

Subthalamic Nucleus-Deep Brain Stimulation Improves Autonomic Dysfunction in Parkinson's Disease

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Abstract

Background

To study the effects of subthalamic nucleus deep brain stimulation (STN-DBS) on autonomic dysfunction in Parkinson's disease (PD) patients.

Methods

57 PD patients, who underwent bilateral STN-DBS from March to December 2018, were retrospectively analyzed, preplanned assessments at baseline and postoperatively at 1, 3 and 6 months also included the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-Aut), the Unified Parkinson's Disease Rating Scale (UPDRS) III score, levodopa equivalent day dose (LEDD), Parkinson's Disease Quality of Life Scale (PDQ-39), the Hamilton Anxiety Rating Scale (HAMA), the Hamilton Depression Rating Scale (HAMD).

Results

The SCOPA-Aut scores improved significantly [14.59% (18.32%), 24.00% (27.05%), 22.16% (27.07%), respectively, all $P < 0.001$] at 1 months, 3 months, 6 months of STN-DBS respectively. Analysis of the SCOPA-Aut subitems showed significant improvement only in urine and thermoregulation subitems at 6 months after operation ($P < 0.001$). There was no significant correlation between the improvement rate of SCOPA-Aut scores and the improvement rate of PDQ-39 scores ($P > 0.05$) at 6 months after operation. SCOPA-Aut scores was positively correlated with age ($r = 0.428$, $P = 0.001$); The improvement rate of SCCOPA-Aut scores was positively correlated with the improvement rate of HAMA and HAMD scores (HAMA: $r = 0.325$, $P = 0.015$; HAMD: $r = 0.265$, $P = 0.049$) at 6 months after operation.

Conclusion

STN-DBS can improve autonomic dysfunction symptoms of PD patients, urinary and thermoregulatory subitems of autonomic dysfunction were improved in the short term after operation. There was a close relationship between improved autonomic symptoms and improved anxiety and depression 6 months after operation. We should pay more attention to the autonomic dysfunction in Parkinson's disease, detailed preoperative evaluation and postoperative follow-up, so as to better improve the QOL of patients.

Background

PD is a common neurodegenerative disease of the central nervous system. Deep brain stimulation (DBS) is an effective treatment in advanced PD patients [1]. Subthalamic nucleus (STN) DBS has been shown to improve motor symptoms and quality of life (QOL) [2–4], whereas the effects on non-motor symptoms (NMS) have been less reported. NMS may have a greater impact on QOL than motor symptoms. Dysfunctions of the autonomic nervous system (gastrointestinal symptoms, urinary symptoms, cardiovascular symptoms, thermoregulation, pupillomotor function, sexual function) are common in PD, autonomic dysfunction may appear earlier than major motor symptoms of PD and significantly impair the quality of life. Autonomic dysfunction are associated with the accumulation of lewy bodies in the nervous system. Parkinson's disease progression and dopaminergic drug therapy may also aggravate autonomic dysfunction. The effect of STN-DBS on autonomic symptoms such as sweating, urgency, increased frequency or incontinence, has not been well studied. The loss of central dopamine leads to motor symptoms, which can also lead to autonomic dysfunction, therefore, we speculated that STN-DBS may improve autonomic dysfunction. we have evaluated the impact of bilateral STN-DBS on

autonomic dysfunction during 6 months of chronic stimulation and explored their relationship to motor symptoms, anxiety and depression and quality of life outcomes.

Materials And Methods

Between March and December 2018, a total of 57 subjects were hospitalized at the Department of Neurosurgery of the Beijing Tiantan Hospital affiliated to Capital Medical University, the First Hospital of Hebei Medical University and General Hospital of Ningxia Medical University for optimizing a previously performed STN-DBS, As mentioned in our previous article [5].

The study was approved by the Medical Ethics Committee of the First Hospital of Hebei Medical University and the Medical Ethics Committee of Beijing Tiantan Hospital affiliated to Capital Medical University, the ethical principles involved in this research strictly in accordance with the "Declaration of Helsinki" and all patients provided written informed consent, As mentioned in our previous article [5].

Patient's Selection

Evaluations were executed by neurologists specialized in movement disorders. Patients with advanced idiopathic PD diagnosed based on the diagnostic criteria for PD in China (2016 edition) and PD surgical treatment evaluation criteria [6, 7]. None of the patients had serious cognitive impairment or mental illness. All patients underwent preoperative testing and analyzed the levodopa challenge test (LCT), 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.

Clinical evaluation

Demographic characteristics (age, gender, age at onset, duration of the disease) and disease severity, assessed by the Unified Parkinson's Disease Rating Scale (UPDRS)-III scores (range 0-132). The Hoehn-Yahr scale (0-5) was used for disease staging. The therapeutic medical regimen was recorded calculating the levodopa equivalent dose (LEDD) according to the method of Tomlinson et al [8]. As part of the preplanned investigations performed at baseline, and after 1, 3 and 6 months of STN-DBS, autonomic symptoms were assessed with the Scopa-Aut questionnaire (0-69) [9], consisting of 26 items. It includes: gastrointestinal symptoms (7 items), urinary symptoms (6 items), cardiovascular symptoms (3 items), thermoregulation (4 items), pupillomotor function (1 item), sexual function (2 separate items for each gender) [9], each item is scored from 0 (never) to 3 (often), except for question 26, which is a yes/no question, and consequently not included in our statistical analysis. SCOPA-Aut score ranges from 0 to 69, with higher scores expressing more severe symptoms. Anxiety and depression outcomes were assessed using the Hamilton Anxiety Rating Scale (HAMA) (14 parts), the HAMA ranges from 0 to 56 and the Hamilton Depression Rating Scale (HAMD) (24 parts), the HAMD ranges from 0 to 68 respectively, and quality of life was assessed using the 39-item Parkinson's Disease Questionnaire (PDQ-39), ranging from 0 to 124. Postoperative improvement rate (%) was calculated as (preoperative score - postoperative score)/preoperative score × 100%. Clinical assessments were performed at preoperative baseline (Med-OFF and Med-ON), 1 month after surgery (follow-up 1), 3 months after surgery (follow-up 2) and 6 months after surgery (follow-up 3).

Surgical procedure

Surgical procedures were carried out as our previously described [5].

Stimulation programming

One month after surgery, we turn on the stimulator and program the IPG [10], test the contacts on each electrode, and select the best stimulation target when the patient obtains satisfactory improvement with minimal side effects. After that, if necessary, the parameters can be adjusted through remote program control. First use the unipolar stimulation mode, the

stimulation parameters: voltage 1.5–2.0V, frequency 130Hz, pulse width 60ms. Then gradually adjust the stimulation parameters until the best therapeutic effect is achieved.

Statistical analyses

All statistical analyses were performed using SPSS 25.0 (v25.0.0.0, SPSS Inc, Chicago/Illinois/USA). Continuous variables that followed, or approximately followed, a normal distribution are presented as mean \pm standard deviation ($\bar{x} \pm s$). Continuous variables that did not follow a normal distribution are presented as the median (M) and interquartile range (IQR). The Friedman test was used for continuous variables that did not follow a normal distribution and the Kruskal-Wallis rank sum test was used for comparison between multiple groups. Correlation analysis method was used to analyze the factors influencing the improvement of autonomic dysfunction after DBS. The statistical significance threshold was fixed at $P < 0.05$.

Results

Patient population

As mentioned in our previous article [5], the study group comprised 34 males and 23 females. The levodopa equivalent daily dose (LEDD) of the 57 patients preoperative was (866.3 ± 357.0) (125–1625) mg/d, the preoperative Hoehn-Yahr stage was (2.9 ± 0.3) (2–4).

Clinical outcomes

In this study, 57 patients were included, operated, and examined preoperatively, with planned follow-up after 1, 3 and 6 months of continuous STN-DBS. Comparisons between preoperative and postoperative (1, 3 and 6 months after surgery) clinical stages are summarized in Table 1 and Figure 1. At 6 months follow-up, the SCOPA-Aut scores (scales for outcomes in PD autonomic symptoms) [M (IQR)] improved significantly [14.59% (18.32%), 24.00% (27.05%), 22.16% (27.07%), respectively, all $P < 0.001$] at 1 months, 3 months, 6 months of STN-DBS respectively. Analysis of the SCOPA-Aut subitems showed significant improvement only in urine and thermoregulation subitems at 6 months after operation ($P < 0.001$).

As mentioned in our previous article [5], UPDRS-III scores (Medication-off) were improved (55.42%), the PDQ-39 scores were improved (47.39%) and the LEDD had decreased by 40.08% at 6 months after surgery. The improvement rate of HAMA scores and HAMD scores of 57 patients was [41.7(34.9) %; 37.5(33.4) %] respectively (both $P < 0.001$).

Table 1
Comparison of preoperative and postoperative clinical state [M (IQR)]

Time	Preoperative	Postoperative			Total <i>P</i>	χ^2	<i>P</i> ₁	<i>P</i> ₂	<i>P</i> ₃
		1month	3month	6month					
SCOPA-Aut									
SCOPA-Aut (0-69) total	22(12)	18(14)	18(10)	16(12)	0.003	5.399	0.001	0.001	<0.001
Gastrointestinal (Q1-7)	4(2.8)	4(4)	4(2.8)	4(2)	0.107	2.133	0.062	0.193	0.065
Urinary (Q8-13)	7(4)	4.5(3.8)	4(5)	4(5)	<0.001	11.062	<0.001	<0.001	<0.001
Cardiovascular (Q14-16)	2(1.8)	2(1)	2(1.7)	2(2)	0.248	1.418	0.049	0.107	0.345
Thermoregulatory (Q17-21)	4(2)	3(2.8)	3(3)	3(2.8)	<0.001	8.049	<0.001	<0.001	<0.001
Pupillomotor (Q19)	1(2)	1(2)	1(2)	1(2)	0.264	1.362	0.159	0.073	0.088
Sexual (Q22-25)	2(1.7)	2(2)	2(1)	2(1.7)	0.792	0.346	0.659	0.871	0.542
HAMA (0-56)	16(14)	11(11)	9(10)	11(11)	<0.001	12.839	<0.001	<0.001	<0.001
HAMD (0-68)	14(13)	9(9)	9(8)	9(9)	<0.001	11.664	0.004	<0.001	<0.001
<i>P</i> ₁ , <i>P</i> ₂ and <i>P</i> ₃ values are, respectively, the results of comparisons between preoperative results and results 1, 3 and 6 months after surgery; SCOPA-Aut: the Scale for Outcomes in PD for Autonomic Symptoms; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale.									

The correlation analyses

1. The correlation between the improvement rate of SCOPA-Aut scores, LEDD, PDQ-39 scores and the improvement rate of UPDRS-III scores (Med-off) (Table 2): There was no significant correlation between the improvement rate of SCOPA-Aut scores and the improvement rate of UPDRS-III scores (Med-off) ($P > 0.05$). The reduction rate of LEDD was positively correlated with the improvement rate of UPDRS-III scores (Med-off) ($r = 0.354$, $P = 0.007$), the improvement rate of PDQ-39 scores was positively correlated with the improvement rate of UPDRS-III scores ($r = 0.461$, $P < 0.001$).
2. The correlation between the improvement rate of SCOPA-Aut scores and the improvement rate of PDQ-39 scores (Table 3): There was no significant correlation between the improvement rate of SCOPA-Aut scores and the improvement rate of PDQ-39 scores ($P > 0.05$).
3. The correlation between SCOPA-Aut scores, PDQ-39 scores, and clinical variables (Table 4): In SCOPA-Aut scores there was no correlation with disease duration and Hoehn-Yahr grade ($P > 0.05$) and positively correlated with age ($r = 0.428$,

$P=0.001$), indicate that the older of the PD patients, the more serious of the autonomic dysfunction symptoms. In PDQ-39 scores there was positively correlated with disease duration ($r=0.296$, $P=0.025$) and Hoehn-Yahr grade ($r=0.366$, $P=0.005$). 4. The correlation between the improvement rate of SCOPA-Aut scores and the improvement rate of HAMA, HAMD scores (Table 5): The improvement rate of SCOPA-Aut scores was positively correlated with the improvement rate of HAMA scores ($r=0.325$, $P=0.015$); The improvement rate of SCOPA-Aut scores; was positively correlated with the improvement rate of HAMD scores ($r=0.265$, $P=0.049$), indicate that the better the improvement rate of anxiety and depression, the better the improvement rate of autonomic dysfunction

Table 2 The correlation between SCOPA-Aut scores, LEDD, PDQ-39 scores and motor symptoms improvement rate 6 months after surgery

	improvement rate (%)	the improvement rate of UPDRS-III scores (Med-off) (%)	r	P
SCOPA- Aut	22.16	55.42	0.086	0.527
LEDD	40.08	55.42	0.354	0.007
PDQ-39	47.39	55.42	0.461	<0.001

Table 3 The correlation between the improvement rate of SCOPA-Aut scores and the improvement rate of PDQ-39 scores 6 months after surgery

	improvement rate (%)	the improvement rate of PDQ-39 scores (%)	r	P
SCOPA- Aut	22.16	47.39	0.126	0.355

Table 4 The correlation between SCOPA-Aut scores, PDQ-39 scores and clinical variables 6 months after surgery

	Age		Disease duration		Hoehn-Yahr grade	
	r	P	r	P	r	P
SCOPA-Aut	0.428	0.001	0.221	0.101	0.086	0.528
PDQ-39	0.006	0.967	0.296	0.025	0.366	0.005

Table 5 The correlation between the improvement rate of SCOPA-Aut scores, and the improvement rate of HAMA, HAMD scores 6 months after surgery

	improvement rate (%)	the improvement rate of SCOPA-Aut scores (%)	r	P
HAMA	34.27	22.16	0.325	0.015
HAMD	26.95	22.16	0.265	0.049

Discussion

DBS is widely used in the clinical treatment of PD because of its minimally invasive, adjustable, reversible. Most PD patients experience autonomic dysfunction at different clinical stages, the incidence rate is 14%-80% [11, 12]. Autonomic dysfunction in PD includes gastrointestinal malfunction (constipation, dysphagia, or choking); urinary disturbance (increased nocturia, frequent urination, and endless urination); sexual dysfunction (impotence, vaginal dryness, etc); thermoregulatory aberrance (sweat, intolerance, etc); cardiovascular dysregulation (postural hypotension and dizziness), pupillo-motor and tear abnormalities [13], which seriously affects the quality of life in PD patients. In this retrospective study of 57 PD patients treated with STN-DBS, through correlation analysis, it was found that the older the patients with Parkinson's disease, the more serious the autonomic dysfunction. It is speculated that the older age of onset of Lewy bodies is related to the deposition of parts related to autonomic dysfunction.

The mechanism for the improvement of the symptoms of autonomic dysfunction may be that STN-DBS directly regulates the basal ganglia-thalamus-cortical circuit, thereby regulating the thalamus, lateral frontal lobe, and anterior cingulate gyrus (the center of the autonomic nervous system) to improve the symptoms of autonomic dysfunction [14]. The effect of STN-DBS on gastrointestinal dysfunction works by improving constipation, dysphagia and salivation [15]. Studies have shown that the effect of STN-DBS on urinary disturbance works by reducing the detrusor muscle tension, increasing bladder capacity and reflexing volume [16]. The severity of bladder dysfunction seems to be associated with the relative degeneration of the caudate nucleus, amongst other areas [17]. STN-DBS can improve the temperature perception of PD patients, DBS can improve hyperhidrosis and heat intolerance [18], which may be related to the stimulation of the tail of STN, the ventral thalamus and the zona incerta (ZI). The effect of STN-DBS on sexual dysfunction may be related to stimulation of the medial preoptic nucleus, anterior hypothalamic nucleus, and nucleus accumbens, resulting in changes in its activity [19]. The effect of STN-DBS on cardiovascular dysfunction works by increasing heart rate, the sensitivity of baroreceptors and peripheral vascular tone, it can improve postural hypotension in PD patients [20], which may be related to stimulating the Limbic of STN or the zona incerta (ZI) [21]. Frontal cortex, cingulate cortex, insula, thalami, basal ganglia and periaqueductal grey matter may be relevant with gastrointestinal function [22]. STN-DBS can activate the nerve fibres projecting from hypothalamus and crossing the subthalamic nucleus, that might be affected gastrointestinal function. Previous studies have shown that STN-DBS can improve autonomic dysfunction in PD patients [23–27]. Few previous reports have used SCOPA-Aut to assess the effect of STN-DBS on autonomic dysfunction. Previous studies have used NMSQ to assess NMS [28], However, this scale is only for NMSS, not for autonomic dysfunction specifically. The improvement of dysautonomic fluctuations after chronic stimulation was remarkable especially for some symptoms. Urinary dysfunction showed the greatest reduction in the number of symptoms reported by patients after the surgery. Regarding autonomic symptoms, the significant improvement of Scopa-Aut total score after 6 months of STN-DBS, the SCOPA-Aut total score were increased by 22.16% ($P < 0.001$) after 6 months of follow-up, indicating that STN-DBS has an improvement effect on autonomic dysfunction of Parkinson's disease in the short term. However, the results were not equal to all categories of symptoms. Analyses of each SCOPA-Aut domain showed significant improvement at 6 months only for the Urinary and thermoregulatory dysfunction showed a remarkable decrease after the chronic stimulation. However, one study of 24 patients reported similar results as presented here, where Scopa-Aut improved after 3 months of follow-up but with subsequent deterioration [29–31]. So We need further follow-up studies to confirm this, a prospective study with pre-operative and post-operative urodynamics would yield more detailed information about the effect of STN-DBS on bladder function. We could not predict the preoperative impact on SCOPA-Aut, but the parallel improvement of PDQ-39 scores were identified as a significant covariate. This might imply that the degree of improvement of autonomic dysfunction plays an important role in improving quality of life. However there was no significant correlation between the improvement rate of SCOPA-Aut scores and the improvement rate of PDQ-39 scores ($P > 0.05$). May be due to so many factors of the STN-DBS on quality of life, in addition to the motor symptoms associated with important role, the NMS impact is very important also, not just the autonomic dysfunction, such as anxiety, depression, numbness, pain, sleep disorders, cognitive impairment, hallucinations and other influence is very significant also, so we need to consider a lot of factors comprehensively, judge comprehensively.

Previous reports SCOPA-Aut scores increase by age and disease duration [32]. In our study, SCOPA-Aut total scores increase by age, it indicates that the autonomic dysfunction will gradually worsen with the age.

Autonomic dysfunction is related to emotional disorders, and there may be a common mechanism [33]. The 5-HT neurotransmitter system in patients with Parkinson's disease may be one of the mechanisms related to autonomic dysfunction and emotional disorders. In our study, the improvement rate of SCOPA-Aut scores was positively correlated with the improvement rate of HAMA scores ($r=0.325$, $P=0.015$); The improvement rate of SCOPA-Aut scores was positively correlated with the improvement rate of HAMD scores ($r=0.265$, $P=0.049$), indicate with the improvement of anxiety and depression symptoms in Parkinson's disease, autonomic dysfunction will also improve.

Quality of autonomic dysfunction deserve more focus both in the preoperative and postoperative evaluation of PD patients for STN-DBS. Future studies should consider including this factor among the main outcomes, especially in studies focusing on optimal electrode location and tissue activated (VTA) in STN, closed-loop DBS, directional electrode, functional brain imaging and brain networks.

Limitations:

There are also some deficiencies in this study :(1) the sample is small and it was retrospective study. (2) SCOPA-Aut scores for preoperative evaluation of autonomic dysfunction are subjective. (3) Postoperative follow-up time was 6 months, and the time is short.

Conclusion

STN-DBS can improve autonomic dysfunction of PD, urinary and thermoregulatory aspects of autonomic dysfunction were improved in the short term postoperatively. There was a close relationship between improved autonomic dysfunction and improved anxiety and depression 6 months. We should pay more attention to the autonomic dysfunction in Parkinson's disease, detailed preoperative evaluation and postoperative follow-up, so as to better improve the QOL of patients.

Abbreviations

PD: Parkinson's disease

STN: Subthalamic nucleus

DBS: Deep brain stimulation

UPDRS-III: Unified Parkinson's Disease Rating Scale-Part III

LEDD: Levodopa equivalent day dose

QOL: Quality of life

PDQ-39: 39-Item Parkinson's Disease Questionnaire

NMS : non-motor symptoms

SCOPA-Aut : the Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire

HAMA : the Hamilton Anxiety Rating Scale

HAMD : the Hamilton Depression Rating Scale

LCT: Levodopa challenge test

Med-off: Medication-off

Med-on: Medication-on

IPG: Implantable pulse generator

Declarations

Ethics approval and consent to participate

All authors clearly consented to and approved this manuscript. The study strictly followed the ethical principles set out in the "Declaration of Helsinki ". All patients and their families (spouse or children) have informed consent and signed an informed consent form, the study was approved by the Medical Ethics Committee of the First Hospital of Hebei Medical University and the Medical Ethics Committee of Beijing Tiantan Hospital affiliated to Capital Medical University, and the ethics committee approved this form of proxy consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study not publicly available due to privacy reasons of patients, but are available from the corresponding author on reasonable request.

Competing interests

There are no competing interests.

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Study concept and design: F Z, FG M. Data collection: F Z, SY F, CL H, DM G, CH L, JW W, YJ X, C Y. Analysis and interpretation: F Z, F W, CH L, JW W. Drafting of the manuscript: F Z. Critical revision of the manuscript: F Z, FG M. Study supervision: F Z, FG M. F Z was a major contributor in writing the manuscript. The authors read and approved the manuscript.

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Figures

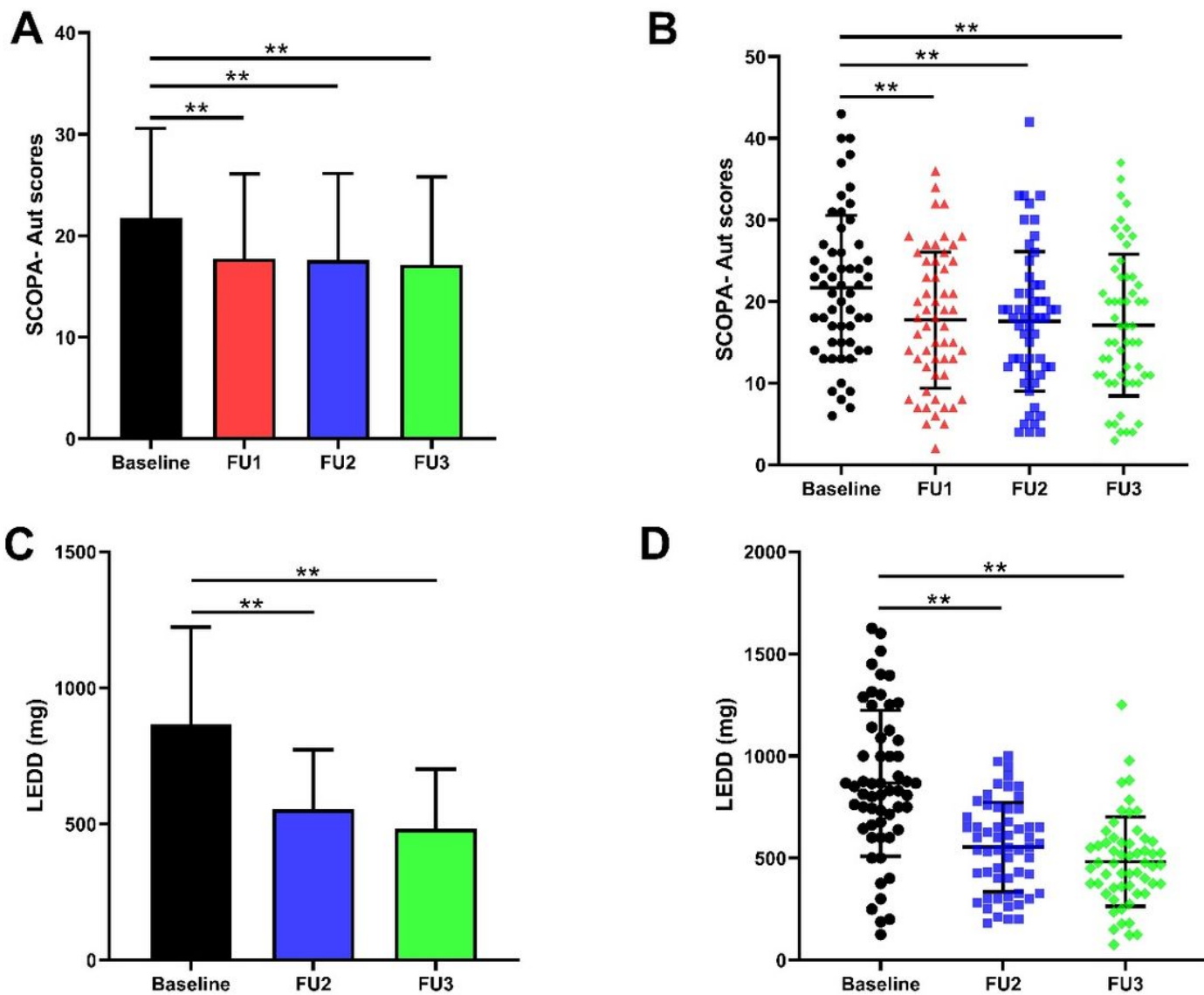


Figure 1

SCOPA-Aut and LEDD comparison between pre and postoperative clinical state. (A-B) SCOPA-Aut scores were improved by 22.16% 6 months after surgery (C-D) the reduction rate of LEDD was 40.08% at 6 months after surgery (**P < 0.001). (STN-DBS: subthalamic nucleus - deep brain stimulation; SCOPA-Aut: the Scale for Outcomes in PD for Autonomic Symptoms; LEDD: Levodopa equivalent dose) [Baseline: baseline; FU1: 1 month after surgery; FU2: 3 months after surgery; FU3: 6 months after surgery]