Relationship Between Electrode Position and Clinical Efficacy of Subthalamic Nucleus Deep Brain Stimulation and Motor Symptoms of Parkinson's Disease

Feng Zhang
Beijing Neurosurgical Institute  https://orcid.org/0000-0002-0898-7861

Feng Wang
Ningxia Medical University

Weiguo Li
Shandong University Qilu Hospital

Ning Wang
Beijing Neurosurgical Institute

Chunlei Han
Beijing Neurosurgical Institute

Shiying Fan
Beijing Neurosurgical Institute

Peng Li
Hebei Medical University First Affiliated Hospital

Lifeng Xu
Hebei Medical University First Affiliated Hospital

Jianguo Zhang
Beijing Neurosurgical Institute

Fangang Meng (fgmeng@ccmu.edu.cn)
Beijing Neurosurgical Institute  https://orcid.org/0000-0002-4030-7811

Research article

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Abstract

Objectives To investigate the relationship between the position of bilateral STN-DBS location of active contacts and clinical efficacy of STN-DBS in the motor symptoms of Parkinson’ disease (PD) patients.

Methods We retrospectively analyzed the clinical data of 57 patients with PD who underwent bilateral STN-DBS from March 2018 to December 2018. UPDRS III scores, LEDD, PDQ-39 scores before operation and within 6 months after operation were determined. The location of activate contacts and volume of tissue activated (VTA) in the Montreal Neurological Institute (MNI) space, and their correlation with the rate of improvement of motor symptoms; UPDRS-Ⅲ score improvement rate were examined.

Results After 6 months of follow up, the UPDRS-Ⅲ scores of 57 patients Med-off were improved by 55.4±18.9% (P<0.001) compared with that before operation. The improvement rate of PDQ-39 score [(47.4±23.2)% , (P<0.001)] and the reduction rate of LEDD [(40.1±24.3)% , (P<0.01)] at 6 months post surgery were positively correlated with the improvement rate of motor symptoms; Med-off (PDQ-39: r=0.461, P<0.001; LEDD: r=0.354, P=0.007) the rate of improvement of UPDRS-Ⅲ (Med-off) and the Z-axis coordinate of the active contact in the MNI space were positively correlated (left side: r=0.349, P=0.008; right side: r=0.369, P=0.005). In the MNI space, there was no correlation between the UPDRS-Ⅲ score improvement rate (Med-off) at 6 months after operation and bilateral VTA in the STN motor subregion, STN associative subregion and STN limbic subregion of the active electrode contacts of 57 patients (all P>0.05). At 6 months after surgery, the difference between the Z-axis coordinate in the different improvement rate subgroups (25%, 25% to 50%, and 50% in the MNI space was statistically significant (left side: P=0.030; right side: P=0.024). In the MNI space, there was no statistically significant difference between the 3 groups in the VTA of the active electrode contacts (all P>0.05).

Conclusions STN-DBS could improve the motor symptoms of PD patients and improved the quality of life. The closer the active stimulation contacts is to the dorsolateral sensorimotor area of STN, the better effect the DBS has on the motor symptoms of PD patients.

Introduction

Parkinson’s disease (PD) is a neurodegenerative disease common in middle-aged and elderly people, and deep brain stimulation (DBS) is an accepted treatment at an advanced stage [1–2]. Studies have shown that subthalamic nucleus (STN) DBS can improve dyskinesias and improve the quality of life (QOL) in PD patients [3–6]. Every now, the STN is publicly preconceived the target of choice [4]. Studies have shown that the improvement in postoperative motor improvement depends in particular on age and disease duration [6] and preoperative response to dopaminergic drugs [7], this makes it critical to screen for the right DBS candidates. In the past, optimizing the parameters of DBS postoperative programming has been proved to be an important factor to improve the therapeutic effect on PD. However, the most important factors that determine the improvement of DBS on motor symptoms are precise stimulation targets and effective stimulation volume, that is, the position of the electrode active contact in STN and volume of tissue activated (VTA) [8–9]. The purpose of this study was to observe the efficacy of motor symptoms in patients with PD receiving bilateral STN-DBS, and to study the relationship between the location of active contacts and VTA and the motor symptoms of Parkinson’ disease (PD) patients.
Methods

Patient's selection

Evaluations were executed by neurologists specialized in movement disorders. All Patients met the diagnostic criteria for PD in China (2016 edition) and evaluation criteria for surgical treatment of PD [10]. All patients underwent preoperative testing and analyzed the levodopa challenge test, confirming that levodopa response needs to be improved by at least 30%, and those who had complete imaging and scoring data and could follow up regularly. Morphologic MRI is performed to exclude patients with severe cerebral atrophy, ischemic disease, and severe cognitive impairment and mental illness.

Patients

We conducted a retrospective to patients upon advanced PD who underwent bilateral STN DBS surgery from March 2018 to December 2018. According to the above criteria, a total of 57 patients were included. Among them, 34 males (59.6%) and 23 females (40.4%); mean age was (64.1 ± 8.0) (46–82); mean onset age (54.0 ± 8.1) (35–73); mean disease duration (10.1 ± 5.1) (2–23). The levodopa equivalent day dose (LEDD) of 57 patients before surgery was (866.3 ± 357.0) (125–1625) mg/d; the preoperative Hoehn-Yahr stage was (2.9 ± 0.3) (2–4). The ethical principles involved in this study strictly followed the "Helsinki Declaration", and all patients or their families gave informed consent and signed informed consent.

Surgical procedure

Articles describe surgical procedures [11–12]. For encircling patients, an image fusion procedure (3T MRI and 1.5T MRI), commonly driven out by our group. Images detach from 3T MRI plagiarized a day before the surgery were fused with CT (with a Leksell stereotactic frame) on the day of surgical procedure. The coordinates of the target and the entrance trajectory were defined on stereotactic MR images by directly visualizing the STN. The STN coordinates were calculated using direct [based on MRI T2 DESS (double-echo steady state)] and indirect (using statistical coordinates) methods. The first operated side was the one contralateral to the most impaired body-side. The electrodes are implanted under local anesthesia, and targets are identified by a combination of neuroimaging, microelectrode recording (MER), and macrostimulation tests. The STN stimulation target was defined using a combination of statistical coordinates of STN (4–6 mm inferior, 2–3 posterior, and 11–13 mm lateral from midcomissural point) [12], and direct visualization on MRI where the STN was chosen at the anterior margin of red nucleus and 2 to 3 mm lateral from its external border. Enhanced T1-weighted images were used to visualize vessels to avoid injury of any vascular structure during surgery. Multi-track microelectrodes were inserted for electrophysiological mapping of the STN. Subsequent macro-stimulations were used to assess the efficacy and side effect profile of the tested electrodes. The optimal track (best micro-recording and widen therapeutic window on macro-stimulation) was chosen for each side and quadripolar DBS leads (model L301, PINS Medical, Beijing, China or model 3389s, Medtronic, Minneapolis, Minn, USA), which had 4 contacts (contact height of 1.5 mm, a spacing of 0.5 mm between each contact and a diameter of 1.3 mm), were bilaterally implanted targeting the STN under local anesthesia in one session. Intraoperative macrostimulation was used to determine the voltage threshold for stimulation-induced adverse effects. At the end of the surgical procedure, a neurostimulator (G102 or G102R, PINS Medical or Activa RC or Activa PC, Medtronic) was implanted into the subclavicular region under general anaesthesia in the same day. Post-operative CT scan was performed immediately after surgery to exclude surgical complications.
Stimulation programming[13]

1 month after operation, stimulator was turned on and programed. Monopolar screening was performed for the contacts on each electrode with a pulse width of 60 µm, a frequency of 130 Hz, and a voltage of 1.5-2.0 V. Thereafter, parameters such as voltage, pulse width or frequency are gradually adjusted according to the follow-up results until the best treatment effect was achieved, and adverse reactions were reduced as much as possible, and the position of the contact can be adjusted if necessary. Some patients use bipolar or double negative stimulation.

Clinical evaluation

All PD patients were assessed by the Unified Parkinson's disease rating scale-part I (UPDRS-I) scores and the Hoehn and Yahr scale was used for disease staging. LEDD calculated based on a previously published algorithm combining dopamine agonist daily dose with levodopa daily dose and Parkinson's Disease Questionnaire-39 (PDQ-39) for QOL. Postoperative motor symptom improvement rate (%) = (preoperative UPDRS-I scores - postoperative UPDRS-I scores) / preoperative UPDRS-I scores × 100%. The drug improvement rate was the result of the preoperative levodopa challenge test. The drug improvement rate (%) = (UPDRS-I baseline scores before taking the drug - UPDRS-I lowest scores after taking the drug) / UPDRS-I baseline scores before taking the drug × 100%. Berg Balance Scale score improvement rate (%) = (postoperative BBS score - preoperative BBS score) / preoperative BBS score × 100%. FOG-Q score improvement rate (%) = (preoperative FOG-Q score - postoperative FOG-Q score) / preoperative FOG-Q score × 100%.

Post-operative evaluation and volume of tissue activated estimation

Patients were reassessed 1 month after surgery and 3 and 6 months after surgery at follow-up. (1) DBS electrode localisation: DBS leads were localized with the Lead-DBS toolbox[8, 14]. (2) VTA: Volume of the STN in standard space was defined by the DISTAL atlas. After verification of electrode locations, VAT was calculated [15].

Statistical analyses

All statistical analyses were performed using SPSS 25.0 (IBM Corp, USA). Continuous variables that obey or approximately obey the normal distribution are expressed as mean ± standard deviation (±). The continuity data that does not obey the normal distribution was expressed by the median and quartile interval. The continuity data that does not obey the normal distribution was based on the Friedman test. The comparison between multiple groups used the rank sum test of the comparison of multiple groups, that was, the Kruskal-Wallis test. Categorical variables were expressed as constituent ratios or percentages, and chi-square tests were used for comparison between groups. Through the Pearson correlation analyze the relationship between the UPDRS-I score and the drug improvement rate, LEDD change rate, PDQ-39 score improvement rate, the VTA, the coordinates of the electrode activate contacts, and the distance from the electrode activate contacts to the STN motor subregion, associative subregion, and limbic subregion were discussed. Statistical significance level was set at $P < 0.05$.

Results
1. DBS on PD patients with motor symptoms and its correlation analysis results:

The follow-up results at 6 months after operation showed that compared with before operation, 57 patients had significantly improved UPDRS-II scores, and the improvement rate of drug off-state was the highest \([(55.4 \pm 18.9)\%, P<0.001]\); The improvement rate of PDQ-39 scores were \((47.4 \pm 23.2)\% (P<0.005)\), indicating that the patient’s quality of life was also significantly improved under chronic high frequency stimulation; LEDD decreased by \((40.1 \pm 24.3)\% (P<0.005,\text{Table 1, Fig. 1})\). The improvement rate of motor symptoms (UPDRS III score) (Med-off)in 57 patients 6 months after operation was positively correlated with the drug improvement rate \((r=0.262, P=0.049)\) (Fig. 2A). At 6 months after surgery, the improvement rate of the PDQ39 scores of 57 patients was positively correlated with the improvement rate of motor symptoms(Med-off) \((r=0.461, P<0.001)\) (Fig. 2B); the decrease rate of LEDD was positively correlated with the improvement rate of motor symptoms(Med-off) \((r=0.354, P=0.007)\) (Fig. 2C).

| MEDICATION OFF | MEDICATION ON |
|---------------|---------------|
| time          | UPDRS-II (0-108) | BBS (0-56) | UPDRS-II (0-108) | BBS (0-56) | LEDD (mg) | PDQ-39 (0-124) | FOG-Q |
| Preoperative  | 60.0(23)        | 44(11)      | 26.2(23)         | 52(7)      | 831(453)   | 49(38)        | 14(12) |
| Postoperative |                |             |                  |            |           |               |        |
| 1 month       | 35.0(22)        | 48(11)      | 15.0(16)         | 53(5)      | -          | -             | 9(12)  |
| 3 month       | 31.5(12)        | 48(10)      | 13.0(13)         | 53(5)      | 550(357.5) | 34(25)        | 9(12)  |
| 6 month       | 31.0(17)        | 48(12)      | 12.0(11)         | 54(5)      | 475(220.5) | 23(20)        | 9(10)  |
| Total P       | <0.001          | 0.084       | <0.001           | 0.058      | <0.001     | <0.001        | 0.068  |
| $\chi^2$      | 109.966         | 35.705      | 74.042           | 29.351     | 62.000     | 104.246       | 7.131  |
| $P_1$         | <0.001          | -           | <0.001           | -          | -          | -             |       |
| $P_2$         | <0.001          | -           | <0.001           | -          | <0.010     | <0.010        | -      |
| $P_3$         | <0.001          | -           | <0.001           | -          | <0.010     | <0.010        | -      |

$P_1$ value is the result of comparison between 1 month and preoperative, $P_2$ value is the result of comparison between 3 months and preoperative, $P_3$ value is the result of comparison between 6 months and preoperative; STN-DBS: subthalamic nucleus - deep brain stimulation, UPDRS-II: Unified Parkinson's Disease Rating Scale, BBS: Berg Balance Scale, LEDD: Levodopa equivalent dose, PDQ-39: 39-Item Parkinson's Disease Questionnaire, FOG-Q: Freeze of gait questionnaire; except LEDD unit is mg, all other index units are points

2. Post-operative DBS setting
Of the 57 patients, 3 (5.3%) required bipolar stimulation, 2 (3.5%) required bipolar negative stimulation, and the remaining 52 patients (91.2%) all received unipolar stimulation. The stimulation parameters of 57 patients: the voltage is (2.04 ± 0.57) V (0.8–3.0 V), the pulse width is (64 ± 10) μs (50–90 μs); the frequency is (135 ± 14) Hz (110–175 Hz).

3. The active contact locations in MNI space and its relationship with the improvement rate of motor symptoms in PD patients

The electrode active contacts: left side: 10 cases with contact 1, 42 cases with contact 2, 5 cases with contact 3; right side: 10 cases with contact 1, 35 cases with contact 2, 11 cases with contact 3 and 1 cases with contact 4 (Contact 1 refers to the most ventral contact and contact 4 the most dorsal one).

(1) The mean coordinates of active contacts in MNI of 57 patients (Table 2). Six months after surgery, the improvement rate (Med-off) of DBS UPDRS III was positively correlated with the z-axis of the active contact locations in MNI (right side: \( r = 0.369, P = 0.005 \); left side: \( r = 0.349, P = 0.008 \) ) (Fig. 3A, B, 4A, B). This indicates that the higher the z-axis (closer to the dorsal STN), the higher the DBS UPDRS III improvement rate.

(2) In the MNI space, the mean distance from the active contact to the STN motor subregion, STN associative subregion, STN limbic subregion \([M(IQR)]\) was: left side: 0.1 (0.5) mm, 0.8 (1.3) mm, 1.0 (1.0) mm; right side: 0.2 (0.6) mm, 1.1 (1.1) mm, 0.8 (1.4) mm. In the MNI space, there was no correlation between the improvement rate (Med-off) of the UPDRS-II scores in 57 patients 6 months after operation and the electrode active contact to the STN motor subregion (left side: \( r = -0.152, P = 0.259 \); right side: \( r = -0.202, P = 0.652 \) ), STN associative subregion (left side: \( r = -0.057, P = 0.671 \); right side: \( r = -0.219, P = 0.101 \) ) and STN limbic subregion (left side: \( r = 0.100, P = 0.461 \); right side: \( r = 0.241, P = 0.071 \) ).

(3) In the MNI space, the active contact VTA in the STN motor subregion, STN associative subregion, STN limbic subregion were: left side: 18.5 (7.5) mm\(^3\), 13.7 (8.4) mm\(^3\), 14.7 (8.2) mm\(^3\); right side: 16.2 (6.3) mm\(^3\), 8.3 (9.9) mm\(^3\), 14.3 (9.0) mm\(^3\). In the MNI space, there was no correlation between the improvement rate (Med-off) of the UPDRS-II scores in 57 patients 6 months after operation and the VTA in the STN motor subregion (left side: \( r = -0.051, P = 0.705 \); right side: \( r = 0.090, P = 0.507 \) ), in STN associative subregion (left side: \( r = -0.113, P = 0.403 \); right side: \( r = 0.205, P = 0.127 \) ), in STN limbic subregion (left side: \( r = -0.108, P = 0.424 \); right side: \( r = -0.236, P = 0.077 \) ).

Table 2

| Axis | Active contact [mm] in MNI | Active contact [mm] in AC/PC |
|------|---------------------------|-----------------------------|
|      | left | right | left | right | left | right | left | right |
|      | mean | SD   | mean | SD   | mean | SD   | mean | SD   |
| X    | -11.5| 1.1  | 12.0 | 1.1  | 11.6 | 1.5  | 12.0 | 1.2  |
| Y    | -13.5| 1.4  | -13.5| 1.3  | -1.7 | 1.5  | -1.6 | 1.4  |
| Z    | -8.2 | 1.0  | -8.3 | 1.5  | -3.9 | 1.0  | -4.0 | 1.1  |

STN-DBS: Subthalamic nucleus deep brain stimulation, MNI: Montreal Neurological Institute
4. Comparison of DBS active contacts position and VTA in different groups with different improvement rates of motor symptoms

Improvement rates < 25% group: 5 cases (8.8%), improvement rates 25%-50% group: 11 cases (19.3%), improvement rates > 50% group: 41 cases (71.9%).

(1) The position of the DBS active contacts of each group (Figure 4 A B): In the MNI space, the difference between the Z-axis coordinate is statistically significant (left side: \( P = 0.030 \); right side: \( P = 0.024 \)), while on both sides of the X, Y-axis, there was no statistically significant difference between them (all \( P > 0.05 \), Table 3); in AC-PC space, there was no statistically significant difference between the three groups on the X, Y, Z-axis coordinate (all \( P > 0.05 \), Table 4). In the MNI space, there was no statistically significant difference between the distances from the active contacts to the STN subregion (all \( P > 0.05 \), Table 5).

(2) The VTA of the electrode active contacts in the MNI space of each group: In the MNI space, there was no statistically significant difference between the groups in the VTA of the electrode active contacts (all \( P > 0.05 \), Table 6) (Fig. 4C.D).

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**Table 3**

Comparison results of active contact coordinates in MNI space in different motor symptom improvement rate groups (Median (IQR), mm)

| group                  | Number of cases | left       |          | right     |          |
|------------------------|-----------------|------------|----------|-----------|----------|
|                        |                 | X          | Y        | Z         | X        | Y        | Z         |
| Improvement rates < 25% group | 5               | -12.1(1.9) | -14.0(2.6) | -9.4(1.0) | 12.1(1.9) | -14.7(2.6) | -9.3(1.5) |
| Improvement rates 25%-50% group | 11             | -11.1(1.9) | -13.2(2.6) | -8.1(1.3) | 11.3(1.9) | -13.5(1.9) | -8.4(2.1) |
| Improvement rates > 50% group | 41             | -11.6(1.2) | -13.4(1.7) | -7.9(1.1) | 12.1(1.6) | -13.6(2.2) | -7.8(1.2) |

Kruskal-Wallis \( \chi^2 \)

|               | X^2  | p   |
|---------------|------|-----|
| Improvement rates < 25% group | 2.366 | 0.306 |
| Improvement rates 25%-50% group | 0.461 | 0.794 |
| Improvement rates > 50% group | 7.036 | **0.030** |
| Kruskal-Wallis \( \chi^2 \) | 1.200 | 0.549 |
| p | 2.261 | 0.323 |
|               | 7.455 | **0.024** |
### Table 4
Comparison results of active contact coordinates in AC/PC space in different motor symptom improvement rate groups (MQedian (IQR), mm)

| group                     | Number of cases | left         | right         |
|---------------------------|-----------------|--------------|---------------|
|                           |                 | X            | Y            | Z            | X            | Y            | Z            |
| Improvement rates < 25%   | 5               | -10.8(1.6)   | -1.7(3.2)    | -4.5(0.4)    | 11.5(1.6)    | -1.9(2.0)    | -4.8(1.2)    |
| Improvement rates 25%-50% | 11              | -11.7(3.2)   | -1.5(2.5)    | -4.3(1.9)    | 11.6(2.4)    | -1.9(1.2)    | -4.3(1.5)    |
| Improvement rates >50%    | 41              | -11.7(2.1)   | -1.8(1.6)    | -3.7(1.6)    | 12.3(1.8)    | -1.7(2.1)    | -3.8(1.2)    |
| Kruskal-Wallis $\chi^2$   |                 | 1.888        | 0.529        | 1.970        | 1.039        | 0.194        | 3.847        |
| P                         |                 | 0.389        | 0.768        | 0.373        | 0.595        | 0.908        | 0.146        |

### Table 5
The mean distance of different motor symptom improvement rate groups in the MNI space from the active contact to the STN subregion (MQedian (IQR), mm)

| group                     | Number of cases | left        | right        |
|---------------------------|-----------------|-------------|--------------|
|                           |                 | STN motor subregion | STN associative subregion | STN limbic subregion | STN motor subregion | STN associative subregion | STN limbic subregion |
| Improvement rates < 25%   | 5               | 0.2(1.2)    | 1.4(1.1)    | 1.5(1.5)    | 0.4(1.2)    | 1.7(1.4)    | 0.4(1.0)    |
| Improvement rates 25%-50% | 11              | 0.1(1.4)    | 0.7(1.4)    | 1.9(0.9)    | 0.1(0.6)    | 0.6(1.2)    | 0.5(0.8)    |
| Improvement rates >50%    | 41              | 0.1(0.4)    | 0.8(1.2)    | 0.9(1.1)    | 0.2(0.5)    | 1.1(1.1)    | 0.9(1.5)    |
| Kruskal-Wallis $\chi^2$   |                 | 0.251       | 1.693       | 0.255       | 2.200       | 4.158       | 2.908       |
| P                         |                 | 0.882       | 0.429       | 0.881       | 0.333       | 0.128       | 0.234       |
Table 6
The mean VTA of different motor symptom improvement rate groups in the MNI space (Median (IQR), mm)

| group                        | Number of cases | left STN motor subregion | left STN associative subregion | left STN limbic subregion | right STN motor subregion | right STN associative subregion | right STN limbic subregion |
|------------------------------|-----------------|--------------------------|--------------------------------|--------------------------|---------------------------|--------------------------------|---------------------------|
| Improvement rates < 25% group| 5               | 12.9(16.6)               | 9.1(13.6)                       | 10.6(9.5)                | 15.6(5.3)                 | 5.6(7.4)                       | 15.7(8.8)                 |
| Improvement rates 25%-50% group | 11             | 18.2(6.3)               | 15.5(8.0)                       | 15.6(10.0)               | 16.2(8.0)                 | 12.1(9.9)                       | 15.2(5.1)                 |
| Improvement rates >50% group | 41              | 20.1 (13.0)             | 13.4(8.3)                       | 14.7(8.2)                | 17.1(10.8)                | 8.6(9.9)                       | 12.6(10.1)                |
| Kruskal-Wallis χ²           |                 | 1.129                    | 1.544                           | 0.140                    | 0.958                     | 3.945                          | 3.613                     |
| P                           |                 | 0.569                    | 0.462                           | 0.933                    | 0.619                     | 0.139                          | 0.164                     |

Discussion

STN-DBS has a good effect on PD motor symptoms [16]. In our study, compared to baseline, STN-DBS improved UPDRS III scores and major motor function, both Med-on and Med-off postoperatively. These results demonstrate that DBS has a unique advantage in relieving motor symptoms, the patient's scores in Med-on / Stim-on postoperatively were lower than the scores in Med-on preoperatively; it has a better effect on improving motor symptoms of PD patients. In addition, the most effective contacts were dorsal contacts, this is similar to reports that the contact selection is dorsal to the STN [17]. In our study, we observed a large reduction in LEDD 6 months after operation, a reduction of more than 40% compared to the preoperative dose, which was related to the improvement of motor symptoms in DBS (UPDRS-III scores reduced by 55.4%), Which was consistent with a 19–80.7% reduction in drug dose and 53–92% improvement in dyskinesia scores [18–19]. The LEDD decrement was positively correlated with the improvement rate of motor symptoms (r = 0.354, P = 0.007). We think that the better the effect of DBS on improving patients' motor symptoms, the more LEDD is reduced. Through the PDQ-39 assessment, the QOL (quality of Life) of our patients improved by 47.4% overall, which also proved the good effect of STN-DBS. This result is consistent with previous studies, with an improvement in quality of life from 30.2–50.6% [20]. In our study the PDQ39 improvement was positively correlated with the improvement rate of motor symptoms, (r = 0.461, P < 0.001), the better the effect of DBS on improving motor symptoms, the better the QOL of patients.

Factors influencing clinical efficacy: active contact location

We observed that electrode active contacts in STN-DBS patients were mainly distributed in dorsolateral STN. As we all know, the dorsolateral STN is involved in motor function, and the dorsolateral STN serves as the target region for STN-DBS in PD patients [21]. Stimulation of the dorsolateral STN (sensory motor function area) is
expected to disrupt pathological neuronal motor activity or afferent fibers and improve clinical symptoms. In our study, with UPDRS-III score improvement rate of more than 50% was basically concentrated in the dorsolateral part of STN, the active contacts location of patients with UPDRS score improvement rate of 25–50% was more concentrated in the middle part of STN, the active contacts position of patients with UPDRS-III score improvement rate of less than 25% was more concentrated in the ventral part of STN. After statistical analysis, it was found that only the z-axis coordinate of the brain was significantly different. Optimal location of DBS stimulation within STN: the dorsolateral part of STN is traditionally considered to represent the optimal location of the motor region and stimulation [22]. So far, this part can only be confirmed by intraoperative electrophysiology, which shows an increase in \( \beta \) oscillation activity [23]. The results of our study support the conclusion that the position of the electrode active contacts help to judge the motor effect of STN-DBS. This study found that the improvement rate of motor symptoms is related to the improvement rate of drugs, but the correlation coefficient is only 0.262, which needs further research.

**Characterising clinical efficacy - VTA**

The effect of programmed parameters (voltage, pulse width, frequency) on the efficacy of DBS surgery is critical. The therapeutic effect is not only on the single contact, but also on the larger electric field range than the contact. Therefore, Andreas Horn's method of VAT calculation [15] was used to analyze the stimulation parameters of postoperative active contacts and calculate the correlation between the volume of tissue activated (VTA) and the UPDRS motor scores. We used the VAT calculation to evaluate the clinical efficacy of STN-DBS in PD patients, although the difference between the VTA of the electrode activate contacts in the MNI space of each group was not statistically significant (all \( P > 0.05 \)), however, it was found that the higher the VTA of the electrode activate contact of the patient in the STN motor subregion, the higher the improvement of motor symptoms. The difference is not statistically significant and may be related to the sample size of this study.

**Limitations:**

(1) It is a retrospective analysis of a small sample of 57 patients, the sample is small; (2) The average follow-up period is half a year and the time is short; (3) The treatment mechanism of DBS in this study has not been clarified. Despite these limitations, our results further confirm that DBS electrode active contacts located dorsolateral to STN can achieve better clinical efficacy and are proportional to the percentage of VTA located in STN motor subregion. Therefore, direct functional evidence supports only a mild dorsal-ventral gradient of STN DBS motor effects, and does not support strict dorsal-ventral dissociation.

**Conclusions**

STN-DBS could improve the motor symptoms of PD patients and improved the quality of life. The closer the active stimulation contacts is to the dorsolateral sensorimotor area of STN, the better effect the DBS has on the motor symptoms of PD patients.

**Abbreviations**

PD: Parkinson's disease; DBS: deep brain stimulation; STN: subthalamic nucleus; LEDD: Levodopa equivalent dose; UPDRS: Unified Parkinson's Disease Rating Scale; PDQ-39: 39-Item Parkinson's Disease Questionnaire; QOL: Quality of Life; VTA: volume of tissue activated
Declarations

Ethics approval and consent to participate:

All participants clearly consent and approved my manuscript. The ethical principles involved in this study strictly followed the "Helsinki Declaration", and all patients or their families gave informed consent and signed informed consent. The research project has been approved by Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University.

Consent for publication

My manuscript does not contain data from any individual person.

Not applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are available in the Fangang Meng repository upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study concept and design: Fan-Gang Meng. Data collection: Feng Zhang, Shi-ying Fan, Ning Wang, Chun-lei Han, Peng Li, Li-Feng Xu. Analysis and interpretation: Feng Zhang, Feng Wang, Shi-ying Fan, Wei-Guo Li. Drafting of the manuscript: Feng Zhang. Critical revision of the manuscript: Jian-Guo Zhang, Fan-Gang Meng. Study supervision: Fan-Gang Meng, Jian-Guo Zhang. Feng Zhang was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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References

1. Kalia LV, Lang AE. Parkinson's Disease[J]. Lancet, 2015,386(9996):896-912. DOI:1016/S0140-6736(14)61393-3.
2. Parsons TD, Rogers SA, Braaten AJ, et al. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis[J]. Lancet Neurol, 2006,5(7):578-588. DOI: 10.1016/S1474-4422(06)70475-6.

3. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease[J]. N Engl J Med, 1998;339(16):1105-1111. DOI: 10.1056/NEJM199810153391603.

4. Benazzouz A, Hallett M. Mechanism of action of deep brain stimulation[J]. Neurology, 2000,55(Suppl 6):S13-6. DOI: 1007/s100720070058.

5. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease[J]. N Engl J Med, 2006,355(9):896-908. DOI: 10.1056/NEJMoa060281.

6. Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes[J]. Mov Disord, 2006,21 Suppl 14:S290-304. DOI: 10.1002/mds.20962.

7. Caire F, Ranoux D, Guehl D, et al. A systematic review of studies on anatomical position of electrode contacts used for chronic subthalamic stimulation in Parkinson's disease[J]. Acta Neurochir (Wien), 2013,155(9):1647-1654; discussion 1654. DOI: 10.1007/s00701-013-1782-1.

8. Horn A, Reich M, Vorwerk J, et al. Connectivity Predicts deep brain stimulation outcome in Parkinson disease[J]. Ann Neurol, 2017,82(1):67-78. DOI: 10.1002/ana.24974.

9. Jahanshahi M, Obeso I, Rothwell JC, et al. A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition[J]. Nat Rev Neurosci, 2015,16(12):719-732. DOI: 10.1038/nrn4038.

10. Lewis SJ, Foltynie T, Blackwell AD, et al. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach[J]. J Neurol Neurosurg Psychiatry, 2005,76(3):343-348. DOI: 10.1136/jnnp.2003.033530.

11. Ostrem JL, Marks WJ, Volz MM, et al. Pallidal deep brain stimulation in patients with cranial-cervical dystonia (Meige syndrome)[J]. Mov Disord, 2007,22(13):1885-1891. DOI: 10.1002/mds.21580.

12. Zhang F, Meng FG. Research progress of functional anatomy of subthalamic nucleus[J]. Chin J Neurosurg, 2020,36(4):426-429. DOI: 10.3760/cma.j.cn112050-20190729-00333.

13. Horn A, Li N, Dembek TA, et al. Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging[J]. Neuroimage, 2019,184:293-316. DOI: 10.1016/j.neuroimage.2018.08.068.

14. Husch A, V PM, Gemmar P, et al. PaCER - A fully automated method for electrode trajectory and contact reconstruction in deep brain stimulation[J]. Neuroimage Clin, 2018,17:80-89. DOI: 10.1016/j.nicl.2017.10.004.

15. Rabie A, Verhagen ML, Fakhry M, et al. Improvement of Advanced Parkinson's Disease Manifestations with Deep Brain Stimulation of the Subthalamic Nucleus: A Single Institution Experience[J]. Brain Sci, 2016,6(4) DOI: 10.3390/brainsci6040058.

16. Castrioto A, Lozano AM, Poon YY, et al. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation[J]. Arch Neurol, 2011,68(12):1550-1556. DOI: 10.1001/archneurol.2011.182.

17. Chen DL, Zhang XM, Nie P, et al. Programming parameter analysis of subthalamic deep brain stimulation for the treatment of Parkinson's disease[J]. Chin J Neurosurg, 2019,35(12):1210-1215. DOI: 10.3760/cma.j.issn.1001-2346.2019.12.005.

18. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease[J]. N Engl J Med, 2003,349(20):1925-1934. DOI: 10.1056/NEJMoa035275.
19. Chen YS, Li Q, Li JG, et al. Influencing factors of effect of subthalamic nucleus deep brain stimulation on Parkinson's disease [J]. Chin J Neurosurg, 2018, 34(4): 374-378. DOI: 10.3760/cma.j.issn.1001-2346.2018.04.011.
20. Martínez-Martín P, Valdeoriola F, Tolosa E, et al. Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease [J]. Mov Disord, 2002, 17(2): 372-377. DOI: 10.1002/mds.10044.
21. Guo S, Zhuang P, Hallett M, et al. Subthalamic deep brain stimulation for Parkinson's disease: correlation between locations of oscillatory activity and optimal site of stimulation [J]. Parkinsonism Relat Disord, 2013, 19(1): 109-114. DOI: 10.1016/j.parkreldis.2012.08.005.
22. Zaidel A, Spivak A, Grieb B, et al. Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease [J]. Brain, 2010, 133(Pt 7): 2007-2021. DOI: 10.1093/brain/awq144.
23. Gross RE, Krack P, Rodriguez-Oroz MC, et al. Electrophysiological mapping for the implantation of deep brain stimulators for Parkinson's disease and tremor [J]. Mov Disord, 2006, 21 Suppl 14: S259-283. DOI: 10.1002/mds.20960.
24. Vanegas-Arroyave N, Lauro PM, Huang L, et al. Tractography patterns of subthalamic nucleus deep brain stimulation [J]. Brain, 2016, 139(Pt 4): 1200-1210. DOI: 10.1093/brain/aww020.

Figures

![Figure 1](image)

**Figure 1**

Comparison of 57 cases of STN-DBS patients with Parkinson's disease pre-and postoperative operation: Six months after operation, 57 patients (A-B) There is a significant improvement of the UPDRS III especially when patients were in Med-OFF with a rate of 55.4%, (C-D) when patients were in Med-ON with a rate of 44.6%, (E-F) LEDD was decreased to 40.1%.(G-H) PDQ-39 scores were improved by 47.4%(*: P<0.05; **: P<0.001); (STN-DBS:
subthalamic nucleus - deep brain stimulation, UPDRS-Ⅲ: Unified Parkinson's Disease Rating Scale, BBS: Berg Balance Scale, LEDD: Levodopa equivalent dose, PDQ-39: 39-Item Parkinson's Disease Questionnaire) [Baseline: baseline; FU1: 1 month after surgery; FU2: 3 months after surgery; FU3: 6 months after surgery]

**Figure 2**

Correlation between the improvement rate of DBS motor symptoms and drug improvement rate, the improvement rate of PDQ39 score and the decrease of LEDD and the improvement rate of motor symptoms: 6 months after surgery, 57 PD patients after STN-DBS (A) DBS motor symptoms improvement rate (UPDRS-Ⅲ score in Med off) was positively correlated with drug improvement rate (B) PDQ39 score improvement rate was positively correlated with motor symptoms improvement rate; (C) The decrease of LEDD is positively correlated with the improvement rate of motor symptoms. (STN-DBS: subthalamic nucleus-deep brain stimulation, UPDRS-Ⅲ: Unified Parkinson's Disease Rating Scale, BBS: Berg Balance Scale, LEDD: Levodopa equivalent dose, PDQ-39: 39-Item Parkinson's Disease Questionnaire)

**Figure 3**
Correlation between the improvement rate of the UPDRS–score and the Z-axis coordinate of the active contacts in the MNI space: A, B. The improvement rate of the UPDRS–score (Med-off) and the Z-axis of the active contacts in the MNI space The axis coordinate values are positively correlated (right side: $r = 0.369, P = 0.005$; left side: $r = 0.349, P = 0.008$) (UPDRS– Unified Parkinson's Disease Rating Scale; MNI: Montreal Neurological Institute).

**Figure 4**

3D illustration of all active electrode contacts: A, B. Electrode position of 57 PD patients (A): Electrode position, posterior view; (B): active contact, posterior view; (The blue dots represent group I (DBS improvement rates <25%), the white dots represent group II (DBS improvement rates between 25 and 50%) and the red dots represent group III (DBS improvement rates >50%).) (C): relationship between active tissue volume (VTA) in STN. (Yellow: STN. Red: red nucleus. Green: Gpi. Blue: Gpe.) (D): relationship between active tissue volume (VTA) in STN subregions. (Dark yellow nucleus: STN motor subregion. Blue nucleus: STN associative subregion. Pale yellow nucleus: STN limbic subregion. Red nucleus: red nucleus.)