Do Stable Patients With a Premorbid Depression History Have a Worse Outcome After Deep Brain Stimulation for Parkinson Disease?

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BACKGROUND: Deep brain stimulation (DBS) has been associated with mood sequelae in a subset of patients operated on in either the subthalamic nucleus or the globus pallidus internus for the treatment of Parkinson disease.

OBJECTIVE: To compare mood and motor outcomes in those with and without a presurgical history of depression.

METHODS: Unilateral subthalamic nucleus or unilateral globus pallidus internus DBS patients followed up for a minimum of 6 months were included. All patients underwent a comprehensive outpatient psychiatric evaluation by a board-certified psychiatrist. Psychiatric diagnoses were based on *Diagnostic and Statistical Manual*, fourth edition, text revision, nomenclature (American Psychiatric Association, 2000). Motor and mood outcomes were compared.

RESULTS: A total of 110 patients were included. There were no significant differences in baseline variables between the 2 groups. Those with a preoperative history of depression had significantly higher Beck Depression Inventory scores than the nondepression group after DBS (8.97 $\pm$ 7.55 vs 5.92 $\pm$ 5.71; $P = .04$). Patients with a depression history had less improvement (11.6%) in pre/post-DBS change when Unified Parkinson Disease Rating Scale motor scores were compared ($P = .03$) after adjustment for stimulation site and baseline demographic and clinical variables. Patients with a higher levodopa equivalent dose had a worse clinical motor outcome.

CONCLUSION: Patients with a preoperative depression history had higher Beck Depression Inventory scores after DBS and significantly less (albeit small) improvement in pre/post-DBS change in Unified Parkinson Disease Rating Scale motor scores than patients without a history of depression.

KEY WORDS: DBS, Deep brain stimulation, Depression, DSM, Outcomes, Psychiatry, Psychology

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Deep brain stimulation (DBS) has been associated with mood sequelae in a subset of patients operated on in either the subthalamic nucleus (STN) or the globus pallidus internus (GPi) for advanced Parkinson disease (PD).[1-4] The mechanisms and frequency of these symptoms remain largely unknown, although many groups have been actively devoting resources to better understand the nonmotor effects of stimulation. Despite the use of neuropsychological testing at many expert centers, psychiatric screening continues to be used less frequently.[1,5] Here, we aim to examine a cohort of STN and GPi DBS patients who preoperatively had interdisciplinary screening (neurology, neurosurgery, neuropsychology, and psychiatry) for psychiatric illness. Patients with a current diagnosis of major depressive disorder were treated before DBS implantation and noted to no longer meet criteria for a major depressive episode before surgery. Additionally, patients

ABBREVIATIONS: BDI, Beck Depression Inventory; **DBS,** deep brain stimulation; **DSM-IV-TR,** Diagnostic and Statistical Manual, fourth edition, text revision; **GPi,** globus pallidus internus; **PD,** Parkinson disease; **STN,** subthalamic nucleus; **UPDRS,** Unified Parkinson Disease Rating Scale; **VAMS,** Visual Analog Mood Scale

with a history of major depression were identified by careful chart review, personal history, and collateral information provided by the family. Our intent was to compare mood and motor outcomes in those with and without a presurgical history of depression.

METHODS

Psychiatric Analysis

A retrospective database review of the University of Florida DBS experience from 2002 to 2008 was performed. Included in the study were PD patients who had either unilateral STN or unilateral GPi DBS who were followed up for a minimum of 6 months. All patients underwent a comprehensive outpatient psychiatric evaluation by a board-certified psychiatrist (H.W.). Psychiatric diagnoses were based on *Diagnostic and Statistical Manual*, fourth edition, text revision (DSM-IV-TR), nomenclature (American Psychiatric Association, 2000).[6] Strict formal use of the structured clinical interview for DSM-IV was not included. In most cases, the psychiatrist's diagnosis was entered into the database by the psychiatrist. In select cases, it was confirmed through chart and database review if in question. All patients had major depressive disorder. Patients were considered to have a history of depression only if information (from all sources) reached the threshold for DSM-IV criteria for a major depressive episode. This included a lifetime history and was not qualified as recurrent or single episode. Baseline preoperative characteristics, including age, disease duration, surgical target, handedness, race, implantation side, levodopa equivalent dose, Beck Depression Inventory (BDI) scores, Visual Analog Mood Scale (VAMS) scores, Unified Parkinson Disease Rating Scale (UPDRS II; activities of daily living) scores, and UPDRS III motor on/off dopaminergic testing at preoperative baseline, were included in the analysis. The UPDRS III motor on/off DBS scores with and without dopaminergic therapy at the 4- and 6-month follow-up visits were also used in the analysis. The PD patients were divided into those with and those without a history of major depression. Motor (UPDRS change) and mood (VAMS and BDI) outcomes were compared between groups. The data were collected and stored as part of an Institutional Review Board–approved prospective database on movement disorders and DBS therapy at the University of Florida Movement Disorders Center, Gainesville, Florida (INFORM). The data were logged prospectively by participating investigators and harvested and managed by a full-time database manager. Proposals to use the data such as those presented in this article were peer reviewed by an interdisciplinary Data Analysis Committee.

Statistical Analyses

Descriptive statistics were used to compare the baseline characteristics between those with and without a depression history. A 2-sample *t* test was used to compare the 2 groups on mood outcome at 4 to 6 months as measured by the BDI. Furthermore, percent change scores for the UPDRS motor evaluations were computed by comparing preoperative off-medi cation and on-medication (denoted by Y0) scores and preoperative off-medication and 4-month off-medication on DBS scores (denoted by Y). These change scores were then compared between those with and without a history of depression through the use of regression analyses with adjustment for baseline demographic, clinical variables, and stimulation site. All statistical tests were performed at a 0.05 significance level with SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 110 patients were included in the study (40 with a DSM-IV diagnosis/history of major depressive disorder and 70 with no depression history). The general characteristics of the positive and negative groups for the presence of depression and the combined group are summarized in Table 1. Of the combined cohort of 110 patients, 33 (30.0%) received GPi stimulation; the overall proportion of patients who received GPi DBS was slightly higher among those who had a screening psychiatric interview incorporating DSM-IV-TR diagnostic criteria and terminology that revealed depression (37.5%) than those without a positive depression history (25.7%). There were no significant differences in baseline demographic and clinical variables between the 2 groups, including no differences between the groups on the mood scales of the VAMS or BDI (see Table 1). There were no differences in UPDRS II activities of daily living scores between groups.

Table 2 summarizes the mean and standard deviation scores for the post-DBS mood outcome measured by VAMS and the BDI scale comparing the depression and nondepression groups. All major depression was treated and in partial remission (no significant symptoms of depression for < 2 months) or full remission (no significant symptoms of depression for > 2 months) before DBS surgery; ie, none of the patients were depressed at the time of surgery. Those in the depression group had significantly higher BDI scores than the nondepression group after DBS (8.97 ± 7.55 vs 5.92 ± 5.71; $P = .04$).

Results from the regression analysis of UPDRS III change between off/on medication before DBS and between pre/post DBS off medication are presented in Table 3. For the off/on-medication change before DBS, we found that younger patients and patients who had had a diagnosis of PD for a longer time were associated with significantly larger motor improvement from medication. For the pre/post-DBS change in UPDRS motor scores, the depression group and patients with larger levodopa equivalent dose had significantly less improvement after DBS surgery after adjustment for stimulation site and baseline demographic and clinical variables.

DISCUSSION

The results of this study reveal that patients with a preoperative positive screening for current major depression or a history of major depression may experience mildly diminished motor and/or mood outcomes. Stated in a more clinically relevant way, the findings suggest that in well-selected DBS patients, the presence of the comorbidity of depression (if stable) may only mildly affect mood or motor outcome. The presence of depression, along with large doses of dopaminergic medications, should be kept in mind by clinicians as being potentially associated with a slightly inferior motor outcome. This could possibly be explained by an increased disease burden in this cohort or alternatively by less effort on motor scales (owing to mood dysfunction); however, the exact

TABLE 1. Comparison of Baseline Demographic and Clinical Characteristics Between the Depression and Nondepression Groups[a]

Variable	Overall	Depression Group (n = 40)	Nondepression Group (n = 70)	P
GPi stimulation, n (%)	33 (30)	15 (37.5)	18 (25.7)	.19
Stimulation on the left side, n (%)	62 (56.4)	22 (55)	40 (57.1)	.37
Age, y	60.85 (8.79)	60.03 (8.38)	61.33 (9.04)	.46
Female, n (%)	29 (26.4)	11 (27.5)	18 (25.7)	.84
Left-handed, n (%)	11 (10.5)	5 (12.8)	6 (9.1)	.55
Hispanic race, n (%)	10 (9.1)	4 (10)	6 (8.6)	.49
Time with motor symptoms, mo	152.09 (60.33)	160.3 (68.2)	147.26 (55.14)	.28
On-medication UPDRS motor score	23.41 (8.01)	24.45 (6.91)	22.75 (8.63)	.30
Off-medication UPDRS motor score	43.48 (11.83)	46.05 (11.94)	41.99 (11.6)	.08
Beck Depression Index	11.78 (6.74)	12.37 (7.13)	11.44 (6.55)	.52
UPDRS section II activities of daily living score	19.12 (6.59)	19.12 (6.48)	19.12 (6.69)	.998

[a]GPi, globus pallidus internus; UPDRS, Unified Parkinson Disease Rating Scale. Values are mean (SD) when appropriate.

reasons remain unknown. One other potential contributing explanation could be that the presence of a history of depression could result in a more severe disturbance of mood-regulating circuits in more severe cases of PD. Our cohort of patients was screened by an experienced interdisciplinary DBS team (neurologist, neurosurgeon, neuropsychologist, and psychiatrist) and therefore may not be representative of all DBS centers. Although the appropriateness of screening and of the use of neuropsychologists and psychiatrists in this process has been discussed intensely by experts,[1,5,7,8] standards have yet to be established.

It is interesting to note that the group receiving GPi DBS had a higher likelihood of premorbid depression. Regarding GPi vs STN, many patients in the cohort came from the National Institutes of Health's Cognition and Mood in Parkinson's Disease STN vs GPi DBS (COMPARE) trial and were randomized to STN or GPi.[4] For those patients, there was no bias. For the other patients included, there was a potential bias in that the interdisciplinary team may have been more inclined to choose GPi over STN for cognitive and mood issues preoperatively. These issues should be considered when the data are being interpreted.

TABLE 2. Mean and Standard Deviation for the Post–Deep Brain Stimulation Mood Outcome Measured by the Visual Analog Mood Scale and Beck Depression Index in the Depression and Nondepression Groups[a]

Subscales	Overall	Depression Group	Nondepression Group	P
Afraid	51.2 (10.97)	51.27 (10.85)	51.16 (11.14)	.96
Confused	50.88 (10.12)	52.21 (11.12)	50.11 (9.51)	.34
Sad	50.66 (10.99)	51.94 (12.78)	49.91 (9.85)	.40
Angry	50.64 (11.18)	50.73 (11.16)	50.6 (11.29)	.96
Energetic	42.17 (11.1)	41.55 (10.83)	42.53 (11.34)	.69
Tired	51.1 (10.12)	49.76 (10.05)	51.88 (10.16)	.34
Happy	48.18 (10.19)	49.82 (7.98)	47.23 (11.24)	.25
Tense	52.24 (11.31)	55.16 (13.7)	50.5 (9.33)	.07
BDI	7.02 (6.56)	8.97 (7.55)	5.92 (5.71)	.04

[a]BDI, Beck Depression Inventory. This table details the information revealing that the depression patients had a tendency to be tenser and had higher BDI scores after deep brain stimulation.

One key issue that has surfaced recently in the DBS field has been the potential risk of suicide. Voon and colleagues[3] performed a 55-center international survey using $>$ 5000 patients. The completed and attempted suicide rates were both $<$ 1%. There was an elevation in suicide in the first postoperative year. These investigators identified "postoperative depression, and a previous history of impulse control disorders" or alternatively "compulsive" medication use to be associated suicide factors.[3] The role of preoperative psychiatric screening was not investigated in this large cohort, and it should be kept in mind that the data were derived by survey. There were no suicide attempts or completed suicides in this study cohort reported during the study interval.

There were several important limitations in our study. First, moderate to severe dementia was excluded in all participants. Furthermore, any active psychiatric disease, if present, was stabilized before any patient was subjected to an operation. We do not know how untreated psychiatric disease would fare, and we do not have scientific equipoise to perform such a comparison. Our study did not examine other psychiatric comorbidities beyond depression. It is unknown, for example, what the impact of premorbid anxiety and premorbid bipolar symptoms may have been on the ultimate outcome of DBS; however, they were infrequent in occurrence in our data set. Our results would have been cleaner if medications were not adjusted postoperatively;

TABLE 3. Results From Regression Analysis on Unified Parkinson Disease Rating Scale III Change Between Off and On Medication Before Deep Brain Stimulation and Between Before and After Deep Brain Stimulation Off Medication[a]

	Off/On-Medication Change (Y0)			Pre/Post-DBS Change (Y)		
Source	Value	SE	P	Value	SE	P
Depression group	−6.248	3.864	.11	−11.647	5.251	.03
GPi stimulation	5.248	4.111	.21	0.956	5.447	.86
Age	−0.717	0.237	.003	−0.550	0.322	.09
Female	0.102	4.455	.98	−5.854	5.812	.32
Left-handed	5.542	6.514	.40	11.994	8.405	.16
Hispanic race	4.625	6.724	.49	8.098	8.463	.34
Left-side stimulation	5.963	3.842	.13	−3.485	4.977	.49
Levodopa equivalent dosage	−0.004	0.005	.34	−0.013	0.006	.03

[a]DBS, deep brain stimulation; GPi, globus pallidus internus; UPDRS, Unified Parkinson Disease Rating Scale. Y0 = (UPDRS off medication at baseline − UPDRS on medication at baseline) × 100 / UPDRS off medication at baseline. Y = (UPDRS off medication at baseline − UPDRS off medication at 4 months) × 100 / UPDRS off medication at baseline. This table reveals the results from a regression analysis on UPDRS III change between off/on-medication before DBS and between before and after DBS off medication. For the off/on-medication change before DBS, younger patients and patients who had had a diagnosis of depression for a longer time were associated with significantly larger motor improvement. For the pre/post-DBS change in UPDRS motor scores, the depression group (not the nondepression group) and patients with larger levodopa equivalent dosage had significantly less improvement from DBS surgery after adjustment for stimulation site and baseline demographic and clinical variables.

however, this would have represented an unsafe practice. A review of available DBS studies has, in general, revealed improvement in depressive symptoms, although our study informs practitioners that there may be less improvement when a premorbid history of depression is uncovered. Additionally, our patients did not have a formal repeat psychiatric interview at 6 months (only an assessment by a neurologist with scales: a BDI and a VAMS score). Although unlikely, psychiatric disease could have been missed by the absence of a full psychiatric evaluation. Depressive symptoms were measured with a self-report instrument, the BDI. Even though the psychometric properties of the BDI are well established in this population, having a clinician-rated scale such as the Montgomery Asberg Depression Rating Scale[9] or the Hamilton Rating Scale for Depression[10] would have strengthened the findings. The addition of these scales should be considered in future DBS studies, as should careful tracking of antidepressant use. Finally, the data from this study were not prospectively acquired but gathered through the use of a database, and important clinical information could have been missed. Despite these limitations, the data revealed an overall positive outcome for well-screened and affectively stable PD patients operated on with STN or GPi DBS; however, the motor and mood outcomes were slightly inferior in the patients with a history of depression.

Disclosure

Dr Okun serves as a consultant for the National Parkinson Foundation and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, and the UF Foundation. Dr Okun has in the past received honoraria from Medtronic for DBS educational talks prior to 2010, but currently receives no support (since July 2009). Dr Okun has received royalties for publications with Demos, Manson, and Cambridge (movement disorders books). Dr Okun has participated in CME activities on movement disorders sponsored by the USF CME office, PeerView, and by Vanderbilt University. The institution and not the PI receives grants from Medtronic and ANS/St. Jude, and the PI has no financial interest in these grants. Dr Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years, but has not received honoraria.

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COMMENTS

The authors present a retrospective analysis of a functional neurosurgery clinical database in which 110 patients with Parkinson disease (PD) were included. Formal psychiatric assessment was performed in all patients preoperatively and used to characterize the psychological profile of PD patients undergoing deep brain stimulation (DBS) within their service and to evaluate the effect on motor outcome.

A strength of the article is the size of the patient population studied, although the article suffers from the biases inherent in a retrospective analysis.

The psychological sequelae of DBS have received a great deal of attention, appropriately. This group looked at the role of psychology from the other perspective, as an index of expected motor outcome. This is an important issue because the process of surgical selection is critical, especially in DBS surgery, for many reasons, including the long-term nature of the therapy, need for ongoing follow-up, maintenance of the hardware, and cost.

This group actively managed depression preoperatively. This is an important example of how the neurosurgical management of PD needs to be multidisciplinary, specifically including the contribution of psychiatrists/psychologists. The fact that there was a history of depression was enough to confer poorer Unified Parkinson Disease Rating Scale (UPDRS) III outcome after DBS. Whether the UPDRS III would have been even worse without preoperative depression management cannot be gleaned from this study. Therefore, it is unclear whether depression is a modifiable or unmodifiable risk factor for poorer motor outcome after DBS for PD. In the surgical decision process, the finding of this study is important because it suggests that a preoperative history of depression should be borne in mind as an extra consideration when weighing the appropriateness of an individual patient for surgery and how the patient is counseled with respect to the benefits that can realistically be expected. Accordingly, this is an important addition to the existing functional literature.

It is an interesting aside to see the higher use of globus pallidus interna stimulation (30%) used by this group to treat PD. Within the regression analysis, globus pallidus interna stimulation did not confer any poorer UPDRS III outcome. Many functional neurosurgical groups tend to focus on subthalamic nucleus stimulation for PD; therefore, this variation in practice is a reminder that there are other functional neurosurgical solutions for movement disorders.

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This retrospective analysis of the effect of unilateral subthalamic nucleus stimulation or unilateral globus pallidus interna deep brain stimulation (DBS) was done in 2 kinds of parkinsonian patients. They underwent a diagnostic clinical interview by a psychiatrist who assigned a *Diagnostic and Statistical Manual*, fourth edition (DSM-IV) code for current major depressive disorder and those with a history of major depressive disorder. Motor and mood outcomes were compared. The study revealed that patients with a preoperative DSM-IV positive screening for a depression history had higher Beck Depression Inventory (BDI) scores after DBS and significantly less improvement in pre/post-DBS change in Unified Parkinson Disease Rating Scale motor scores than those without a history of depression.

The BDI is an inventory of 21 reagents that considers mood and other behavioral processes such as "I feel sad, I have difficult in taking decisions, irritability" but also considers items of physical symptoms like loss of appetite, lack of energy, fatigue, weight loss, and lack of interest in sex. All of these items are directly related to the characteristic symptoms of Parkinson disease, so the instrument is detecting them without making a difference. Taken together, it is difficult to differentiate the data, even more so because the results of both groups (with and without history of depression) are very similar. They fluctuate between normal and mild (0 to 9 is normal, and the scores here were 8 and 5), making it difficult to form a definitive assumption with these data. Separating the reagents (cognitive and motor) would be a good way to analyze the results. The authors take care of this situation in their Discussion, acknowledging that although the psychometric properties of the Beck Depression Inventory are well established in this population, it would have strengthened the findings to have a clinician-rated scale such as the Montgomery Asberg Depression Rating Scale or the Hamilton Rating Scale for Depression in future studies.

This insight into psychological data in patients who are planning to receive DBS (in this article, unilateral DBS) for both subthalamic nucleus stimulation and globus pallidus interna results in the recommendation that it would be useful to consider this aspect routinely.

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The study examines the motor and mood outcomes in a large sample of patients with Parkinson disease after deep brain stimulation (DBS) and the influence of having a history of depression. Although the study is retrospective, one of the main strengths of the study is that it has been carried out in a large sample of patients who have been studied in a fairly systematic and comprehensive way. The results show that those patients with a history of depression have a worse outcome after DBS. From a clinical viewpoint, the study shows that other clinical variables besides the motor symptoms may be associated with outcome after DBS. Additionally, the results provide more data about the interaction between mood and motor outcomes when modulating specific neural circuits through DBS. Patients with a history of depression showed a worse outcome for both motor and mood symptoms, which suggests several potential explanations (as the authors have commented) at different levels: psychological (increased disease burden), clinical (less effort on motor scales in patients with depressive symptoms), and neurobiological (more severe disturbance of mood regulating circuits in more severe cases of Parkinson disease). In fact, corticothalamo-striatal circuits have been related to affective and cognitive processing, and their dysregulation may be involved in depression. This study shows that the relationship between Parkinson disease and depression is found not only within the symptoms domain as comorbid disorders but also at the outcome level, which emphasizes the need for better knowledge of the interactions between these 2 disorders.

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