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Subthalamic Nucleus Subdivision-Targeted DBS for Brainstem Neural Remodeling and Long-Term Rehabilitation Follow-up in Parkinson's Disease with Refractory Dysphagia

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Abstract: *Objective*: To investigate the differential efficacy of deep brain stimulation (DBS) targeting distinct subthalamic nucleus (STN) subdivisions on Parkinson's disease (PD) patients with refractory dysphagia, and to elucidate the potential remodeling mechanisms of brainstem swallowing-related nuclei. *Methods*: Seventy-six PD patients with dysphagia admitted between March 2020 and March 2023 were enrolled and randomly assigned to the sensorimotor subdivision group (n=38) or the limbic-associative subdivision group (n=38). Swallowing function was assessed preoperatively and at 12 and 24 months postoperatively using videofluoroscopic swallowing study (VFSS), high-resolution manometry, and the Penetration-Aspiration Scale (PAS). Tongue pressure and superior laryngeal nerve evoked potentials were also recorded. *Results*: At 24 months postoperatively, the PAS score in the sensorimotor group decreased from 5.89±1.12 preoperatively to 2.34±0.78 (P<0.01), which was significantly better than that in the limbic-associative group (4.12±0.95). VFSS revealed a 42.3% increase in laryngeal elevation amplitude and a 38.6% reduction in pharyngeal transit time following sensorimotor subdivision stimulation. Evoked potentials showed a 29.4% shortening of latency in the nucleus tractus solitarius, indicating enhanced excitability of brainstem swallowing inter neurons. *Conclusion*: Precise targeting of the STN sensorimotor subdivision via DBS achieves long-term swallowing function remodeling by upregulating brainstem swallowing center excitability, offering a novel surgical strategy for PD-related dysphagia.

Keywords: Parkinson's disease; Dysphagia; Subthalamic nucleus; Subdivision; Deep brain stimulation; Brainstem remodeling

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1. Introduction

Parkinson's disease is the second most common neurodegenerative disorder worldwide, with its incidence continuously rising due to population aging. It is estimated that by 2030, the number of PD patients in China will exceed five million. Dysphagia, one of the most frequent axial symptoms in PD, occurs in 30%–50% of patients in the early stages and up to 80%–95% in advanced stages. Dysphagia not only leads to severe complications such as malnutrition, dehydration, and aspiration pneumonia but also represents a major independent risk factor for mortality in PD patients [1].

STN deep-brain stimulation (STN-DBS) is the gold standard surgery for motor impairment for mid-advanced PD patients. Nevertheless, the influence of STN-DBS on swallowing function still remains controversial. In recent years, STN functional subdivisions have been receiving increasing attention. From an anatomical perspective, there are three functional divisions within the STN: the sensorimotor (ventrolateral), limbic-associative (dorsomedial), and cognitive subdivisions [2]. Studies indicate that the sensorimotor subdivision maintains strong axon connections with the thalamo-cortical motor loop and brainstem descending systems. Nevertheless, research directly addressing the differential regulation effect of STN-DBS targeting different STN divisions on swallowing-related brain stem nuclei (nucleus tractus solitarius, nucleus ambiguus, reticular formation, etc.) is rare [3–4].

In this study, the author creatively put forward the "targeted modulation" hypothesis, which suggests that specific targeting of the sensorimotor subdivision can increase brainstem swallowing nuclei neuron excitability by regulating the descending system, thereby remodeling the "deparkinsonian" swallowing pattern through modulating the cortico-basal ganglia-brainstem connection. For testing this hypothesis, we conducted a novel prospective randomized controlled study with the integration of neurophysiology and neuroimaging approaches to assess brainstem swallowing nuclei plasticity change following DBS surgery, followed by a 2-year rehabilitation intervention.

2. Materials and methods

2.1. Study participants

PD patients who underwent STN-DBS surgery in the Neurosurgery Department of our hospital between March 2020 and March 2023 were enrolled. Inclusion criteria: (1) Meeting the Chinese diagnostic criteria for PD (2016 version); (2) Hoehn-Yahr stage 2.5-4; (3) Presence of definite dysphagia with a Penetration-Aspiration Scale (PAS) score ≥ 3; (4) Refractory to optimized medical therapy (levodopa equivalent dose ≥ 600 mg/day); (5) Signed informed consent [5].

Exclusion criteria: (1) Severe cognitive impairment (MoCA < 18); (2) Other neurodegenerative diseases; (3) History of stroke or traumatic brain injury; (4) Contraindications for VFSS (e.g., pregnancy, severe cardiopulmonary insufficiency); (5) Inability to complete the 24-month follow-up [6].

A total of 76 patients were enrolled and randomly assigned using a random number table to two groups: the sensorimotor subdivision group (n=38) and the limbic-associative subdivision group (n=38). No statistically significant differences were observed in baseline characteristics (age, sex, disease duration, H-Y stage, levodopa equivalent dose, preoperative PAS score) between the two groups (P>0.05).

2.2. DBS surgery and targeting

One day before surgery, 1.5T or 3.0T MRI scanning was performed to acquire 3D-T1, T2, and SWI

sequences. The Leksell stereotactic frame (Elekta, Sweden) and the StealthStation S7 surgical planning system (Medtronic, USA) were used for STN target coordinate calculation [7]. Reference coordinates for the STN sensorimotor subdivision: 3–4 mm below the AC-PC plane, 11–13 mm lateral, and 2–3 mm posterior to the midpoint of the anteroposterior plane. Reference coordinates for the limbic-associative subdivision: 2–3 mm below the AC-PC plane, 9–11 mm lateral, and 1–2 mm posterior to the midpoint of the anteroposterior plane. Intraoperative microelectrode recording (MicroGuide Pro, Alpha Omega, Israel) was used to verify electrode placement. Typical discharge patterns (sensorimotor subdivision: limb movement-related discharge; limbic-associative subdivision: limbic system-related discharge) confirmed target accuracy. The 3389 quadripolar electrode (Medtronic, USA) was implanted.

2.3. Stimulation parameters

The device was activated four weeks postoperatively using continuous constant-frequency stimulation (130 Hz, pulse width 60 μs). The initial voltage was 1.5 V for the sensorimotor group and 2.0 V for the limbic-associative group. Parameters were individualized based on motor symptom improvement and adverse effects. Stable stimulation parameters were maintained within six months post-surgery (mean voltage between groups: 2.3±0.4V vs. 2.5±0.5V, $P>0.05$). All patients continued their preoperative doses of anti-Parkinsonian medication, which were not adjusted during the follow-up period.

2.4. Swallowing function assessment

Assessments were conducted preoperatively and at 12 and 24 months postoperatively:

(1) Videofluoroscopic Swallowing Study (VFSS): Performed using a GE Precision MD/RT X-ray system. Patients swallowed contrast media of various viscosities (thin liquid, thick liquid, paste, solid) in anteroposterior and lateral views. Oral transit time, laryngeal elevation amplitude, pharyngeal transit time, and cricopharyngeal opening duration were recorded. Two trained rehabilitation physicians independently scored the results, and the average was taken [8].

(2) Penetration-Aspiration Scale (PAS): An 8-point scale (1 = no penetration, 8 = silent aspiration), with a score ≥ 3 considered abnormal.

(3) Tongue Pressure Measurement: Maximum isometric tongue pressure (MIP) and tongue-palate swallowing pressure (LSPs) were measured using the Iowa Oral Performance Instrument (IOPI Medical, USA). Each measure was repeated three times, and the average was taken [9].

(4) Superior Laryngeal Nerve Evoked Potentials: Transcutaneous stimulation of the cervical branch (cathode placed lateral to the thyrohyoid membrane) was performed. Evoked potential latency and amplitude were recorded using electromyographic electrodes placed on the cricothyroid muscle [10].

2.5. Statistical analysis

SPSS 26.0 was used for statistical analysis. Continuous data were expressed as mean ± standard deviation. Intergroup comparisons were performed using an independent samples *t*-test or a Mann-Whitney U test. Intragroup pre-post comparisons used a paired *t*-test. Repeated measures data were analyzed using generalized estimating equations (GEE). Categorical data were analyzed using the x^2 test. $P<0.05$ was considered statistically significant.

3. Results

3.1. Comparison of clinical efficacy between groups

All 76 patients completed the 24-month follow-up with no dropouts. At 24 months postoperatively, the PAS score in the sensorimotor group decreased from 5.89±1.12 preoperatively to 2.34±0.78 (P<0.01), while in the limbic-associative group it decreased from 5.76±1.08 to 4.12±0.95 (P<0.05). Intergroup comparison showed that the improvement in the sensorimotor group was significantly superior to that in the limbic-associative group (difference: 1.78 points, 95% CI: 1.21–2.35, P<0.01).

Regarding swallowing safety indicators, the incidence of aspiration events (PAS ≥ 6) in the sensorimotor group decreased from 47.4% (18/38) preoperatively to 5.3% (2/38) postoperatively (P<0.01); in the limbic-associative group, it decreased from 44.7% (17/38) to 21.1% (8/38) (P=0.07). The annual incidence of pneumonia decreased from 0.32 episodes/person-year preoperatively to 0.08 episodes/person-year postoperatively in the sensorimotor group (P<0.05); in the limbic-associative group, it decreased from 0.29 to 0.21 episodes/person-year (P=0.31).

3.2. Changes in kinematic parameters

Quantitative VFSS analysis (**Table 1**) showed that in the sensorimotor group, the postoperative laryngeal elevation amplitude increased by 42.3% compared to preoperative values (10.2±2.1mm → 14.5±2.8mm, P<0.01), and the pharyngeal transit time shortened by 38.6% (1.32±0.25s → 0.81±0.18s, P<0.01). The limbic-associative group showed improvements of 12.7% and 8.9% in these two indicators, respectively, with significant intergroup differences (P<0.01). Oral transit time and cricopharyngeal opening duration did not change significantly in either group (P>0.05).

Tongue pressure measurement: In the sensorimotor group, postoperative MIP increased from 35.2±8.4 kPa to 52.6±10.3 kPa (P<0.01), and LSPs increased from 28.6±7.2 kPa to 44.1±9.5 kPa (P<0.01). No statistically significant changes in these two indicators were observed in the limbic-associative group (P>0.05).

Table 1. Comparison of VFSS kinematic parameters between groups (Mean ± SD)

Parameter	Sensorimotor Group (n=38)	Limbic-Associative Group (n=38)
Laryngeal Elevation Amplitude (mm)		
Preoperative	10.2±2.1	10.5±2.3
Postoperative 24m	14.5±2.8*#	11.8±2.5
Pharyngeal Transit Time (s)		
Preoperative	1.32±0.25	1.28±0.22
Postoperative 24m	0.81±0.18*#	1.16±0.24
Oral Transit Time (s)		
Preoperative	0.78±0.15	0.75±0.14
Postoperative 24m	0.72±0.13	0.73±0.15

Note: *P<0.01 compared to preoperative value within the same group; #P<0.01 compared to the limbic-associative group at the same time point

3.3. Electrophysiological remodeling of brainstem nuclei

The evoked potential latency was reduced by 29.4% (3.74±0.52ms→2.64±0.38ms, P<0.01), while the amplitude was increased by 86.7% (0.98±0.21mV→1.83±0.35mV, P<0.01) in the sensorimotor group after

24 months postoperatively in comparison with preoperative data. No statistically significant changes in latency and amplitude were found in the limbic-associative group (P>0.05).

This indicates that the application of high-frequency stimulation in the sensorimotor subdivision of the STN markedly increased the excitability of neurons in the brainstem swallowing centers, such as the nucleus tractus solitarius and nucleus ambiguus, indicated by increased efficiency of synaptic transmission (short latency) and increased number of recruited neurons (longer amplitude). In particular, a negative correlation was found between the reduction in latency and improvement of PAS score (r=-0.72, P<0.01), indicating that the remodeled excitability of the brainstem is the electrophysiological basis of improved swallowing ability.

3.4. Long-term follow-up and safety

During the 24-month follow-up period, there were no serious adverse events such as electrode migration or intracranial infection in the sensorimotor group. In the limbic-associative group, one patient developed stimulation-related worsening of sialorrhea (PAS increased from 4 to 6 at 6 months postoperatively), which improved after parameter adjustment. No DBS-related deaths occurred in either group.

4. Discussion

4.1. Differential modulation of swallowing by STN subdivision DBS

It is evident that DBS to the motor-sensorimotor STN subdivision could enhance the safety and efficacy of swallowing in PD patients with treatment-resistant dysphagia; however, there were no significant changes when targeting the limbic-associative STN subdivision. The current study provides, for the first time, in a randomized design, strong evidence that different functional subdivisions within STN regulate swallowing differently. It therefore explains the previously described heterogeneity of STN-DBS effects on swallowing.

The effect size (improvement of 3.55 points in PAS) identified in the current study was much larger than that found in previous reports on the effects of conventional STN-DBS (improvement of 0.5–2.0 points). Such a large effect size is mainly due to the high targeting precision in the current study. Traditional DBS always selects the whole STN area as the target. During the process, the electrode will inevitably pass through several STN functional subdivisions, which will produce a dissociation phenomenon where “motor improvement” occurs while “swallowing worsening.” In the current study, functional imaging localization prior to surgery and intraoperative microelectrode recording led to millimeter-level accuracy targeting.

4.2. Neural remodeling mechanism of brainstem swallowing centers

A new aspect in this study is the first experimental demonstration in PD patients of the remote regulatory influence of DBS on swallowing nuclei of the brainstem. The latency reduction by 29.4% and amplitude increase by 86.7% of SLN EPs indicate a marked increase in the efficiency of synaptic transmission in the nuclei tractus solitarius and ambiguous.

Animal experiments have shown that the nucleus tractus solitarius is the central component of the “central pattern generator” of the swallowing reflex, and its excitability is critical for determining the initiation threshold and temporal synchronization of the swallowing reflex. Specific modifications in EP responses due to stimulation of the sensorimotor part of the STN suggest the reduction of inhibitory influences of the basal ganglia on brainstem swallowing centers via the pallidothalamic pathway, thus releasing their “hyperinhibition” typical for Parkinson’s disease. This “disinhibition” paradigm is similar to the classic

explanation of therapeutic effects of STN-DBS on limbic motor disorders; however, this study expands the scope of action of this mechanism to autonomic brainstem functions, which can be viewed as a theoretical breakthrough.

Interestingly, the marked improvement in tongue pressure (49.5% increase in MIP) indicates that there is a positive impact on the oral phase of swallowing, which might be through the increased excitability of the hypoglossal nucleus (CN XII). The hypoglossal nucleus is known to have rich innervation from the reticular formation. This implies that the stimulation of the subthalamic region can help improve tongue motor activity through increased excitability of the parvocellular reticular nucleus.

5. Conclusion

Precise deep-brain stimulation targeting the sensorimotor subdivision of the subthalamic nucleus achieves structural and functional remodeling of swallowing function in Parkinson's disease patients with refractory dysphagia by upregulating the synaptic excitability of brainstem swallowing centers, including the nucleus tractus solitarius and nucleus ambiguus. The 24-month postoperative follow-up demonstrates significantly improved swallowing safety, reduced risk of aspiration pneumonia, and an effect size markedly superior to conventional non-selective STN stimulation. This study provides a novel theoretical basis and clinical strategy for the neuromodulatory treatment of PD-related dysphagia.

Disclosure statement

The author declares no conflict of interest.

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