Parkinsonism and Related Disorders 15 (2009) 587–591

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Long-term effects of bilateral deep brain stimulation of the subthalamic nucleus on depression in patients with Parkinson's disease

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ARTICLE INFO

Article history:
Received 13 November 2008
Received in revised form
13 February 2009
Accepted 18 February 2009

Keywords:
Parkinson's disease
Deep brain stimulation
Subthalamic nucleus
Depression

ABSTRACT

Objective: To study the long-term effects of deep brain stimulation (DBS) of the bilateral subthalamic nucleus (STN) on depression in patients with Parkinson's disease (PD) and to discuss the mechanism.

Methods: A STN–DBS group ($n = 27$) and anti-Parkinson's medication control group with paired designing were set up. The evaluation of the depression and motor function was performed a total of six times. Depression was evaluated by the Self-Rating Depression Scale (SDS) and Hamilton Rating Scale for Depression (HAMD). Motor function was evaluated by the third part of the Unified Parkinson's Disease Rating Scale (UPDRS-III).

Results: Compared with the preoperative and the medication control group, the UPDRS-III scores of the STN–DBS group decreased remarkably within 18 months postoperatively ($P \leq 0.001$), and the SDS scores decreased notably within 6 months postoperatively ($P \leq 0.05$), and the HAMD scores decreased notably within 3 months postoperatively ($P \leq 0.05$). The UPDRS-III scores were strongly correlated with their SDS scores within 6 months postoperatively ($P \leq 0.05$), especially at 5 weeks postoperation ($P \leq 0.001$). UPDRS-III scores were also strongly correlated with HAMD scores at 5 weeks postoperation ($P \leq 0.05$). The mean value of the bilateral voltages was obviously correlated with SDS and HAMD scores ($P \leq 0.05$) within 18 months postoperatively.

Conclusion: The improvement in motor symptoms resulting from STN–DBS can improve depression in PD patients, but its long-term effects were unremarkable. Within the treatment range, the higher the mean value of bilateral voltages then the more severe was the depression in PD patients.

1. Introduction

Parkinson's disease (PD) may be accompanied by cognitive disorders, depression, and anxiety, among which depression has a major effect in decreasing patients' quality of life [1]. As Deep Brain Stimulation (DBS) of the Subthalamic Nucleus (STN) for treating PD has been extensively employed. Its therapeutic effectiveness on symptoms has been confirmed [2]. Recently, the focus of research on STN–DBS has been redirected towards its impact on the non-motor symptoms of PD. The influence of STN–DBS on depression in PD patients is still controversial [3–8].

Previous studies have shown that antiparkinsonan drugs, especially levodopa, have an influence on depression in PD patients [9]. In the present study, we set out to investigate the long-term effects of STN–DBS on depression in PD patients by evaluating the improvement in motor symptoms and levels of depression in PD patients, who underwent bilateral STN–DBS implantation, at different time points preoperatively and postoperatively, comparing the results with a control group on medication only, and to discuss its mechanism.

2. Patients and methods

2.1. Patients

In the present study, an STN–DBS group and a medication control group were recruited. The subjects of both groups were selected from PD patients who attended the department of neurology, or who underwent bilateral STN–DBS implantation in the department of neurosurgery at our hospital between June 2004 and January 2007. Both groups had only taken levodopa without an obvious dosage change, and had not taken antidepressant drugs during the period of the study. The study was approved by the ethics' committee of the Fourth Military Medical University. Written informed consent was obtained. Once a patient was enrolled in the

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doi:10.1016/j.parkreldis.2009.02.006

Table 1
Information of PD patients of the STN–DBS group and the medication control group.

Group	Mean age	Gender		Education			History	H–Y grade	Mean daily dose of levodopa (mg)
		Male	Female	Primary school	Middle school	College or above			
STN–DBS group	52.41 ± 9.89	17	10	7	11	9	5.72 ± 1.91	2.85 ± 0.62	950 ± 260
Medication control group	51.89 ± 10.14	17	10	9	10	8	5.48 ± 1.87	2.63 ± 0.53	980 ± 290

The difference in each item of the two groups above showed no significance (t-test and χ^2-test).

STN–DBS group, another patient who was only receiving medication treatment and was of the same gender, educational level, Hoehn–Yahr grade, age (±5 years), history (±1 year), and daily levodopa dose (±125 mg), was assigned to the medication control group as a paired sample. All patients had not been found obvious mood disorder, personality disorder, serious neuropsychiatric illnesses, and other illnesses which might influence results of this study. We evaluated the motor function and depression scale of all patients and collected their information. Data from 32 pairs were obtained during the study period. Five pairs did not complete the 18-month follow-up study (one pair was excluded as the patient in the medication control group had STN–DBS implantation; two pairs were excluded due to a severe change in levodopa dose, and the other two pairs were excluded for taking other antiparkinsonian drugs because of the worsebning condition of their PD). The data from 27 pairs were available, and their information is shown in Table 1.

2.2. Clinical evaluation

The third part of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was applied to evaluate the motor function of PD patients. Depression was evaluated by patients using the Self-Rating Depression Scale (SDS). Every patient whose SDS score showed a mild depression, or more, was evaluated again by two experienced psychologists using the Hamilton Depression Scale (HAMD), and the final score was the mean of these results. The total scores were recorded for HAMD and UPDRS-III, while the depression severity index (accumulative scores of each item/maximum scores of the scale) was recorded for SDS. The higher scores were those mentioned above, the more severe the motor symptoms and depression were. The evaluations were done at 1 month preoperatively, 5 weeks (1 week after DBS "on"), 3 months, 6 months, 12 months and 18 months postoperatively, for a total of six times. For the control group, the time point for evaluations began when the subject was enrolled in the trial, and continued at the same intervals as the STN–DBS group. All the evaluations were carried out 3 h after taking levodopa. For the STN–DBS group, the evaluations were done with the stimulator on.

2.3. Surgical procedure

All the patients in the STN–DBS group underwent bilateral STN–DBS implantation under the guidance of a magnetic resonance imaging (MRI) scan. A Cosman-Roberts-Wells (Radionics Inc., Burlington, Mass., U.S.A.) stereotactic head ring was positioned under local anesthesia, with the baseline paralleling to the anterior commissure–posterior commissure (AC–PC) line. The imaging location was performed by 1.0T MRI T2-weight thin-slice scanning (30 slices, 3 mm thickness, 0 mm interval). The coordinates for the STN were as follows: 2–3 mm below the AC–PC plane, 12–14 mm lateral to the median line, and 2.5–4 mm posterior to the midpoint (MP). A burr hole was drilled 2.5–3 cm from the midline, anterior to the coronal suture on each side. Microelectrode recording and stimulation techniques were used to further refine the target location. Once an optimal position was selected, macrostimulation was performed. If no side effects were demonstrated, the DBS quadripolar electrode (model 3389; Medtronic Inc., Minneapolis, Minn., U.S.A.) was implanted and secured at the burr hole site. Stimulation was delivered again to confirm the therapeutic effect and confirm there were no side effects. An extension (Lead 7482-51) was attached to the DBS electrode. The patients were then given a general anesthesia and the implantable pulse generator (Kinetra 7428, Medtronic Inc.) as implanted in a subclavicular subcutaneous pocket. The implanted pulse generators were programmed 4–6 weeks after the procedure. The stimulation parameters for DBS were: pulse width 60–90 μS, frequency 135–185 Hz, and voltage amplitude 1.4–3.4 V.

2.4. Statistical analysis

Data were analyzed using SPSS 11.0 software. The scores for UPDRS-III, SDS and HAMD were expressed as Mean ± S.D. Multiple comparisons were adopted including paired t-test, correlation analysis (using Pearson's Correlation Coefficient, Multiple Serial Correlation and Point Biserial Correlation, respectively, according to data type), variance analysis and regression analysis. A p value ≤ 0.05 was considered significant.

3. Results

3.1. Comparison of results of UPDRS-III, SDS and HAMD scores between the two groups

Comparing the preoperative and the control group, UPDRS-III scores of the STN–DBS group were significantly improved at each time point during the 18 months of the study with the stimulator on, while improvement was not significant at any time points postoperation. There were no changes in UPDRS-III scores for the control group during the 18-month evaluation period. Comparing the preoperation and control group, SDS scores of the STN–DBS group were significantly decreased within 6 months postoperatively, but no significant changes were seen at 12 and 18 months, postoperatively. There were no significant changes in SDS scores for the control group within the evaluation period. In the STN–DBS group, depression levels in 15 cases (55.6%) were mild, or higher by SDS self-rating. Comparing the preoperative and the control group, their HAMD scores were significantly decreased at three months with the stimulator on ($P \leq 0.005$), while changes were insignificant at 6, 12 and 18 months postoperatively. In the control group, depression in 13 patients (48.1%) was mild or higher by SDS self-rating, and their HAMD scores were not significantly changed within the evaluation period. The difference in the proportion of mild and slightly above depression between the two

Table 2
Comparison of UPDRS-III and SDS/HAMD scores between the STN–DBS group (A group) and the medication control group (B group).

Items	Scores					
	Evaluating time point					
	1 Month pre surgery	5 Weeks post surgery	3 Months post surgery	6 Months post surgery	12 Months post surgery	18 Months postoperation
A group, UPDRS-III	39.07 ± 9.19	7.74 ± 1.68***	7.41 ± 1.67***	7.89 ± 1.55***	8.30 ± 1.41***	8.11 ± 1.53***
B group, UPDRS-III	39.70 ± 8.96	41.04 ± 8.75	40.59 ± 8.82	40.15 ± 9.02	41.70 ± 8.41	41.33 ± 8.49
A group, SDS	0.56 ± 0.17	0.49 ± 0.13**	0.50 ± 0.10*	0.49 ± 0.12*	0.51 ± 0.13	0.52 ± 0.07
B group, SDS	0.57 ± 0.16	0.59 ± 0.10	0.57 ± 0.15	0.56 ± 0.13	0.56 ± 0.17	0.59 ± 0.14
A group, HAMD	16.15 ± 7.40	10.96 ± 4.69*	12.37 ± 4.32*	13.33 ± 4.76	17.52 ± 5.41	15.26 ± 6.41
B group, HAMD	15.93 ± 7.11	16.52 ± 7.02	16.26 ± 7.18	16.19 ± 7.22	17.44 ± 6.70	16.96 ± 6.84

Note: "***" shows the comparison between the A and B groups, $P \leq 0.001$ by t-test; "**" shows $P \leq 0.01$ by t-test; and "*"shows $P \leq 0.05$ by t-test. The following expressions of significance are the same as this.
* $P < 0.05$ by statistical test.

Table 3
Correlation coefficient and significance test between UPDRS-III and SDS/HAMD scores of the STN–DBS group (A group) and the medication control group (B group).

Items		Correlation coefficient					
		Evaluating time point					
		1 Month pre surgery	5 Weeks post surgery	3 Months post surgery	6 Months post surgery	12 Months post surgery	18 Months postoperation
UPDRS-III and SDS	A group	0.255	0.839***	0.383*	0.322*	0.289	0.291
	B group	0.234	0.242	0.267	0.270	0.284	0.287
UPDRS-III and HAMD	A group	0.151	0.300*	0.158	0.130	0.166	0.159
	B group	0.131	0.181	0.188	0.220	0.118	0.136

* $P < 0.05$ by statistical test.

groups was insignificant. The UPDRS-III, SDS and HAMD scores are shown in Table 2.

3.2. Correlation analysis of UPDRS-III and SDS/HAMD scores between two groups

In the STN–DBS group, there was a significant correlation between UPDRS-III and SDS scores within 6 months with the stimulator on. In the control group, there was no significant correlation between UPDRS-III and SDS scores at any evaluating time point. In the STN–DBS group, the correlation between UPDRS-III and HAMD scores was significant at 1 week with the stimulator on. In the control group, the correlation between UPDRS-III and HAMD scores was insignificant during the evaluation period. The Pearson Correlation Coefficient between UPDRS-III and SDS/HAMD scores of the two groups is shown in Table 3.

3.3. Correlation analysis of electrode stimulating parameters, and SDS and HAMD scores of STN–DBS group

In the STN–DBS group, the mean value of bilateral electrode stimulating voltage amplitude was a random continuous variable. Their frequency was divided into three intervals as follows: 130–145 Hz, 150–165 Hz and 170–185 Hz, and pulse widths were only set at two values: 60 μS and 90 μS. Because of the features of the data, Pearson's Correlation Coefficient, Multiple Serial Correlation and Point Biserial Correlation were used to analyze the correlation between the stimulating parameters and SDS/HAMD scores. Within 18 months postoperatively, the correlation between the mean value of bilateral voltage amplitude and SDS/HAMD scores was significant, while there was no correlation between frequency/pulse width and SDS/HAMD scores. The correlation coefficients are shown in Table 4.

3.4. Regression analysis for the impact of mean value of voltage amplitude of bilateral STN–DBS and UPDRS-III scores on depression of the STN–DBS group

According to the correlation analysis results in Tables 3 and 4, all corresponding UPDRS-III scores, mean values of voltage amplitude of bilateral electrode stimulation and SDS, and the HAMD correlation coefficient in the STN–DBS group, were adjusted to standard scores. Regression analysis was carried out by setting up UPDRS-III scores and mean values of voltage amplitude of the bilateral electrode stimulating as independent variables, and the SDS and HAMD scores as dependent variables. The results demonstrated that correlation between UPDRS-III scores, mean value of bilateral voltages and the standard binary regression equations and the regression coefficient (also called the contribution rate) of SDS scores were significant in the STN–DBS group for 3 months postoperatively. The correlation between mean value of bilateral voltages and the standard unitary regression equations of SDS scores was significant at 6, 12, and 18 months postoperatively. The correlation between UPDRS-III scores/mean value of bilateral voltages and the standard binary regression equations of HAMD scores was not significant at 5 weeks after surgery. There was a significant correlation between the mean value of bilateral voltages and the standard unitary regression equations and regression coefficients of HAMD scores for 18 months postoperatively. All standard regression equation coefficients and test coefficients are shown in Table 5.

4. Discussion

4.1. Analysis of the relations between PD patients' depression state and their improvement of movement disorder

In this study, there are two possible reasons for the improvement of the depressive state of PD patients after the STN–DBS. One is via the relief of the motor symptoms resulting from the STN–DBS and the other is the STN–DBS stimulus itself.

Table 4
Correlation coefficient and significance test between the mean value of voltage/frequency/pulse width of bilateral electrode stimulators and SDS/HAMD scores of the STN–DBS group with PD.

Items	Correlation coefficient				
	Evaluating time point				
	5 Weeks post surgery	3 Months post surgery	6 Months post surgery	12 Months post surgery	18 Months post surgery
Voltage and SDS	0.388*	0.407*	0.387*	0.399*	0.384*
Voltage and HAMD	0.417*	0.413*	0.465*	0.431*	0.404*
Frequency and SDS	0.132	0.298	0.242	0.177	0.120
Frequency and HAMD	0.244	0.176	0.110	0.164	0.206
Pulse width and SDS	0.119	0.105	0.120	0.211	0.132
Pulse width and HAMD	0.286	0.246	0.296	0.269	0.254

* $P < 0.05$ by statistical test.

Table 5
Standard regression coefficients and significance tests between the mean value of bilateral voltages/UPDRS-III scores to the SDS/HAMD scores in the STN–DBS group.

Items		Correlation coefficient				
		Evaluating time point				
		5 Weeks post surgery	3 Months post surgery	6 Months post surgery	12 Months post surgery	18 Months post surgery
UPDRS-III	SDS	0.513**	0.393*	0.314	–	–
Mean voltage		0.484*	0.491*	0.478*	0.383*	0.377*
Test coefficient		0.496	0.310	0.228	0.147	0.142
UPDRS-III		0.279	–	–	–	–
Mean voltage	HAMD	0.445*	0.468*	0.412*	0.403*	0.419*
Test coefficient		0.198	0.219	0.170	0.162	0.176

In the STN–DBS group, the correlation between scores evaluating motor symptoms and depression was not significant pre-operatively or at 12 and 18 months postoperatively, and neither were they in the control group within 18 months postoperatively, which is in agreement with previous studies [10–13]; however, in the STN–DBS group, the correlation between the UPDRS-III and SDS scores was significant at 5 weeks, 3 months and 6 months postoperatively. Standard regression coefficients for UPDRS-III to SDS at 5 weeks and 3 months postoperation were significant, but not at 6 months postoperatively. These results imply that the improvement in the motor symptoms caused by the STN–DBS relieved the depressive mood of PD patients remarkably in the short term.

After the DBS stimulators were switched on there was a notable improvement in the motor symptoms of PD patients, which consequently improved their quality of life, and resulted in remarkable relief of their depressed mood; however, because of the progressive nature of PD, the motor symptoms of most PD patients gradually become worse with time. Moreover, most PD DBS patients were very sensitive to changes in their motor symptoms and repeatedly asked to have the stimulus parameters adjusted; they never felt as comfortable as they had the first time the stimulator was switched on. Although their motor symptoms improved remarkably compared with those of their preoperative state ($P \leq 0.001$), and their UPDRS-III scores remained stable within 18 months after the DBS was "on", they gradually lost the confidence that they would be able to control their progressive disease. It was shown that the long-term effect of improvement in their depression by improvement in their motor symptoms was uncertain.

4.2. Analysis about the impact of the STN–DBS stimulus parameters on PD patients' depression

Some studies have revealed that in humans and primates, five cortico-basal anglia-thalamocortical circuits exist in the brain, which consist of the motor, oculomotor, two prefrontal circuits (dorsolateral and lateral orbitofrontal) and the limbic circuits. The two prefrontal circuits (also referred to as associative circuits) are the dorsolateral prefrontal circuit (DPC) and the lateral orbitofrontal circuit (LOC). These associative circuits and limbic circuits have a close relationship with the function of cognition, emotion and behavior control. Yet the STN is located in the center of these circuits and is a potent adjustor of the circuits' function. For these reasons, the STN–DBS itself may have an impact on depression in PD patients [14–18]. The primate STN has three anatomical subdivisions: the dorsolaterally located somatomotor part (two-thirds of the STN), the ventromedially located associative part (one-third of the STN), and the medial tip represents the limbic part [19,20].

The parameters of the DBS include voltage, frequency, pulse width and contact. In the present study, the dorsolateral motor subregion of the STN was selected as the stimulation target for all the cases. The stimulation mode was unipolar stimulation. The reason behind choosing stimulating contact was to improve the motor symptoms and avoid complications as far as possible. Thus, the brain region which is stimulated can be considered to be identical. Therefore, we considered that selecting the contact area had no relationship with the depressive state of patients. Among DBS parameters, only the mean value of bilateral voltages correlated notably to the SDS/HAMD scores. Together with regression analysis results, it indicated that in the STN–DBS group, the contribution rate of the UPDRS-III to SDS/HAMD scores gradually decreased after the stimulators were on, while the contribution rate of the mean value of bilateral stimulation voltages to SDS/HAMD scores remained relatively stable. We must stress one limitation in our study here. SDS was employed as a screening measure for further evaluation by HAMD. This likely resulted in an under diagnosis of depression and/or depressive symptoms since impaired insight is a common feature of PD patients. However, we hadn't found competing results from the two different scales. This suggests that the mean value of bilateral stimulation voltage of the STN–DBS has a consistent impact on depression in patients. The higher the voltage, the more severe the depression in the patients. This study showed that implanting a DBS electrode in the dorsolateral subregion of the STN has the highest level of effectiveness on motor symptoms in PD patients, and the fewest number of patients suffered from depression [21]. If a DBS electrode were placed deeply into the substantia nigra pars reticulate (SNr), depression may occur [22]. In the present study, depression was made worse as the mean value of bilateral voltages increased. As the voltage increases, DBS may involve more brain regions around the contacts. In view of the new functional model of STN [23], it can be divided into limbic, associative and motor parts without clear-cut segregation between them. So the reason may be involvement of the limbic parts of STN, or other structures associated with mood around STN, such as SNr. Another reason might be inactivation of more voltage dependent ion-channels [24], which is one possible mechanism of DBS.

In the present study, the correlation between STN–DBS frequency/pulse width and depression in PD patients was in significant. This may be due to the relatively low number of cases, to the value features of frequency and pulse width, or to the non-linear relationship between the STN–DBS frequency/pulse width and depression in PD patients. Therefore, we were unable to conclude that frequency and pulse width of the STN–DBS are not associated with depression in PD patients, just because multiple-series relevant and point biserial correlation analysis was not significant. In addition, we used the mean value of bilateral DBS voltage for analysis, paying less attention to the impact of bilateral difference of the DBS voltage. Further research is needed. For example, adding postoperative MRI scanning to confirm the location of contacts, or changing the DBS voltage unilaterally, may aid in understanding these issues more fully in particular, the impact of the STN–DBS itself on the changes in depression levels in PD patients may be clarified. Nevertheless, the present study indicates that voltage of the STN–DBS may have an influence on depression in PD patients.

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