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The Effect of Unilateral Subthalamic Nucleus Deep Brain Stimulation on Depression in Parkinson's Disease

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Abstract

Background—Depression is common in Parkinson's disease (PD) and adversely affects quality of life. Both unilateral and bilateral subthalamic (STN) deep brain stimulation (DBS) effectively treat the motor symptoms of PD, but questions remain regarding the impact of unilateral STN DBS on non-motor symptoms, such as depression.

Methods—We report changes in depression, as measured by the Hamilton Depression Rating Scale (HAMD-17), in 50 consecutive PD patients who underwent unilateral STN DBS. Participants were also evaluated with UPDRS part III, Parkinson's Disease Questionnaire-39, and Pittsburgh Sleep Quality Index. The primary outcome was change in HAMD-17 at 6 months versus pre-operative baseline, using repeated measures analysis of variance (ANOVA). Secondary outcomes included the change in HAMD-17 at 3, 12, 18, and 24 months post-operatively and correlations amongst outcome variables using Pearson correlation coefficients. As a control, we also evaluated changes in HAMD-17 in 25 advanced PD patients who did not undergo DBS.

Results—Participants with unilateral STN DBS experienced significant improvement in depression 6 months post-operatively (4.94 ± 4.02) compared to preoperative baseline (7.90 ± 4.44) (mean $\pm$ SD) ($p < 0.0001$). HAMD-17 scores did not correlate with UPDRS part III at any time-point. Interestingly, the HAMD-17 was significantly correlated with sleep quality and quality of life at baseline, 3 months, and 6 months post-operatively. Participants without DBS experienced no significant change in HAMD-17 over the same interval.

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Conclusion—Unilateral STN DBS improves depression 6 months post-operatively in patients with PD. Improvement in depression is maintained over time and correlates with improvement in sleep quality and quality of life.

Keywords

Parkinson's disease; subthalamic nucleus; deep brain stimulation; depression; sleep; non-motor symptoms

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease, which is clinically diagnosed by motor symptoms of bradykinesia, rigidity, rest tremor, and postural instability. Many patients also suffer from non-motor symptoms, including autonomic dysfunction, cognitive changes, depression, or sleep disturbances, which in many cases can be more disabling and detrimental to quality of life than the motor symptoms(1, 2). Of these non-motor symptoms, depression is the strongest predictor of negative health-related quality of life(3–5). Importantly, while depression affects 30–40% of PD patients(4, 6), this symptom often cannot be explained as simply a reaction to the diagnosis of a chronic disease(7), nor to therapy with medications used to treat Parkinson's disease(6, 8). Non-motor symptoms often occur before motor symptoms, and 10–15% patients already have a diagnosis of depression when diagnosed with PD(3, 6, 8). Due to the prevalence and impact of depression in PD, it is important to recognize how current PD treatments affect this disabling symptom.

Like depression, sleep dysfunction also influences quality of life(5, 9). This non-motor symptom affects 74–98% of PD patients and manifests as insomnia, sleep fragmentation, REM behavior disorder, excessive daytime sleepiness, and/or nocturia(2, 10, 11). In the general population, there is a well-recognized association between sleep disorders and depression and sleep dysfunction predicts poor response to treatment of mood disorders(12, 13). Although this association has also been proposed in PD(14, 15), gaps remain in our understanding of the relationship between sleep dysfunction and depression in response to PD therapeutics.

Whether performed bilaterally or unilaterally, subthalamic nucleus (STN) deep brain stimulation (DBS) is safe and effective for motor symptoms, quality of life, and activities of daily living in patients with moderate to advanced PD(16–19). Though bilateral STN DBS improves motor symptoms more than unilateral surgery, PD motor symptoms are typically asymmetric and responsive to dopaminergic therapy. In this context, we and others have argued that unilateral DBS (followed by staged contralateral surgery if needed) is well-tolerated and can provide sufficient motor improvement for up to 5 years(18, 20, 21). The effects of bilateral STN DBS on mood are controversial. Some studies show that DBS ameliorates depressive symptoms and improves quality of life(22, 23), while one case study showed that stimulation can reversibly evoke severe depressive symptoms(24). Further, a large multicenter study reported a higher than expected rate of attempted and completed suicide in PD patients with STN DBS, as compared to World Health Organization statistics, suggesting potential effects on impulsivity and/or depression(25). However, this study did

not have control subjects with PD who did not have DBS(25). While unilateral STN DBS improves motor symptoms, its effects on depression have not been extensively investigated(26). To better characterize the impact of DBS therapy on this disabling symptom, we hypothesized that unilateral STN DBS improves depression in patients with moderate to advanced idiopathic PD. Additionally, we examined the relationships between depression and changes in motor symptoms, quality of life, and sleep quality in PD patients following unilateral STN DBS.

METHODS

Patients

Selection of patients for STN DBS has been previously described(27). Briefly, each potential DBS candidate underwent pre-surgical neuropsychological testing and brain MRI. Our multidisciplinary DBS committee discusses all potential DBS candidates to determine suitability for surgery and recommendations for treatment. Patients were excluded if neuropsychological testing or history revealed active depression (uncontrolled on medications), dementia, or psychosis, or if MRI demonstrated severe cortical or subcortical atrophy or significant ischemic changes. As previously described, surgical targeting for electrode localization was achieved with frame-based stereotaxy, microelectrode recordings, and intra-operative evaluation of clinical effects of stimulation(18). Post-operative 1.5 Tesla volumetric brain MRI was used to confirm appropriate electrode placement and to screen for potential complications. In all cases, the DBS electrode was placed contralateral to the side most affected by motor symptoms. Our routine practice for PD is to place unilateral DBS, followed by a staged implantation on the contralateral side at a later time if necessary(18, 21).

Eighty-seven consecutive patients with PD (UK Brain Bank criteria (2)) who underwent unilateral STN DBS surgery at UAB were evaluated before surgery and at regular intervals post-operatively. Patients who underwent the staged contralateral procedure earlier than 6 months after the initial procedure (N=6), or who had incomplete data at the 3- or 6-month assessment period were excluded, leaving 50 participants in the final analysis. Participant demographics including age, sex, duration of disease, side of DBS placement, and DBS settings 6 months post-operatively are shown in Table 1. This study was approved by the local Institutional Review Board (IRB) at UAB, which approved a waiver of consent for collection of these data as part of routine clinical care and quality control.

Study design

In this prospective, within-subject evaluation, participants completed the Hamilton Depression Rating Scale(28) (HAMD-17) pre-operatively, and at 3, 6, 12, 18, and 24 months following unilateral STN DBS. The HAMD-17 questionnaire has been validated as a screening and diagnostic tool for depression in PD(29). Subgroup analyses were performed on participants with left and right STN DBS and on those who screened positive for depression at baseline (HAMD-17 > 11) and those with HAMD-17 ≤ 11(29). All participants were also evaluated with the Unified Parkinson's Disease Rating Scale (30)(UPDRS) Part III in the "practically defined off" medication state (morning assessment following at least 12

hours with no antiparkinsonian medication)(31) at baseline and “off” medicines with stimulation on at the 3 and 6 month post-operative time points. Additional outcomes included the Pittsburg Sleep Quality Index (PSQI)(32) and the Parkinson’s Disease Questionnaire-39 (PDQ-39)(33). The outcomes on the PSQI, UPDRS Part III, and the PDQ-39 in this cohort have previously been reported(18, 21, 34). Levodopa equivalent dose (LED) was calculated for each time point using the following conversion: 100 mg dose of levodopa was defined as equivalent to 133 mg of controlled-release levodopa; 75 mg of levodopa plus entacapone; 1 mg of pramipexole, pergolide, lisuride, or cabergoline; 5 mg of ropinirole; and 10 mg of bromocriptine or apomorphineI (16).

To evaluate longitudinal change in HAMD-17 over a similar time interval in participants receiving best medical therapy who did not undergo DBS, we evaluated 25 age and gender matched PD patients in a cohort of participants being screened for other non-motor symptoms. These values were descriptively compared to those who underwent DBS.

Statistical analysis

The primary outcome measure was the change in HAMD-17 at 6 months compared to the pre-operative baseline. Secondary outcomes included the change in HAMD-17 at 3, 12, 18 and 24 months post-operatively. The UPDRS, Part III in the “off” medication state and the LED were evaluated as covariates. Additionally, correlations between the HAMD-17 and sleep quality, measured by PSQI; quality of life, measured by PDQ-39; and motor symptoms, measured by UPDRS Part III were calculated. Descriptive statistics were employed to calculate mean, standard deviation, and standard error of the mean. Multivariable regression analysis with repeated measures within patients was used to analyze outcome measures using changes from baseline to assess incremental changes per patient. Correlations amongst variables were calculated with Pearson Correlation Coefficients. Statistical significance was considered achieved when the p-value was <0.05.

RESULTS

Depression improved at 6 months post-operatively and was sustained over time

Unilateral STN DBS significantly improved depression scores 6 months post-operatively compared to pre-operative baseline, with the average HAMD-17 score decreasing from 7.9 ± 4.4 (mean $\pm$ SD) to 4.9 ± 4.0 ($p < 0.001$). These outcomes did not change after adjustment for age, sex, disease duration, or side of surgery. Specifically, there were similar improvements in HAMD-17 scores in those with left (baseline: 7.3 ± 4.4 ; 6-month: 4.7 ± 4.4 ; $p = 0.0013$) and right (baseline: 8.5 ± 4.5 ; 6-month: 5.2 ± 3.7 ; $p = 0.0044$) STN DBS.

To determine the influence of baseline depression status on HAMD-17 outcomes, we performed subgroup analyses on participants who screened positive for depression (HAMD-17 > 11) (N=11) prior to surgery and those who did not (HAMD-17 $\leq$ 11) (N=39). Those with a positive screen for depression showed improvement from pre-operative baseline (13.1 ± 2.4) to 6 months post-operatively (6.7 ± 4.4) ($p < 0.001$). Interestingly, improvements in HAMD-17 scores were significant even among participants who did not screen positive for depression at baseline, improving from 6.2 ± 3.2 to 4.4 ± 3.8 ($p = 0.0035$).

Only 3 participants had HAMD-17 scores >11 at the 6-month time point. Improvement in depression was apparent as early as 3 months post-operatively ($p<0.001$) and was sustained over time through the last available assessments at 24 months (Figure 1).

Use of antidepressant and anxiolytic medications was similar between the pre-operative baseline and 6-month follow up. Specifically, at pre-operative baseline, 48% of participants were taking antidepressant medications and 24% were on anxiolytics. At 6-months post-operatively, 46% and 24% of participants were taking antidepressants and anxiolytics, respectively. This was stable at the time of last follow up, with 46% and 17% on antidepressants and anxiolytics, respectively.

In a cohort of 25 age- and sex-matched participants who did not undergo DBS, there was no change in HAMD-17 over time (6.96 ± 5.19 at baseline and 5.48 ± 4.59 at follow up; $p=0.138$). Those in this group did have shorter disease duration (8.1 ± 4.7 years) compared to those in the DBS group (11.6 ± 5.5 years) ($p=0.009$), but with no significant difference in age or sex between groups.

Motor improvements

As previously reported(34), patients who underwent unilateral STN DBS had a significant improvement in motor symptoms, measured by the UPDRS Part III in the “practically defined off” medication state, at 3 months post-operatively compared to pre-operative baseline. This improvement continued to 6 months, with little change between the 3- and 6-month post-operative evaluations (Table 2). This motor improvement allowed for decreased anti-Parkinsonian medications by 24.8% as measured by LED (Table 2).

Depression correlates with sleep quality and quality of life

Scores on the HAMD-17 were significantly positively correlated with sleep quality, as measured by the Pittsburgh Sleep Quality Index at baseline ($p<0.001$), 3-months ($p<0.001$), and 6-month post-operatively ($p<0.001$), indicating that depression correlates with worse sleep quality. Additionally, the degree of depression was significantly correlated with the quality of life measurements at the pre-operative ($p<0.001$), 3-month ($p<0.001$), and 6-month ($p=0.005$) time points (Table 3). Interestingly, HAMD-17 scores did not correlate with motor symptoms, as measured by the UPDRS, Part III, at any time point ($p=0.963$ pre-operatively and $p=0.076$ 6 months post-operatively). Further, there was no correlation between the change in HAMD-17 and UPDRS from pre-operative baseline to 6-months post-operative follow-up ($p=0.663$).

Adverse behaviors

Of the 50 participants in the study, 3 reported adverse behavioral events. One participant was incarcerated for sexual assault after staged placement of the second stimulator, which occurred 22 months after the initial stimulator was placed. These behaviors ceased once dopamine agonists were discontinued. An additional participant developed impulsive behavior with hypersexuality and alcohol abuse 2 years after left STN DBS placement. These symptoms also resolved with reduction of dopamine agonists. Another participant had two suicide attempts, the first occurred 6 months after placement of right STN DBS. This

participant's suicidal ideation seemed to improve for several months by turning the DBS off at night, but he attempted suicide again 14 months post-operation. He did not have any reported history of suicidal ideation or attempt prior to surgery. Baseline HAMD-17 for these participants was 9, 14, and 3, respectively.

DISCUSSION

This within-subject, prospective, longitudinal study provides evidence that unilateral STN DBS improves depression for up to 2 years after surgery in patients with moderate to advanced idiopathic PD. In contrast, an age- and sex-matched sample of 25 PD patients without DBS demonstrated no significant improvement in depression over 6 months. Additionally, we demonstrate robust correlations between depression and subjective sleep quality and quality of life at baseline and at 3 and 6 months after unilateral STN DBS surgery. This is the only study of which we are aware to demonstrate this relationship between mood and sleep following treatment with unilateral STN DBS. Further, we did not find a correlation between depression and motor symptoms, supporting the idea that depression is not simply a reaction to motor deficits, but also a separate symptom of the underlying neurodegenerative process of advanced PD(35).

Our results suggest that unilateral STN DBS has beneficial effects on depression for up to 2 years. Further, our findings do not support the notion that STN DBS is behaviorally adverse at the group level, as even the most severely depressed patients in our sample showed improvement in depression following unilateral surgery. Similar to our findings, Chopra and colleagues observed a reduction in depression by HAMD in 49 participants 6 months after STN DBS(22) and Funkiewiez and colleagues showed improvement in depression for up to 3 years following bilateral STN DBS(23). In contrast, Weaver and colleagues found no improvement in depression following bilateral surgery(19). Few other studies have investigated the effects of unilateral STN DBS on mood outcomes. One such study randomized PD patients to receive unilateral STN or globus pallidus interna (GPI) DBS and found no differences in mood between the two groups, but an evaluation of all the participants regardless of stimulation target did show an improvement in "happiness" on a visual analog mood scale(36).

Given its clinical heterogeneity, improvement in depression following unilateral STN DBS is likely multifactorial and related to improvements in motor function, sleep quality, quality of life, and/or to medication reduction in individual patients. However, levodopa therapy can reduce depression(37), which would further support efficacy of unilateral STN DBS improving depression, even in the setting of reduced LED. Further, it is possible that STN DBS stimulation could influence brain structures responsible for mood. Specifically, STN has limbic territories, and spread of stimulation to these sites could influence depression(38). Stimulation could also be affecting other monoaminergic pathways important for mediating mood. Though dopaminergic dysfunction can certainly play a role in depression, other monoaminergic structures are also implicated in depression (serotonergic raphe nucleus and the noradrenergic locus coeruleus) and are involved in the neurodegenerative pathogenic process of PD(39). These systems are also involved in regulation of behavioral state and may

therefore explain the correlation noted in this study between depression and sleep dysfunction.

This study has several strengths and some limitations. Strengths include the repeated assessment of depression over time, the relatively large sample size, the novel exploration of relationships between depression and sleep quality in the context of DBS, and the inclusion of age- and sex-matched PD patients who did not have DBS. Additionally, this study provides reassuring safety data regarding the effects of unilateral STN DBS for PD on mood and behavior. The most important limitation of this study is the lack of a sham stimulation group. Thus, a potential contribution of the placebo effect is unmeasured. Despite this, we would not have expected a placebo effect to persist over the entire 24-month study duration. Second, although HAMD has been verified as an appropriate questionnaire to use for dichotomizing PD patients into depressed and not depressed groups and used as a secondary outcome in numerous DBS studies, it is not PD-specific and some of the items could be worsened by physical symptoms of PD and not depression per se. Third, a relatively small minority of patients (N=6) underwent the contralateral DBS surgery before the 6 month time point and were excluded, potentially excluding patients with more severe motor and depression symptoms. However, we calculated the baseline “off” UPDRS part III and HAMD-17 scores for the 6 participants who underwent staged surgery before 6 months and found no difference between that group and the 50 participants included in this analysis (UPDRS $p=0.511$; HAMD-17 $p=0.324$).

Although some severe adverse behavioral events occurred, these are difficult to interpret because of the lack of a parallel control group and the infrequency of these events. Importantly, without a sham stimulation or randomized medical control group, the conclusion that DBS caused behavioral side effects can seldom be made with great confidence, especially given the severity of PD symptoms in these patients and their ongoing need for dopamine agonists and other medications with potentially potent effects on behavior. In fact, in two studies that randomized patients to DBS or best medical therapy, one showed a similar number of adverse psychiatric events in both groups, while another showed depression as an adverse event more frequently in the DBS group (19, 40). In an evaluation of potential contributors to suicide in PD patients following STN DBS, Voon and colleagues found that pre-operative history of depression, younger age, being single, previous suicide attempts, and impulse control disorders were associated with attempted suicides (25). For our cases, impulse control disorders associated with dopamine agonist use appeared to contribute in at least two of the three cases. Regardless of underlying cause, the current findings emphasize the importance of discussion of both potential positive and negative mood/behavioral outcomes with candidates for DBS prior to surgery. Further research is needed to understand the etiology of these outcomes in the setting of overall improvement in subjective mood symptoms.

In summary, this study provides evidence that unilateral STN DBS improves depression in patients with moderate to advanced PD and that this improvement correlates with improved sleep quality and quality of life. Further, improvement in depression did not correlate with changes in motor symptoms. Our findings support that well selected patients who undergo unilateral STN DBS surgery will benefit not only from motor improvement but also from

improvement of these two disabling non-motor symptoms. These findings also support the bidirectional relationship between mood and sleep. Further research is needed to understand the mechanisms of improvement in mood dysfunction induced by both unilateral and bilateral STN DBS.

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Abbreviations

DBS	deep brain stimulation
ESS	Epworth Sleepiness Scale
GPI	globus pallidus interna
HAMD-17	Hamilton Depression Rating Scale
LED	Levodopa Equivalent Dose
PD	Parkinson's disease
PDQ-39	Parkinson's disease Questionnaire-39
PSQI	Pittsburgh Sleep Quality Index
STN	subthalamic nucleus
UPDRS	Unified Parkinson's disease Rating Scale

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HIGHLIGHTS

- Unilateral STN DBS improves depression in patients with Parkinson's disease.
- Improvement in depression correlates with improvements in subjective sleep quality and quality of life, but not with motor symptoms.
- Improvement in depression following unilateral STN DBS is sustained over up to 2 years.

Figure 1.

Improvement in depression is sustained over time. Fifty participants were evaluated at baseline, 3 months, and 6 months. Fewer participants were available for follow-up evaluation at the 12-month (N=31), 18-month (N=24), and 24-months (N=11) post-operative time points.

* $p < 0.0001$, ** $p = 0.0002$, *** $p = 0.0291$ compared to baseline

Table 1

Participant Demographics

Age (years)	
Mean $\pm$ SD	60.3 $\pm$ 9.6
Range	37 – 76
Sex (% male)	62%
Duration of Disease (years)	
Mean $\pm$ S.D.	11.6 $\pm$ 5.5
Range	2.8 – 30.1
Side of Stimulator Placement (% Left)	52%
DBS settings at 6 months: Mean $\pm$ SD	
Amplitude (V)	3.4 $\pm$ 0.6
Pulse width (μ sec)	86.4 $\pm$ 26.9
Frequency (Hz)	159.4 $\pm$ 14.8

Table 2

Motor symptoms scores and Levodopa equivalent dose at baseline and follow up

	Pre-operative baseline	3 months post-op	6 months post-op
UPDRS part III, “off” medication	35.16 ± 1.39	20.95 ± 1.42 *	20.42 ± 1.41 *
Levodopa equivalent dose	1180.55 ± 76.29	909.02 ± 68.73 *	887.08 ± 61.21 *

Values are mean ± SEM

*
p-value <0.0001 compared to baseline

Table 3

Correlation of depression with sleep quality and quality of life

	HAMD-17 baseline r (p-value)	HAMD-17 3 months r (p-value)	HAMD-17 6 months r (p-value)
PSQI at baseline	0.62 (p < 0.0001)		
PSQI at 3 months		0.67 (p < 0.0001)	
PSQI at 6 months			0.61 (p < 0.0001)
PDQ-39 at baseline	0.47 (p = 0.0008)		
PDQ-39 at 3 months		0.58 (p < 0.0001)	
PDQ-39 at 6 months			0.39 (p = 0.0050)