 0.96	2.19 ± 0.94	2.50 ± 0.98	P_A=0.966$^{\beta}$	P_B=0.305$^{\beta}$
The speech sections of the UPDRS-3 scores/item no.18 during LFS stimulation (point)	1.55 ± 0.61	1.60 ± 0.68	1.42 ± 0.64	1.75 ± 0.61	P_A=0.920$^{\beta}$	P_B=0.110$^{\beta}$
The speech sections of the UPDRS-3 scores/item no.18 during off-stimulation (point)	1.70 ± 0.73	1.70 ± 0.92	1.54 ± 0.86	1.88 ± 0.78	P_A=0.811$^{\beta}$	P_B=0.196$^{\beta}$
Left STN amplitude (volt)	2.84 ± 0.94	3.14 ± 1.01	2.99 ± 0.87	3.03 ± 1.13	P_A=0.209$^{\beta}$	P_B=0.619$^{\beta}$
Right STN amplitude (volt)	3.08 ± 1.20	2.94 ± 1.10	3.26 ± 1.12	2.68 ± 1.09	P_A=0.675$^{\beta}$	P_B=0.068$^{\beta}$
Left STN pulse width (μsec)	79.50 ± 20.13	71.79 ± 22.12	77.31 ± 24.26	72.27 ± 17.71	P_A=0.091$^{\beta}$	P_B=0.566$^{\beta}$
Right STN pulse width (μsec)	79.50 ± 20.13	72.86 ± 17.18	77.31 ± 19.29	73.64 ± 17.87	P_A=0.241$^{\beta}$	P_B=0.504$^{\beta}$

$^{\varphi}$: Chi-square test; $^{\beta}$: Mann-Whitney *U* test; *: Statistically significant; Value in parentheses are shown as percentage; P_A: *p*-value between ventral and dorsal contact of the left STN; P_B: *p*-value between ventral and dorsal contact of the right STN; dB: decibel unit; LED: levodopa equivalent dosage; HY: Hoehn & Yahr score; UPDRS: The Unified Parkinson's Disease Rating Scale; STN: Subthalamic nucleus; HFS: High frequency stimulation; LFS: Low frequency stimulation.

Table 4
Predictors and Odd ratios Exp(B) of low vocal intensity (less than 70 dB).

Predictors	Odd ratios/Exp(B)
PD-DBS patients	9.534*
Age	-
Female gender	-
Disease duration	-
Current HY score during the 'on' period	-
Current total UPDRS-3 scores during the 'on' period	-
Model summary	
Hosmer and Lemeshow test	$\chi 2(8) = 10.441$, $p = 0.235$
Nagelkerke R square	0.347

*; statistically significant; PD-DBS: Parkinson's disease patients treated with subthalamic nucleus deep brain stimulation; HY: Hoehn & Yahr score; UPDRS: The Unified Parkinson's Disease Rating Scale.

tremor, since we excluded two patients with severe tremors during the LFS and off-stimulation, LFS did not improve the tremors in these two patients. Similarly, a previous study reported that some patients receiving DBS for medication-refractory tremor did not show tremor improvement with LFS compared to HFS [23]. Secondly, the lack of a formal speech-language pathology assessment may have influenced the interpretation of the patients' speech difficulties. However, speech assessment was conducted by a board-certified neurologist (OP) and a PD nurse specialist (KB) due to their established experience in UPDRS assessment, and, in a recent systematic review on speech outcomes following STN-DBS, the authors have highlighted a variety of designs and methodologies for speech assessment, including chart review, patient self-perception, neurologist and nurse assessment, speech intelligibility, and acoustic analysis [11]. Additionally, we mainly diagnosed the effect of STN-DBS on hypophonia and stuttering features without evaluations of other types of dysarthria, and clinical assessment based on subjective tools, including the speech sections of the UPDRS may have led to inaccurate speech problem interpretations. Finally, this study was not conducted in an advanced speech laboratory. However, all patients were evaluated in a soundproof room with a digital sound pressure meter and a microphone for objective assessment.

This study investigated the association between speech impairment in PD patients and DBS. Our results revealed that stuttering can be exacerbated by STN-DBS and that vocal intensity is reduced to a greater extent during HFS than during LFS. In addition, while active contacts in dorsal zone areas are associated with better motor outcomes and active ventral contacts influence both neuropsychiatric and cognitive outcomes, vocal intensity was significantly lower in patients with active dorsal zone contacts compared to patients with active contacts in ventral zone areas for both HFS and LFS settings, with similar results in both hemispheres, suggesting that an active electrode location in dorsal zone areas, rather than ventral zone areas, may influence speech deterioration. Overall, our findings demonstrate the importance of balancing symptom control with speech problems and other side effects when considering electrode location and stimulation settings in patients undergoing STN-DBS.

Author contributions

1) Research project: A. Conception, B. Organization, and C. Execution.

2) Statistical Analysis: A. Design, B. Execution, and C. Review and Critique.

3) Manuscript: A. Writing of the first draft and B. Review and Critique.

Onanong Phokaewvarangkul: 1ABC, 2AB, and 3A

Kamolwan Boonpang:1AB and 3B

Roongroj Bhidayasiri: 1ABC, 2C, and 3B

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.07.020.

Declaration of interest

None.

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