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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 ± 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.

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.

1. 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

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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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.

2. Methods

2.1. 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 intraoperative evaluation of clinical effects of stimulation [18]. Postoperative 1.5 T 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 postoperatively. 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.

2.2. 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 $\leq$ 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 h 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.

Table 1
Participant demographics.

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