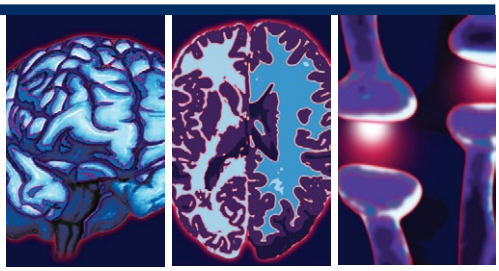

Neuropsychiatric Effects of Subthalamic Nucleus Deep Brain Stimulation in Parkinson Disease in China: A Prospectively Controlled Study

Yi Xie, Junjian Zhang†, Jinsong Xiao

Abstract

Background:

The effects of subthalamic nucleus deep brain stimulation (STN-DBS) on motor symptoms receive much attention, but neuropsychiatric outcomes require further study in China.

Aim:

To investigate the influence of STN-DBS on neuropsychiatric outcomes in patients with PD and the predictive factors in China.

Methods:

We compared 6-month clinical and neuropsychiatric data between 21 PD patients selected for STN-DBS group and 21 PD patients who only received dopatherapy with Mann-Whitney test or independent t test. Main outcome measures included motor symptoms, orientation and attention, memory, verbal fluency, language and visuospatial ability, disease stage, activity of daily life (ADL), anxiety, depression and drug complications. The correlations between baseline data and clinical outcomes were calculated by linear regression.

Results:

Motor abilities (p=0.000), ADL (p=0.047), depression (p=0.009), anxiety (p=0.003) and dopaminergic dosage (p=0.000) outcomes were markedly superior in the DBS group versus control group. No significant changes occurred in global cognition or specific cognitive domains. We also detected negative correlations between motor symptoms and ADL (p=0.002), suggesting recovery in motor symptoms can help predict ADL improvement.

Conclusion:

STN-DBS is a preferable solution to advanced PD in China considering its beneficial effects in motor abilities, ADL, anxiety, depression, dopaminergic medication dosage and cognitive function. ADL improvement can be attributed to recovery in motor symptoms.

Keywords:

Subthalamic nucleus, Deep brain stimulation, Parkinson's disease, Cognition, Psychiatry, Depression, Anxiety

Department of Neurology, Zhongnan Hospital of Wuhan University, Wuhan, China

†Author for correspondence: Junjian Zhang, Department of Neurology, Zhongnan Hospital of Wuhan University, Donghu Road, 169#, Wuhan, China. Tel: +86-027-67812885, Fax: +86 27 68758670, email address: wdsjkx@163.com

Background

In China, approximately 1.99 million people were diagnosed with PD in 2005, and this number is expected to increase to 4.95 million by 2030, accounting for more than 50% of all the PD patients worldwide [1,2]. Nowadays, subthalamic nucleus deep brain stimulation (STN-DBS) is commonly proposed for the treatment of advanced PD, as is widely acknowledged that chronic high frequency stimulation of STN remarkably improves motor symptoms and reduces motor fluctuations, dyskinesia and levodopa requirement [3-4].

Apart from motor symptoms, PD patients also present neuropsychiatric disorders such as cognitive and behavioral disturbances [5]. Some authors declared STN-DBS was relatively safe from the cognitive standpoint, but showed a decline of phonemic and semantic verbal fluency after operation, while others reported a trend towards improved executive functions, attention and working memory [6,7]. The transient verbal fluency decline might be caused by the microlesion effect of the surgery itself, and the long-term verbal fluency impairment might be correlated with the deactivation of the left inferior frontal and temporal gyri [8,9]. A study concerning its effects on mental health as well as quality of life showed that depression and anxiety weren't significantly different in STN-DBS compared with dopatherapy, while a subtle decline in quality of life concerning communication was reported [10]. On the other hand, some authors detected better depression, anxiety and quality of life 3 and 6 months after STN-DBS [11].

Due to the expensive cost of the operation and insufficient attention paid in this field, similar studies fell behind in China and most of them focus on motor symptoms, single depression or anxiety outcomes, resulting in inconsistent conclusions. In the present study we adopted a prospectively controlled design to explore the effects of STN-DBS on multiple neuropsychiatric results, including cognition, depression, anxiety as well as motor abilities, ADL and dopaminergic medication reduction in PD patients in China. We also analyzed possible correlations between baseline data and neuropsychiatric data to explore predictive factors for neuropsychiatric outcomes.

Methods

Patients

In DBS group, 21 patients (9 males and 12 females) were diagnosed with PD according to the UK Parkinson's Disease Brain Bank criteria [12] and underwent DBS at the site of STN at Zhongnan Hospital of Wuhan University. The control group comprised 21 sex- and age-matched patients who didn't meet the surgery indications or refused to receive surgery. All patients gave written informed consent. The study was approved by Medical Ethical Committee of the Zhongnan Hospital of Wuhan University.

Inclusion criteria included 1) a diagnosis and clinical findings of moderately advanced (off-medication Hoehn and Yahr score of 3 or more); 2) age 18-75 years; 3) idiopathic PD with at least 30% improvement in motor symptoms assessed by Unified Parkinson's Disease Rating Scale part III (UPDRS-III) after a levodopa challenge test; 4) severe levodopa-induced motor complications, such as disabling motor fluctuations and dyskinesia's despite optimal adjustment of dopaminergic treatment; 5) able to coordinate in neuropsychiatric assessment. Exclusion criteria included 1) severe psychiatric/behavioral /metabolic/cardiac/respiratory/renal/hepatic diseases; 2) diagnosis of secondary Parkinsonism or multiple system atrophy; 3) surgery contraindications; 4) abnormal brain magnetic resonance image (MRI).

Study protocol

For DBS group, patients were assessed one week before surgery in medication "on" state and 6 months after the surgical procedure in medication "on" and stimulation "on" state to minimize the influence of motor disorders on neuropsychiatric results. For control group, patients were assessed at enrollment and 6 months later in medication "on" state. The "on" state was defined as optimal dopaminergic management or stimulation parameters.

Surgery procedure

The overall surgery methodology was similar to that previously described [3]. The implantable pulse generator (IPG) was turned on a month after surgery and patients returned to the clinic regularly for follow-up. Stimulation parameters were checked to achieve optimal control of motor symptoms.

Clinical evaluations

Clinical evaluation included: 1) psychiatric, behavioral and emotional state, assessed by UPDRS-I; 2) ADL, assessed by UPDRS-II and Schwab-England test; 3) motor abilities, assessed by UPDRS-III; 4) dopaminergic drug

complications, assessed by UPDRS-IV; 5) disease stage, assessed by Hoehn-Yahr scale (H-Y).

Neuropsychiatric evaluations included: 1) cognitive functions, assessed by Addenbrooke's Cognitive Examination-Revised (ACE-R); 2) anxiety and depression, assessed by Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HADA) respectively. ACE-R consisted of 5 components: attention and orientation, memory, verbal fluency, language and visuospatial abilities [13]. Mini Mental State Examination (MMSE) results could be extracted from scores of ACE-R.

Dosage of dopaminergic drugs, stimulation parameters, and adverse effects of surgery were also documented during each evaluation. Medications were converted into levodopa equivalent daily dosage (LEDD) as stated before [14].

■ Statistical analyses

Continuous data were displayed as mean (standard deviation). The magnitude of change was compared between the DBS group and control group with independent *t* test or Mann-Whitney U test. Linear regression was used to determine associations between neuropsychological outcomes and baseline data. $p <= 0.05$ shows statistical significant

Results

■ Baseline characteristics

Baseline characteristics are summarized in Table 1. The DBS group included 21 patients (9 males and 12 females; age ranged from 55 to 75), and the control group included 21 sex/age-matched patients (13 males and 8 females; age ranged from 52 to 75). According to the results, DBS patients had longer disease duration, worse ADL, were more severely affected according to H-Y stage and took more dopaminergic medicine than control group patients. While no significant difference existed concerning sex, age, education, baseline MMSE, UPDRS-III score (medication-on), HAMA, HAMD and verbal fluency between two groups.

■ DBS and control group comparisons

As shown in Table 2, the overall comparison between the two groups yielded no significant differences except for improvement in depression scores on HAMD(p=0.009), anxiety scores on HAMA(p=0.003), psychiatric scores on UPDRS-I(p=0.034), ADL on Schwab-England test(p=0.047) and UPDRS-II(p=0.001), motor abilities on UPDRS-III(p=0.000), dopaminergic drug complications on UPDRS-IV(p=0.022), disease stage on H-Y scale(p=0.034) and LEDD(p=0.000) for DBS group *vs.* control group.

Table 1: Baseline characteristics.

	DBS group (n=21)	Control group (n=21)	*p*
M:F	9:12	13:8	0.226
Age(years)	64.19(6.81)	67.62(7.16)	0.120
Disease duration (years)	8.95(3.65)	4.19(3.12)	0.000*
Education (years)	10.10(3.92)	11.76(4.32)	0.198
MMSE	25.95(3.23)	26.57(2.54)	0.494
H-Y stage (on)	3.07(0.95)	2(0.81)	0.000*
ADL	0.58(0.20)	0.71(0.23)	0.047*
UPDRS-III (on)	19.57(7.97)	15.38(6.03)	0.062
LEDD (mg/day)	875.95(500.64)	453.48(240.57)	0.001*
HAMA	11(8.23)	10.67(6.64)	0.886
HAMD	13.76(10.15)	13.05(10.16)	0.821
Verbal fluency	6.67(2.29)	6.76(2.95)	0.907

*$p <= 0.05$ shows statistical significant

Table 2: Comparison outcomes of mean change scores DBS vs. Control.

	DBS group (n=21)	Control group (n=21)		
	Post minus pre-operation	Follow-up minus baseline	U	*p*
H-Y	-0.29(0.89)	0.095(0.30)	-2.125	0.034*
ADL	0.048(0.17)	-0.048(0.06)	-1.986	0.047*
UPDRS-I	-0.76(1.26)	0.14(1.06)	-2.125	0.034*
UPDRS-II	-5.24(6.12)	0.19(1.69)	-3.468	0.001*
UPDRS-III	-4.33(7.51)	0.95(1.20)	-3.716	0.000*
UPDRS-IV	-1.05(2.46)	0(0.55)	-2.295	0.022*
LEDD	-360.96(455.32)	44.81(116.63)	-4.012	0.000*
MMSE	0.048(1.86)	0.24(1.00)	-0.647	0.517
ACE-R	-0.29(4.60)	-0.38(2.13)	-0.456	0.648
Attention and orientation	0.048(1.07)	-0.14(0.91)	-1.032	0.302
Memory	-0.14(2.52)	- 0.19(1.12)	-0.246	0.806
Verbal fluency	-0.71(1.38)	-0.48(1.02)	-1.574	0.116
Language	-0.048(1.50)	0.048(1.16)	-0.636	0.525
Visuospacial abilities	0(1)	-0.05(0.74)	-0.599	0.549
HAMA	-2.67(3.07)	-0.38(1.66)	-2.926	0.003*
HAMD	-3.43(7.76)	-0.48(2.64)	-2.613	0.009*

*$p <= 0.05$ shows statistical significant

■ Correlational analyzes

The overall results of correlation analyzes were shown in Table 3.

Percent change in LEDD was calculated as (follow-up minus baseline)/baseline. So the higher the value was, the more dopaminergic drug was taken. Briefly, the effects of STN-DBS on cognition, anxiety, depression, ADL, motor

symptoms (differences between follow-up and baseline) did not correlate with demographic data or change in LEDD, although we detected a relationship between motor symptoms on UPDRS-III and ADL(p=0.002), as well as between MMSE and ACE-R(p=0.015).

■ Stimulation parameters and adverse effects

Overall, the stimulation frequency ranged from 100Hz to 150Hz, pulse width from 60us to 90us, and voltage from 1.1v to 2.7v (Table 4). One patient suffered hallucination for 2 consecutive days and recovered back to normal the third day after surgery. Stimulation-related adverse effects included feeling of numbness, pain and discomfort and could be avoided by adjusting to optimizing stimulation parameters during regular outpatient services.

Discussion

The focus of this study is to investigate the changes in neuropsychiatric function and the predictive factors regarding STN-DBS as a therapy for PD in China under medication-on and stimulation-on conditions. Improved depression, anxiety, motor symptoms and ADL, decreased LEDD and unchanged global cognition or other cognitive domains were observed in DBS. Significant linear relationships between motor symptoms and ADL suggested improved motor abilities might predict better ADL. No severe adverse effects occurred during the study.

We should be cautious when interpreting the results. First, baseline disease duration, H-Y stage, ADL and LEDD of the two groups are not matching because patients in DBS group are usually in the more advanced stage. Consequently, the beneficial effects of DBS on motor and ADL is more convincing for DBS group patients considering their worse baseline conditions compared with control group. Second, the recruit of a control group allowed us to assess the net influence of STN-DBS on cognitive and psychiatric function during follow-up. Actually we also detected verbal fluency decline post-surgery in DBS group, which became insignificant when comparing with control, suggesting the decline might originate from the natural process of the disease itself instead of the influence of STN-DBS. Third, no correlation was detected between motor/LEDD and depression/anxiety, suggesting that the improvement in depression/anxiety should be attributed to the surgery itself, but not to recover motor symptoms or less anti-parkinsonism medicine.

Nowadays, STN-DBS is the well-accepted method to treat motor symptoms of advanced PD patients afflicted with levodopa-resistance and motor complications. Through sophisticated pathways, the loss of dopamine neurons in substantia nigra results in hyperactivation of STN, therefore inhibiting cortical activity and causing motor disorders [15]. Chronic high frequency stimulation (above 100Hz) of STN causes effects similar to surgical lesion at the level of brain network, the synapses, the cell and axon membrane, or the neuronal message, resulting in alleviation of motor disorders and alternation of other clinical symptoms.

PD is a progressive neurodegenerative disorder with motor, cognitive, behavioral and autonomic symptoms. Achieving therapeutic effects through chronically stimulating STN, STN-DBS inevitably influences the symptoms anatomically or functionally associated with STN. The expression of post-operative cognitive changes is highly variable across individuals, due

Table 3: Correlation analyses of baseline data and clinical outcomes.

	Motor	MMSE	ACE-R	ADL	Depression	Anxiety
Age	-0.168(0.467)	-0.361(0.108)	-0.200(0.386)	0.141(0.541)	-0.006(0.980)	-0.044(0.850)
Education	0.093(0.689)	-0.255(0.265)	-0.270(0.236)	-0.036(0.877)	-0.151(0.513)	-0.210(0.360)
Duration	0.012(0.958)	-0.059(0.801)	0.094(0.684)	-0.036(0.877)	0.146(0.529)	0.117(0.612)
LEDD	0.168(0.466)	-0.089(0.701)	-0.324(0.152)	-0.036(0.878)	0.173(0.454)	-0.082(0.722)
Motor	-	0.188(0.415)	-0.309(0.174)	-0.641(0.002)*	0.232(0.313)	0.094(0.686)
MMSE	0.188(0.415)	-	0.523(0.015)*	0.102(0.660)	0.078(0.737)	0.225(0.327)
ACE-R	-0.309(0.174)	0.523(0.015)*	-	0.271(0.235)	0.396(0.075)	0.354(0.115)
ADL	-0.641(0.002)*	0.102(0.660)	0.271(0.235)	-	0.016(0.945)	-0.013(0.957)
Depression	0.232(0.313)	0.078(0.737)	0.396(0.075)	0.016(0.945)	-	0.419(0.058)
Anxiety	0.094(0.686)	0.225(0.327)	0.354(0.115)	-0.013(0.957)	0.419(0.058)	-

*p <= 0.05 shows statistical significant

to specific study design, population, personality traits, social environment, and learned behaviors and so on. Up to now, it is widely acknowledged that STN-DBS does not impair overall cognition, although there is a selective decrease in certain cognitive domains. Some found unchanged global cognition, impairments in nonverbal recall, oral information processing speed, and verbal fluency in STN-DBS patients compared to PD controls 2 years after surgery [16]. One Japanese study found improvement in motor and anxiety apart from decline in abstract thinking and verbal fluency 1 month post-surgery in the medication-on and stimulation-on condition. The improvement of motor score remained unchanged while cognitive and psychiatric scores returned to baseline 6 months after surgery [17]. The findings of the present study are partly consistent with previous ones that chronic stimulation of STN is generally safe from the cognitive standpoint.

In North America, most PD patients implant electrode made by Medtronic, USA. While in China, many patients choose electrode produced by Pins, China due to financial reasons. The quality of electrode and stability of impulse generator have been proved credible, but few studies have investigated the clinical outcomes after the application of Pins electrode. In present study, 15 out of 21 patients in DBS group implanted Pins electrode and impulse generator and give us implications about its clinical application.

Appropriate voltage, pulse width and frequency can achieve the best clinical results while minimizing side effects at the same time. In the present study, DBS patients were treated with voltage ranging from 1.1-2.7v, pulse width ranging from 60-90μs and frequency ranging from 100-150Hz. Theoretically, there are 12964 combinations of the three parameters [18], so it is necessary for both neurosurgeons and neurologists to cooperate on programming during follow-ups. If patients develop cognitive disorders, stimulation site should avoid non-sensory/motor subdomains and parameter should favor low-frequency stimulation. Higher frequency might also lead to acute depression so caution should be paid during programming [19].

In China, neurosurgeons mainly focus on motor outcomes and limited attention is paid to neuropsychiatric symptoms before and after STN-DBS. Qian [20] and Jiang [1] reported that bilateral STN-DBS can significantly ameliorate motor symptoms without worsening nonmotor symptoms in patients with moderate or advanced Parkinson's disease, but they only use MMSE and Moca to assess cognition. Another study also found improved motor abilities, ADL and psychiatric symptoms, but didn't assess cognition [21]. Therefore, our comprehensively examined outcomes in multiple cognitive domain, depression and anxiety will contribute to the incomplete data in China.

Table 4: Stimulation parameters of patients in DBS group.

DBS Patient	Frequency	Impulse Width	Voltage
1	100Hz	60μs	1.5V
2	100Hz	60μs	1.5V
3	100Hz	60μs	2.2V
4	130Hz	60μs	2.2V
5	120Hz	60μs	1.6V
6	150Hz	90μs	2.3V
7	150Hz	90μs	2.2V
8	130Hz	60μs	2.7V
9	130Hz	60μs	2.3V
10	150Hz	60μs	2.0V
11	100Hz	60μs	1.1V
12	100Hz	80μs	1.9V
13	130Hz	60μs	1.3V
14	100Hz	60μs	2.1V
15	100Hz	60μs	1.7V
16	100Hz	60μs	2.0V
17	150Hz	60μs	2.3V
18	130Hz	60μs	1.2V
19	130Hz	60μs	1.5V
20	130Hz	60μs	2.0V
21	150Hz	90μs	2.6V

The various cognitive outcomes can be attributed to several factors. The first is the lead trajectory and electrode position. Passage of lead through head of the caudate is associated with global cognitive decline and working memory performance, which emphasizes the importance of precise positioning of the active stimulation electrode within the STN [22]. The second reason is microlesion caused by surgery. Verbal fluency decline shortly after surgery (3-10 days) might be caused by minor fresh hemorrhage, perifocal edema, while long-term decline (10-180 days) is related to the direct effect of STN-DBS [23]. The third reason is the changes in regional cerebral blood flow (rCBF) in associative, limbic, and cerebellar basal ganglia circuits adjusted by STN-DBS [24]. For example, postoperative rCBF in the middle temporal gyrus, medial frontal gyrus and cerebellum was significantly greater in patients with >60% improvement of

UPDRS part III score than in patients with 40-60% improvement [25].

The immediate positive effects on psychiatric symptoms, such as depression, anxiety and fatigue, might be mediated through direct involvement of STN in fear-processing networks and limbic circuits, as well as indirect dopaminergic effects of STN-DBS [20,26,27]. The occurrence of anxiety and acute worsening of depression were most likely due to misplacing of electrodes ventrally to the STN [28], while optimal electrode positions can lead to immediate anti-depressive and mood-elevating effects [29]. Another study reported improvement in emotional well-being 1 year after surgery [30], while a long-term prospective study carried out in China showed scores of HAMA and HAMD stayed unchanged 1 year, 3 years and 5 years post-surgery [1]. We assumed that the improvement in emotional manifestation was most obvious for a short period after surgery, and gradually disappeared several years post-surgery.

The Addenbrooke's cognitive examination-Revised is a brief cognitive screening instrument assessing five domains including orientation and attention, memory, verbal fluency, language and visuospatial ability. Its total score of 100 incorporates the score of widely used MMSE, and provides a more thorough investigation of cognitive function [13]. A cut-off value of 80 gives sensitivity of 94% and specificity of 94%, proving its usefulness as a tool for diagnosing PD dementia [31]. The verbal fluency part contains two items: one is to name words that include Chinese character "□"(which means car) in one minute; while the other is to name animal as many as possible in one minute. Education is the main factor influencing ACE-R results and since education is balanced between groups at baseline, it's fair that we took advantage of ACE-R to assess cognitive state in the present study [32].

Brain stimulation is now mainly applied to the treatment of movement disorders and is also under study for psychiatric applications, which, as a result, may become a new strategy for the modification of cognitive functions. A 71-year-old man with slowly progressive Parkinson-dementia syndrome underwent DBS of the nucleus basalis of Meynert (NBM) besides STN. Stimulation at the site of NBM markedly improved various aspects of cognitive functions by enhancing cholinergic innervation to the cortex [33]. Other stimulation targets include fornix, amygdala, rhinal cortex, hippocampus, pedunculopontine tegmental nucleus and entorhinal cortex as to indicate an alternative way to cope with cognitive disorders in clinical practice [34].

The limitations of this study were the small sample size, which may account for failures to detect statistically significant difference, subjective ratings of scales due to patients' unrealistic expectations of the surgical outcomes, relatively short follow-up period for cognition changes begin to appear obviously and the absence of randomization.

Conclusions

Results from a series of standardized measures demonstrated that in China, STN-DBS was safe for global cognition, and improvement of motor symptoms, ADL, depression and anxiety also favored surgery over dopatherapy in advanced PD stage. Post-operational improvement of ADL is associated with recovered motor symptoms. We suggest further attention should be paid to the possibility of stimulating potential nucleus, such as NBM, hopefully to slow down, even reverse cognitive disorders in the future.

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Yi Xie, Junjian Zhang conducted conception, design of the study, acquisition and interpretation of data, takes responsibility for the integrity of the data and the accuracy of the data analysis, drafting the article, final approval of the version to be published. Jinsong Xiao conducted design of the study, recruit of patients, and final approval of the version to be published.

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