Deep Brain Stimulation in Parkinson's Disease

Lead Guest Editor: Raja Mehanna
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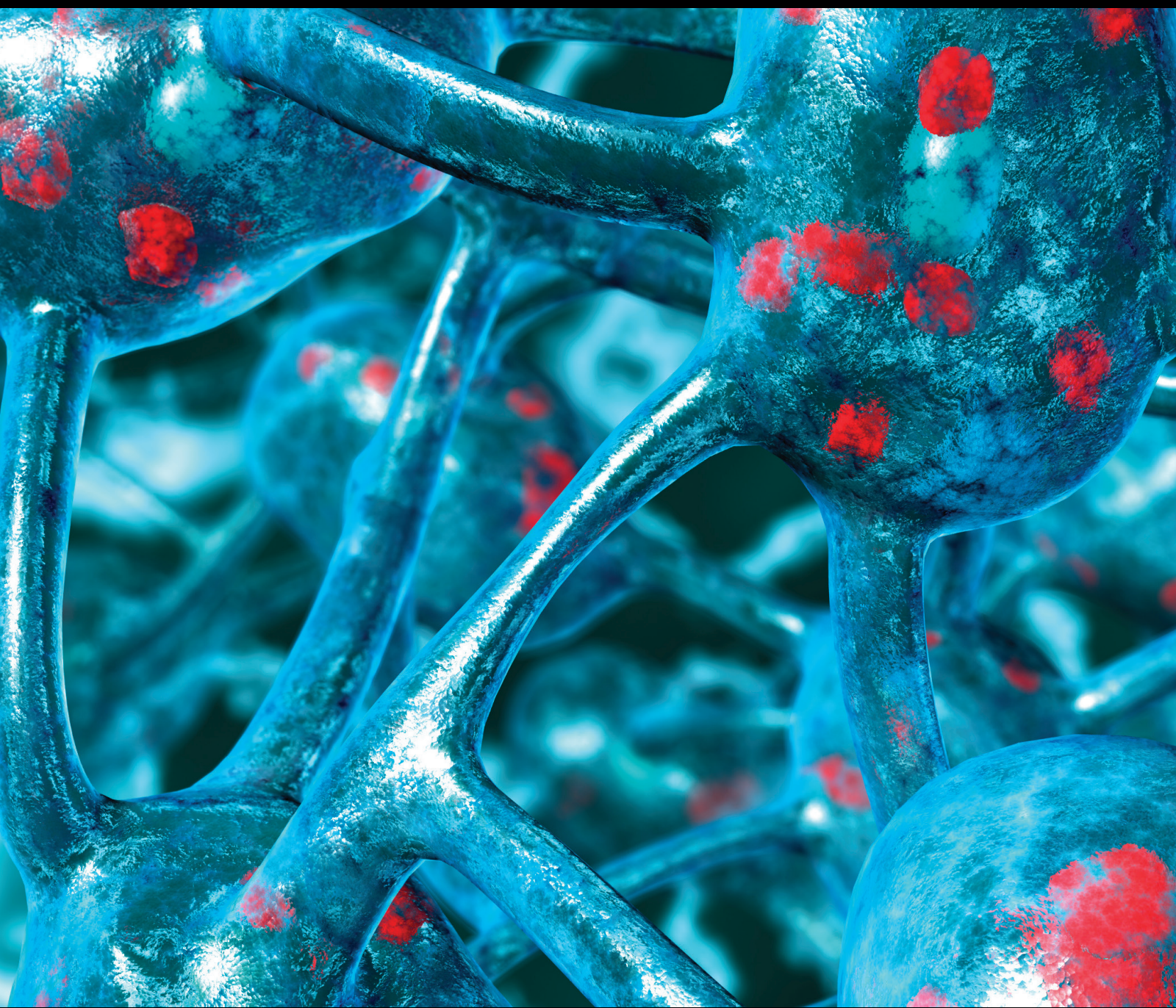

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Editorial Board

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Editorial

Deep Brain Stimulation in Parkinson's Disease

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) is considered an essential therapy in the management paradigm of Parkinson's disease (PD). Its success stems essentially from its remarkable efficacy and, compared to the lesions created with thalamotomy and pallidotomy, its flexibility through programming that allows modification of the stimulation delivered to the precise brain targets, thereby obtaining maximal benefit with minimal side effects. In light of the impressive pace of advances in DBS technology, relentless exploration of new targets, development of programming paradigms, and continued controversy on patient selection and timing of DBS surgery, a special issue on this fascinating topic is pertinent and timely.

The choice of the DBS target between STN and GPi is driven by the constellation of motor and nonmotor symptoms which are key determinants to quality of life. U. Yazdani et al. discuss the pros and cons of each target and emphasize the need for these considerations while determining the final choice in a given individual. A widely accepted notion is that GPi DBS causes less cognitive decline than STN DBS and can be considered as the preferred target in PD patients with preoperative cognitive impairment. R. Mehanna et al. reevaluate this issue in a review of 72 studies totaling 2,410 STN DBS patients and 702 GPi DBS patients and draw a set of recommendations regarding the cognitive impact of DBS in PD patients.

While STN and GPi are the main targets of DBS in PD patients as they alleviate a broader spectrum of motor symptoms, in contrast to Vim which helps primarily with tremors [1], the benefit of their stimulation on axial and nonmotor symptoms is limited [2]. D. Anderson et al. describe the role of emerging alternative DBS targets such as the pedunculopontine nucleus, caudal zona incerta, substantia nigra pars reticulata, and the motor cortex for control of axial symptoms such as freezing, postural instability, gait, speech, and swallowing and nonmotor symptoms such as memory impairment, attention decline, and sleep disturbances in PD patients. Although initial reports are promising, carefully designed and larger controlled studies are required to verify the efficacy of these alternative DBS targets.

In addition to appropriate patient screening and target selection, careful programming is critical for a positive clinical outcome. Although general guidelines for DBS programming are available, a systematic protocol is lacking. Programming can thus be challenging, time-consuming, and labor-intensive. Nevertheless, with the advent of technological improvements, programming algorithms are expected to become more effective and less frustrating. A. Wagle Shukla et al. review the current approaches to DBS programming and summarize the most recent advances in the DBS field, including interleaving of DBS pulses, fractionated current, directional steering of current, use of biphasic DBS pulses, and closed-loop stimulation. The authors also discuss the role of computer-guided programming and the possibility of remote Internet-based programming which are promising approaches to impact access to DBS care in the near future.

Although the clinical efficacy of DBS in PD is well established, its mechanism of action is still partially understood but is being actively explored, especially in animal studies [3]. There are limited data on the impact of DBS on cognitive and emotional traits, the efficacy of unipolar versus

bipolar stimulation, and the long-term sustainability of symptom alleviation after the cessation of DBS [4]. These are all addressed in an original article from K. Badstuebner et al.

In 2013, the EARLY-STIM trial provided Class I evidence for the use of DBS earlier in PD [5]. This finding led to the 2016 FDA approval of DBS in patients with at least 4 years of disease duration and 4 months of motor complications as an adjunct therapy for patients not adequately controlled with medications. A review from G. Suarez-Cedeno et al. highlights the changes overtime in DBS implantation, its current application, and the challenges that come with earlier intervention such as selecting appropriate candidates, predicting outcome, and managing side effects. The authors also discuss the current knowledge of the impact of DBS on mortality and its possible neuroprotective effects.

However, in a survey of 23 Swedish patients interviewed at a mean of 8 years after diagnosis, M. Sperens et al. report that patients in moderate stages of PD seem to be resistant to an earlier intervention. Despite the EARLY-STIM trial, a significant subset of patients still consider DBS as a last resort procedure. According to the authors, patients in their cohort had a reasonable perception of DBS, expressing caution "and well considered attitudes towards its outcome." Their resistance to early intervention is thus not stemming from inappropriate concern or relative ignorance.

On the other hand, in a retrospective study of 29 patients, K. LaFaver et al. report that while all patients are at least partially content to have undergone DBS and will recommend it, only one-third feel that their preoperative education was *very adequate*, an additional 46% rate it as *adequate*, while 3.6% find it to be *completely inadequate*. This study underscores the need for a better preoperative education in order to insure realistic expectations and successful DBS outcomes [6].

Finally, determining predictors of functional and quality of life outcomes after DBS in PD would be useful to better tailor treatment to the individual patient's needs. H. Abboud et al. report on a retrospective review of pre- and postoperative data in 130 patients, suggesting that postural instability and worse pre-DBS motor score are the strongest predictors of poorer functional and QOL outcomes, while age at surgery and duration of the disease did not seem to influence the outcome. On the other hand, the presence of tremors and the absence of dyskinesia and of freezing of gait are reported as the greatest predictors of global improvement, confirming prior reports [7, 8]. This study is also the first to report preoperative high BMI as a potential predictor of poorer functional outcome. Furthermore, many reports suggested the possibility of significant weight increase after DBS in advanced PD, creating some concern among patients, especially in cases of obesity, diabetes, and other metabolic disorders [9]. It is thought to be secondary to reduction in the metabolic rate after resolution of tremor and/or dyskinesia and/or a direct stimulation effect on appetite centers [10–12]. In an original article, S. H. Millan et al. report different findings in early PD and offer insightful explanation to the difference. A phase III randomized controlled trial is underway and will look further into this question.

In summary, this special issue provides an updated overview of the ever-expanding field of DBS for PD, while probing into emerging and controversial themes. It compares and reevaluates effectiveness of STN versus GPi DBS targets on motor and nonmotor symptoms, objectively analyzes the available data on the impact of other potential targets, and challenges the conventional wisdom on factors that predict better outcome, optimal timing of surgery, and the appropriateness of patients, including their perceptions of the procedure prior to DBS surgery.

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Review Article

Cognitive Impact of Deep Brain Stimulation on Parkinson's Disease Patients

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Subthalamic nucleus (STN) or globus pallidus interna (GPi) deep brain stimulation (DBS) is considered a robust therapeutic tool in the treatment of Parkinson's disease (PD) patients, although it has been reported to potentially cause cognitive decline in some cases. We here provide an in-depth and critical review of the current literature regarding cognition after DBS in PD, summarizing the available data on the impact of STN and GPi DBS as monotherapies and also comparative data across these two therapies on 7 cognitive domains. We provide evidence that, in appropriately screened PD patients, worsening of one or more cognitive functions is rare and subtle after DBS, without negative impact on quality of life, and that there is very little data supporting that STN DBS has a worse cognitive outcome than GPi DBS.

1. Introduction

Parkinsonism is defined as bradykinesia with rest tremor or rigidity. Parkinson's disease (PD) is the most frequent cause of parkinsonism and defined by the presence of parkinsonism in the absence of exclusion criteria [1]. With a prevalence of 1 to 2% above the age of 60 years [2], it typically develops between the ages of 55 and 65 years. Pathologically, PD is associated predominantly with the loss of dopaminergic neurons in the substantia nigra. However other brainstem neurons also degenerate in PD, likely contributing to non-motor impairment [3]. Indeed, PD is a complex syndrome with motor, dermatological, autonomic, neurobehavioral, sensory, and special sense disorders [4]. Many studies have also reported cognitive changes, including impairments in executive functions, language, memory, vision, and psychomotor speed [5–8]. In a cohort comparing 115 patients with newly diagnosed PD to 70 healthy controls, for example, Muslimović et al. [8] reported statistically worse performance in PD patients in most cognitive measures, particularly attention/concentration and executive functions, with 24% of newly diagnosed PD patients (versus 4% of controls) meeting the criteria for cognitive impairment.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the globus pallidus pars interna (GPi) improves quality of life and decreases motor complications in PD and has been approved as such by the Food and Drug Administration in the USA since 2002 [9]. Ablative surgery or DBS of the ventral intermediate (Vim) nucleus of the thalamus is being used for essential and other secondary causes of tremor. However, because it does not address the other cardinal motor symptoms of PD, Vim DBS is rarely used for that disorder [10]. Patients considered for DBS should undergo a thorough multidisciplinary preoperative screening, including a neuropsychological test to rule out dementia or psychiatric comorbidities that could be a contraindication to surgery, in order to avoid implanting poor candidates that will either not benefit enough from DBS or poorly tolerate it [11–15]. However, the cognitive impact of DBS in appropriately selected PD patients is unclear, with

various studies producing conflicting results as we will see below. We here endeavor to review the available literature on this subject.

We will first review the available studies on the impact of STN and GPi DBS on each of the following cognitive domains: language, executive function, attention and concentration, memory, visual function, psychomotor and processing speed, and global cognition. We will then review more specifically controlled studies as well as studies directly comparing the cognitive impacts of STN and GPi DBS.

2. Methods

Preliminary literature search was conducted through PubMed. Keywords used were "deep brain stimulation", "parkinson", and "cognition". The reference lists of relevant articles were also inspected to locate any potential cited articles that address cognition following STN or GPi DBS. Since Vim DBS is rarely used for PD, and with most of the data on DBS in PD patients stemming from studies on the STN and GPi, studies on Vim DBS in PD patients were not included in our search.

The research terms were intentionally broad to capture as many studies as possible. Studies were reviewed if they were published in the English language and met our minimum inclusion criteria: (1) patients with idiopathic PD who underwent STN or GPi DBS, (2) reporting neuropsychological data after DBS surgery, (3) using at least one standardized neuropsychological instrument, and (4) including at least five subjects followed for a mean of at least 3 months postoperatively.

3. Results

3.1. Cognitive Changes after DBS. 72 studies totaling 2,410 STN DBS patients and 702 GPi DBS patients were reviewed (Tables 1 and 2). Among these, only 20 included statistical correction for multiple analyses or did not require correction because of the statistical method used [16–35], 20 had a control arm formed by PD patients who did not undergo DBS (nonsurgically treated PD patients) [16, 17, 21, 24, 32, 33, 36–49], and 9 compared outcomes between GPi and STN DBS patients [26, 34, 47, 50–55]. All these studies were reviewed with post hoc corrections for multiple analyses when required.

We will first briefly summarize studies that investigated the cognitive outcomes related to STN and GPi and were not designed to directly compare the two targets. There were 62 such studies, totaling 1,913 STN DBS patients and 165 GPi DBS patients.

Our findings are summarized below (Tables 1 and 2).

3.1.1. Language. In the reviewed studies, language was most often assessed using the Boston Naming Test and the subtest Similarities of the Wechsler Adult Intelligence Scale III (WAIS-III), phonemic fluency, and sematic fluency.

(1) STN. Statistically significant worsening in one or more language functions was reported in 27 studies, most often a decrease in fluency, while 3 studies [24, 29, 46] reported improvement in at least one measure of language. There was no significant change in at least one assessed measure of language in 38 studies (Table 1), 21 of which reported no change in any measure of language.

Among the studies reporting worsening, it is unclear if one [56] was corrected for multiple analyses by its authors and, if not, whether such a correction would change the conclusions. Another study [57] was not corrected for multiple analyses, and a post hoc correction was not possible due to the lack of reported p value, making it unclear if such a correction would have made the reported worsening statistically not significant.

In all these studies, cognitive outcomes after surgery were compared to baseline preoperative performance (Table 1). In addition, 9 studies compared language performance ON and OFF stimulation [29, 31, 38, 49, 58–62]. After correcting for multiple analyses, a study from Daniele et al. [58] reported worsening of letter verbal fluency compared to the preoperative assessment only at 3 months, when the stimulation was OFF, but not at 6 or 12 months, when the stimulation was ON. This might suggest that a decline in verbal fluency was either more pronounced in the early postoperative stages or attenuated by stimulation. On the other hand, after correction for multiple analyses, Pillon et al. [60] reported no worsening of fluency at 3 months but worsening at 12 months after implant with stimulation ON or OFF. Since patients were assessed ON medications in the study earlier study [58] and, and OFF medication in latter [60], this might suggest a positive synergistic effect of medication and stimulation on fluency. Castner et al. [31] assessed 8 patients ON and OFF stimulation at least 4 months after STN DBS and found that stimulation increased errors in word generation suggesting that STN stimulation might affect the ability to select from many competing lexical alternatives during word generation. In contrast, Silveri et al. [29] studied 12 patients 8 years after STN DBS implant and found an improvement in performance (accuracy and response time) when STN DBS was ON compared to OFF, with less semantic errors, suggesting STN DBS might improve lexical search. The 5 other studies [38, 49, 59, 61, 62] could not elicit any statistical difference between ON and OFF stimulation states.

Most recently, Tröster et al. [35] reported on a total of 136 STN DBS patients followed for 12 months after surgery, divided between 101 receiving constant current stimulation immediately after surgery and 35 starting activation 3 months after surgery. The cognitive assessment at 3 months did indicate some decrease in attention and language even before the device was turned on, with additional deterioration from stimulation. However, the study showed an overall good safety profile of constant current STN DBS.

With regard to the timing of a potential decline in language, Funkiewiez et al. [22] reported worsening of category fluency and total score of fluency at 1 and 3 years compared to baseline, without any further worsening between the two time points.

A parasagittal trajectory for electrode implantation was suggested as a cause of language worsening in some studies [60, 63], as activation of the paracingulate and cingulate sulci

Table 1: Studies assessing cognitive change in PD patients after STN DBS.

Author, year	*N*	F/u (mo)	Controlled	Status of stimulation/medication at cognitive assessment	Improved cognitive measure(s)	Worsened cognitive measure(s)	Unchanged cognitive measure(s)
Alberts et al., 2008 [18]	8	N/A	No	UL, BL, ON, OFF/ON	None	E	None
Alegret et al., 2001 [75]	15	3	No	ON/OFF	None	None	E, PS, L, M, V
Ardouin et al., 1999 [25]	49	3–6	No	ON/inconstant	E	L	GC, E, PS
Asahi et al., 2014 [27]	11	12	No	Unspecified	None	None	GC, A/C, M, L, V
Castelli et al., 2006 [56]	72	15	No	ON/-	E	L	E, L, M
Castelli et al., 2007 [90]	19	17	No	ON/ON	None	L	E, V, M, L,
Castelli et al., 2010 [39]	27	12	Yes	ON/ON	None	L	E, A/C, M, L
Castner et al., 2007 [30]	18	At least 4	No	ON and OFF/ON	A/C	None	A/C
Castner et al., 2008 [31]	8	At least 4	No	ON and OFF/ON	None	L	L
Cilia et al., 2007 [16]	20	12	Yes	ON/ON	None	L	GC, L, E, A/C
Contarino et al., 2007 [91]	11	60	No	ON/ON	None	None	L, V, M, E
Daniele et al., 2003 [58]	20	12	No	ON or OFF/ON	None	L	GC, L, E, A/C, M
De Gaspari et al., 2006 [21]	12	12	Yes	ON/ON	None	L	L, GC, E
Dujardin et al., 2001 [92]	9	3	No	ON/ON	None	None	GC, E, M, PS, L
Erola et al., 2006 [93]	19	12	No	ON/ON	None	L	GC, E, PS
Fasano et al., 2010 [57]	16	96	No	ON/ON	None	E, L, M	GC, M, E, L
Fraraccio et al., 2008 [62]	15	16	No	ON and OFF/ON	None	A/C	E, A/C, M, L, V, CG
Funkiewiez et al., 2003 [94]	50	12[a]	No	ON/OFF	None	None	GC, E
Funkiewiez et al., 2004 [22]	70	36	No	ON/69% OFF	None	L	GC, E, M, PS
Gironell et al., 2003 [36]	8	6	Yes	ON/ON	None	None	L, E, A/C, M, V, PS
Hälbig et al., 2004 [59]	12	16	No	ON and OFF/ON	None	None	PS, M, GC, E, L
Heo et al., 2008 [95]	46	12	No	ON/ON	None	None	GC, A/C, M, L, E
Hershey et al., 2004 [67]	24	7[b]	No	ON and OFF/OFF	None	E	None
Hilker et al., 2004 [37]	8	4	Yes	ON/-	M	None	GC, E, L, A/C, M, V
Jahanshahi et al., 2000 [63]	7	12	No	ON and OFF/OFF	E, A/C, PS	M	None
Kim et al., 2014 [78]	103	42[b]	No	ON/ON	None	GC, but similar incidence to incidence of PDD	None
Krack et al., 2003 [20]	42	60	No	ON/ON	None	None	GC, E

Table 1: Continued.

Author, year	*N*	F/u (mo)	Controlled	Status of stimulation/medication at cognitive assessment	Improved cognitive measure(s)	Worsened cognitive measure(s)	Unchanged cognitive measure(s)
Krugel et al., 2014 [96]	14	N/A	No	ON/ON	None	None	L
Lhommée et al., 2012 [97]	63	3	No	ON/ON	None	L	GC, E
Limousin et al., 1998 [70]	24	12	No	ON/OFF	None	None	E, L, V, PS
Moretti et al., 2003 [46]	9	12	Yes	ON/ON	L	L, E	E, L, A/C, M, V
Moro et al., 1999 [98]	7	9	No	ON/ON	None	None	GC, E, L, M
Morrison et al., 2004 [38]	17	3	Yes	ON and OFF/OFF	None	None	L, A/C, M, E, V
Rukmini Mridula et al., 2015 [48]	50	23[b]	Yes	ON/ON	None	None	GC, A/C
Page and Jahanshahi, 2007 [68]	12	N/A	No	ON and OFF/ON	PS, A/C	None	PS, A/C, E
Perozzo et al., 2001 [69]	20	6	No	ON/ON and OFF	None	None	E, A/C, M, PS
Phillips et al., 2012 [49]	11	13.8[b]	Yes	ON and OFF/ON and OFF	None	None	L
Pillon et al., 2000 [60]	63	12	No	ON and OFF/75% OFF	None	L	E, PS, L, M
Rothlind et al., 2007 [50]	15	21	No	ON/ON	None	L	A/C, E, L, V, M
Rothlind et al., 2015 [47]	84	6	Yes	ON/ON	None	E, A/C, PS (see text)	E, M, A/C, L, PS
Sáez-Zea et al., 2012 [44]	9	6	Yes	ON/ON	None	L, A/C	A, M, V, E, L
Saint-Cyr et al., 2000 [99]	11	12	No	ON/ON	None	L	E, L, M, A/C, V
Saint-Cyr and Albanese, 2006 [82]	99	6	No	ON/ON	None	L, E	E, L, A/C, M, PS
Schüpbach et al., 2005 [23]	37	60	No	ON/ON	None	CG, E	None
Silveri et al., 2012 [29]	12	96	No	ON and OFF/ON	L	None	None
Smeding et al., 2011 [33]	105	12	Yes	ON/ON		GC, E, L, V, M, A/C	L, A/C
Smeding et al., 2006 [43]	99	6	Yes	ON/ON	None	L, A/C	L, M, V, A/C
Tang et al., 2015 [73]	27	12	No	ON/ON	M	L	GC, M, V, A/C, E, L
Tremblay et al., 2015 [28]	8	At least 7 wks	No	OFF DBS and then ON DBS/unspecified med status	None	L	L
Trepanier et al., 2000 [87]	9	6	No	ON/ON	None	None	A/C, M, V, L, E
Whelan et al., 2003 [24]	5	3	No	ON/ON	L	L	None

Table 1: Continued.

Author, year	*N*	F/u (mo)	Controlled	Status of stimulation/medication at cognitive assessment	Improved cognitive measure(s)	Worsened cognitive measure(s)	Unchanged cognitive measure(s)
Williams et al., 2011 [40]	19	24	Yes	ON/ON	None	None	GC, M, E, A/C, L, V, PS
Witt et al., 2004 [61]	23	12	No	ON and OFF/ON	None	None	L, E, GC
Witt et al., 2008 [42]	60	6	Yes	ON/ON	None	A/C	GC, E, L, A/C
Witt et al., 2013 [41]	31	6	Yes	ON/ON	None	None	GC, A/C, L
Yágüez et al., 2014 [100]	30	9	No	ON/ON	None	L, M	GC, M, L, V, E
York et al., 2008 [17]	23	6	Yes	ON/ON	None	M	GC, E, A/C, M, L, V, PS
Zangaglia et al., 2009 [45]	32	36	Yes	ON/ON	None	L	GC, M, E, A/C
Zangaglia et al., 2012 [32]	30	96	Yes	ON/ON	None	L	GC, M, E, A/C

PD: Parkinson's disease; STN: subthalamic nucleus; *N*: number of patients; mo: months; A/C: attention/concentration; E: executive; GC: global cognition; L: language; M: memory; PS: psychomotor/processing speed; V: visual. [a]Median; [b]mean. *Note*. Multiple tests were performed for each domain in each study, and often a few of these showed a difference while other tests assessing the same domain did not. This explains why the same domain might appear more than once and under different results for the same study. Adapted from Mehanna [101] with permission from the author.

Table 2: Studies assessing cognitive change in PD patients after GPi DBS.

Author, year	*N*	F/u (mo)	Controlled	Status of stimulation/medication at cognitive assessment	Improved cognitive measure(s)	Worsened cognitive measure(s)	Unchanged cognitive measure(s)
Ardouin et al., 1999 [25]	13	3–6	No	ON/inconsistent	E	L	GC, E, PS
Jahanshahi et al., 2000 [63]	6	12	No	ON and OFF/OFF	None	None	E, A/C, PS, M,
Pillon et al., 2000 [60]	13	12	No	ON and OFF/75% OFF	None	None	E, PS, L, M
Trépanier et al., 2000 [87]	4	6	No	ON/ON	None	None	A/C, M, V, L, E
Rothlind et al., 2007 [50]	14	21	No	ON/ON	None	L	A/C, E, L, V, M
Fields et al., 1999 [74]	6	5	No	ON/ON	M	None	GC, E, A/C, V, L, M
Tröster et al., 1997 [66]	9	3	No	ON/ON	None	V, L	GC, E, A/C, V, M, L
Tröster et al., 2017 [35]	136	12	No	ON/not specified	None	L, A/C	GC, A/C, E, M
Vingerhoets et al., 1999 [76]	20	3	No	ON/ON	None	None	M, V, E, PS
Rothlind et al., 2015 [47]	80	6	Yes	ON/ON	None	E, A/C	E, M, A/C, L, PS

PD: Parkinson's disease; GPi: globus pallidus interna; *N*: number of patients; mo: months; A/C: attention/concentration; E: executive; GC: global cognition; L: language; M: memory; PS: psychomotor/processing speed; V: visual. *Note*. Multiple tests were performed for each domain in each study, and often a few of these showed a difference while other tests assessing the same domain did not. This explains why the same domain might appear more than once and under different results for the same study. Adapted from Mehanna [101] with permission from the author.

was visible on fMRI during word generation [64]. On the other hand, STN DBS might impact the cognitive circuit involved in language as decreased perfusion in the ventral caudate nucleus, anterior cingulate cortex, and left dorsolateral prefrontal cortex (DLPFC) is visible on single photon emission computed tomography (SPECT) in patients with decreased fluency after STN DBS [16]. A more recent study comparing brain positron emission tomographies (PET) in STN DBS patients with and without decreased fluency reported metabolism change in the right middle occipital gyrus, right fusiform gyrus, and right superior temporal gyrus when deficit in phonemic fluency was detected. Decline in semantic fluency however was associated with metabolic changes in the left inferior precentral/postcentral gyrus and the left inferior parietal lobule. Thus, different brain areas were involved in post-DBS deficits in phonemic or semantic fluency in this study, and none of them were frontal areas involved in cognitive functions [65].

On the other hand, Silveri et al. [29] hypothesized that the observed improvement in response time was secondary to improvement of motor components and increased accuracy was due to restoration of the corticostriatal circuits involved in selection processes of a target word among different alternatives.

(2) GPi. Decline in one or more measures of language, most often fluency, was reported in 3 studies totaling 36 patients followed up to 21 months after GPi DBS [25, 50, 66]. While one of these [66] reported this deterioration in both DBS and ablation of GPi, suggesting a consequence of the procedure itself rather than stimulation, this study was not corrected for multiple analyses, and a post hoc correction was not possible due to the lack of reported p value, making it unclear if such a correction would have made the reported worsening statistically not significant. In addition, fluency was the only worsened measure of language in 2 of these studies [50, 66].

Three other studies totaling 97 patients followed up to 12 months reported no change in any measure of language (Table 2).

3.1.2. Executive Function. Executive functions were most often assessed using the Wisconsin Card Sorting Test, Trail Making Test Part (Trails B), and Stroop Color-Word Test (Stroop Color-Word).

(1) STN. Worsening in at least one measure of executive function was reported in 8 studies. However, one [57] of these was not corrected for multiple analyses, and a post hoc correction was not possible due to the lack of reported p value, making it unclear if such a correction would have made the reported worsening statistically not significant. On the other hand, improvement was reported in 3 studies and no statistical difference in any assessed measures of executive function was reported in 36 studies (Table 1).

Executive function ON and OFF stimulations were compared in 10 studies [18, 38, 58–63, 67, 68]. Spatial delayed response was worse with stimulation ON under a high but not low memory load condition in 2 studies [18, 67]. In particular, Alberts et al. [18] reported further worsening in executive functions when multitasking in bilateral compared to unilateral stimulation. On the other hand, one study [63] reported improvement of frontal executive functions with stimulation ON, and the 7 other studies reported no statistically significant change in the assessed measures of executive functions. Additionally, no change in executive function 6 months after surgery with DBS ON, whether ON or OFF medications, was reported in another study [69].

Improvement in executive functions and attention/concentration after STN DBS might be secondary to a decrease in the excessive inhibitory output from the basal ganglia to the frontal cortex [63], and increased activation of the DLPFC on PET scan was reported after STN DBS [70].

(2) GPi. No statistically significant change in any measure of executive function up to 21 months after GPi DBS was reported in 7 studies, while one study reported improvement of at least one measure of executive function at 6 months [25] (Table 2). One study by Rothlind et al. [47] showed worsening on some measure of executive functions and attention 6 months after GPi DBS, visible at a population level but unlikely to affect individual patients as we will detail in the controlled studies section below.

3.1.3. Attention and Concentration. Attention and working memory were most often assessed using the Stroop Word Test, Trail Making Test part A, the subtests Letter and Number Sequencing and Digit Span of the Wechsler Adult Intelligence Scale III (WAIS-III), the Vienna Test System's simple and choice reaction speed tests, and the Symbol Digit Modalities administration.

(1) STN. All reported measures of attention and concentration (A/C) were improved with stimulation ON compared to OFF in 7 patients [63]. Another series of 12 patients reported similar improvement in some of the reported measures [68]. Comparing 18 patients ON and OFF stimulation at least 4 months after DBS, Castner et al. [30] reported improvement in one measure of attention and no change in another one with ON stimulation. It must be noted that there was no comparison to the pre-DBS level of A/C in these 3 studies to assess if DBS implant, rather than stimulation alone, might be the cause of these changes. Conversely, 8 studies with assessments up to 16 months after STN DBS follow-up reported worsening of at least one measure of A/C, one of which reported no difference between ON and OFF stimulation [62]. Finally, no statistically significant impact of STN DBS implant and/or stimulation on A/C was reported in 21 other series (Table 1), including 2 evaluating patients ON and OFF stimulation [38, 58] and one evaluating patient ON DBS and ON and OFF medications [69].

The missing digit task, used by some studies, specifically activates the posterior premotor cortex and the DLPFC on PET [71], giving a substratum for the observed improvement since the STN projects to these cortical sites [72].

(2) GPi. Five studies assessing attention and concentration up to 21 months after GPi DBS reported no statistically significant change (Table 2), including no change with DBS

ON versus OFF in one study [63]. However, Rothlind et al. [47] reported worsening in some, but not all, measures of A/C 6 months after GPi DBS.

3.1.4. Memory. Memory was most often assessed by the Rey Auditory Verbal Learning Test (RAVLT), the Brief Visuospatial Memory Test, and the Hopkins Verbal Learning Test.

(1) STN. Memory improvement 4 months after STN DBS was reported in a series of 8 patients [37]. However, the study was not corrected for multiple analyses, and a post hoc correction was not possible due to the lack of reported p value, making it unclear if such a correction would have made the reported improvement statistically not significant. Tang et al. did report such improvement, in a series of 27 patients followed for 12 months [73], in a study corrected for multiple analyses. Conversely, worsening in at least one measure of memory was reported in 5 studies, up to 16 months after DBS (Table 1). However, one of these [57] was not corrected for multiple analyses and a post hoc correction was not possible due to the lack of reported p value, making it unclear if such a correction would have made the reported worsening statistically not significant. In addition, there was no difference in memory assessment ON and OFF stimulation in 2 of these studies after correction for multiple analyses [59, 63].

Finally, no statistically significant impact of DBS implant and/or stimulation on memory was reported in 30 other studies (Table 1), including one evaluating patients ON DBS and ON and OFF medications [69].

(2) GPi. Worsening in one but not all measures of memory was reported in one series of 6 bilateral GPi DBS patients followed for 5 months [74]. However, this study was not corrected for multiple analyses and a post hoc correction was not possible due to the lack of reported p value, making it unclear if such a correction would have made the reported worsening statistically not significant. Conversely, no significant change in any measure of memory was detected in 7 other studies totaling 146 patients followed for up to 21 months (Table 2), including 2 studies comparing patients ON and OFF stimulations [60, 63].

3.1.5. Visual Function. Visual function was most often assessed by the subtest Matrix Reasoning of the WAIS-III and Clock Drawing.

(1) STN. Alegret et al. [75] first reported worsening of visuospatial function after STN DBS that was not statistically significant after correction for multiple analyses. However, Smeding et al. [33] reported decrease in visual function in a controlled study of 105 STN DBS patients followed for 12 months. Conversely, 18 other studies, including 2 assessing patients ON and OFF stimulation [38, 62], reported no impact on visual function (Table 1).

(2) GPi. Worsening of one but not all measures of visual function was reported in one series of 9 patients followed for 3 months after bilateral GPi DBS [66]. However, this study was not corrected for multiple analyses and a post hoc correction was not possible due to the lack of reported p value, making it unclear if such a correction would have made the reported worsening statistically not significant. Conversely, no significant change in any used measure of visual function was detected in 4 studies totaling 44 patients followed up to 21 months (Table 2).

3.1.6. Psychomotor and Processing Speed. The assessment of psychomotor and processing speed is usually included in the assessment of executive and A/C. In some studies though, it was assessed separately, most often assessed using the Stroop Word Test, Trail Making Test part A, the subtest Digit Span of the WAIS-III, and the Symbol Digit Modalities Test oral administration.

(1) STN. Improvement in processing and psychomotor speed with STN stimulation ON compared to OFF was reported in 2 studies [63, 68], while another [47] reported worsening of some measures of psychomotor and processing speed when compared to PD patients controls in the medication ON state [47]. Conversely, 13 other studies, including 2 evaluating patients with stimulation ON and OFF [59, 63] and one evaluating patients ON and OFF medications with stimulation ON [69], could not detect significant change after STN DBS (Table 1).

(2) GPi. No significant change in psychomotor and processing speed from GPi implant with or without stimulation could be detected in 5 studies totaling 132 patients [25, 47, 60, 63, 76] (Table 2).

3.1.7. Global Cognition. General cognition was most often assessed by the Mini Mental Status Exam and the Mattis Dementia Rating Scale.

(1) STN. Two series totaling 140 patients evaluating ON stimulation and ON medications reported significant worsening of global cognition 5 years after surgery [23, 76]. However, the reported worsening might have been secondary to the natural evolution of PD [77] since none of these studies had a control arm. On the other hand, a controlled study with 105 STN DBS patients [33] reported worsening of all cognitive domains 12 months after surgery (global cognition, memory, executive function, visual function, attention/concentration, and language).

No significant change was reported in 27 other studies up to 8 years after surgery, including 7 controlled studies comparing a total of 265 STN DBS patients to nonsurgically treated PD patients [16, 17, 32, 40–42, 45, 48] (Table 1). In addition, the incidence of dementia 3 years after bilateral STN DBS in 50 PD patients was estimated at 89 per 1000 by Aybek et al. [19], while Kim et al. [78] had an incidence rate of 35.7 per 1000 person-years in their cohort of 103 STN DBS patients followed for 42 months. Both rates were comparable to the reported incidence in medically managed PD (42.6 to 112 per 1,000) [79].

(2) GPi. No statistically significant change in global cognition up to 6 months after surgery could be detected in 3 studies totaling 28 patients [25, 66, 74] (Table 2).

Table 3: Controlled studies assessing cognitive change in PD patients after DBS.

Author, year	*N* of DBS patients	F/u (mo)	Lead location	Status of stimulation/medication at cognitive assessment	Cognitive performance(s) improved in DBS group	Cognitive performance(s) worsened in DBS group	Cognitive performance(s) not different between DBS and control group
Castelli et al., 2010 [39]	27	12	STN	ON/ON	None	L	E, A/C, M, L
Cilia et al., 2007 [16]	20	12	STN	ON/ON	None	L	GC, L, E, A/C
De Gaspari et al., 2006 [21]	12	12	STN	ON/ON	None	L	GC, E, L
Gironell et al., 2003 [36]	8	6	STN	ON/ON	None	None	L, E, A/C, M, V, PS
Hilker et al., 2004 [37]	8	4	STN	ON/-	M	None	GC, E, L, A/C, M, V
Moretti et al., 2003 [46]	9	12	STN	ON/ON	L	L, E	E, L, A/C, M, V
Morrison et al., 2004 [38]	17	3	STN	ON and OFF/OFF	None	None	L, A/C, M, E, V
Rukmini Mridula et al., 2015 [48]	50	23[a]	STN	ON/ON	None	None	GC, A/C
Phillips et al., 2012 [49]	11	13.8[a]	STN	ON and OFF/ON and OFF	None	None	L
Rothlind et al., 2015 [47]	281	6	STN $n = 84$ and GPI $n = 80$	ON/ON	None	A/C, E, PS, see text	A/C, E, L, M, PS
Sáez-Zea et al., 2012 [44]	9	6	STN	ON/ON	None	None	A, M, V, E, L, A/C
Smeding et al., 2011 [33]	105	12	STN	ON/ON	None	GC, E, L, V, M, A/C	L, A/C
Smeding et al., 2006 [43]	99	6	STN	ON/ON	None	L, A/C	L, M, V, A/C
Whelan et al., 2003 [24]	5	3	STN	ON/ON	L	L	None
Williams et al., 2011 [40]	19	24	STN	ON/ON	None	None	GC, M, E, A/C, L, V, PS
Witt et al., 2008 [42]	60	6	STN	ON/ON	None	A/C	GC, E, L, A/C
Witt et al., 2013 [41]	31	6	STN	ON/ON	None	None	GC, A/C, L
York et al., 2008 [17]	23	6	STN	ON/ON	None	M	GC, E, A/C, M, L, V, PS
Zangaglia et al., 2009 [45]	32	36	STN	ON/ON	None	L	GC, M, E, A/C
Zangaglia et al., 2012 [32]	30	96	STN	ON/ON	None	L	GC, M, E, A/C

PD: Parkinson's disease; STN: subthalamic nucleus; *N*: number; mo: months; A/C: attention/concentration; E: executive; GC: global cognition; L: language; M: memory; PS: psychomotor/processing speed; V: visual. [a]mean. *Note*. Multiple tests were performed for each domain in each study, and often a few of these showed a difference while other tests assessing the same domain did not. This explains why the same domain might appear more than once and under different results for the same study. Adapted from Mehanna [11] with permission from the author.

3.2. Controlled Studies. Because most of the available information is provided by open label uncontrolled series, a major concern is that Parkinson's' disease natural history, rather than DBS, might be the cause of any detected cognitive worsening. It is thus important to consider more attentively the 20 controlled studies available (Table 3).

Among these, seven reported no difference between DBS and non-DBS PD patients. Gironell et al. [36] reported worse semantic verbal fluency in the DBS group when comparing 8 bilateral STN DBS patients 6 months after surgery to 8 age- and stage-matched PD patients who refused surgery. However, this difference was not statistically significant when

corrected for multiple analyses, and there was no difference in the other cognitive tasks assessed. A year later, Morrison et al. [38] reported no statistically significant difference at 3 months after surgery between 17 bilateral STN DBS patients and 11 nonsurgically treated PD patients. In addition, within the DBS group, there was no difference between the preoperative assessment and stimulation ON at 3 months, or between stimulation ON and stimulation OFF at 3 months. York et al. [17] reported worse verbal memory in 23 STN DBS patients at 6 months compared to 27 medically managed PD patients. There was no difference in visual memory or other cognitive measures. However, in a follow-up to this study including 19 STN DBS patients and 18 controls 2 years after surgery, Williams et al. [40] reported worsening of some measures of memory, processing, and fluency, but these differences were not significant after correction for multiple analyses. More recently, Sáez-Zea et al. [44] reported no difference 6 months after surgery between 9 bilateral STN DBS patients and 12 nonsurgical PD patients, with worsening of 4 measures of language and attention in each group, out of the 18 cognitive measures assessed. In addition, STN DBS patients had a nonstatistically significant trend to worse phonemic verbal fluency that was significantly correlated with reductions in the L-dopa-equivalent daily dose, suggesting that a decrease in the antiparkinsonian medication might be the actual cause of worse fluency observed after STN DBS. Witt et al. [41] also reported worsening of semantic fluency, but not of letter fluency or other cognitive measures assessed, 6 months after surgery in 31 bilateral STN DBS patients compared to 31 nonsurgical PD patients. However, this difference was not statistically significant after correction for multiple analyses. In a prospective study comparing 11 BL STN DBS and 11 PD controls and 18 healthy controls, Phillips et al. [49] reported improvement in some aspects of language with STN DBS but worsening of others. However, after correction for multiple analyses, these differences were not statistically significant except for a longer reaction time with DBS ON and medication ON compared to DBS OFF and medication OFF, for regular verbs in past tense only, through indirect comparison. However, a direct comparison of these results did not show a statistical significance. Finally, Rukmini Mridula et al. [48] prospectively compared 56 patients who underwent bilateral STN DBS to 53 PD controls in the ON state with a mean follow-up of 23 months, showing no difference in any of the cognitive measures assessed.

In contrast, worsening of some cognitive measures after DBS, sometimes mitigated by improvement of others, was reported in 11 controlled studies. Moretti et al. [46] reported worsening of semantic and syllabic fluency as well as some executive functions, but with an increase in control of linguistic production, 12 months after surgery in 9 bilateral STN DBS patients compared to 9 nonsurgical PD patients. Zangaglia et al. [45] reported worsening of verbal fluency but none of other cognitive measures assessed, 3 years after surgery in 32 STN DBS patients compared to 33 nonsurgical PD patients. In a follow-up publication on that cohort, the authors reported a similar cognitive status 8 years after surgery, concluding that STN DBS was safe from a cognitive standpoint and did not modify the cognitive evolution along the course of the disease [32]. Witt et al. [42] reported worse scores on 2 measures of attention but none of other cognitive measures assessed, 6 months after surgery in 60 bilateral STN DBS patients compared to 63 nonsurgical PD patients, but without comparison to the preoperative baseline. Smeding et al. [43] reported a significantly worse decline in fluency and attention/concentration but none of the other cognitive measures assessed, 6 months after surgery in 99 STN DBS patients compared to 39 nonsurgical PD patients. Cilia et al. [16] reported statistically significant worsening of category fluency but not of phonemic fluency or other cognitive measures assessed, 12 months after surgery in 20 STN DBS patients compared to 12 nonsurgical PD patients. De Gaspari et al. similarly reported decrease in category fluency 12 months after surgery in 12 STN DBS patients compared to 13 nonsurgical PD patients [21]. Last, Castelli et al. [39] reported worsening of phonemic fluency but not of semantic fluency or other cognitive measures assessed, 12 months after surgery in 27 STN DBS patients compared to 31 matched nonsurgical PD patients. In a study comparing 105 STN DBS patients with 40 non-DBS PD controls 12 months after surgery, Smeding et al. [33] reported worsening of all cognitive domains (global cognition, memory, executive function, visual function, attention/concentration, and language) with no worsening in one or more measures of attention/concentration and language. However, disease duration was statistically longer in the STN group, so the possibility of cognitive decline related to the disease rather than DBS cannot completely be ruled out. Regardless, quality of life was significantly better in STN group than in the control group. Whelan et al. [24] compared language 3 months after surgery in 5 bilateral STN PD patients, 16 nonsurgical PD patients, and 16 healthy aged matched subjects. Compared to the nonsurgical PD patients, DBS patients had improvement on the word test-revised but worsening in the accuracy of lexical decisions about words with many meanings and a high degree of relatedness between meanings. The impact of these detailed differential results on the patients' daily life is unclear. More recently, in a prospective unblinded randomized controlled study comparing neuropsychological outcomes between patients treated with bilateral DBS ON stimulation and ON medication (164 patients, 84 implanted in the STN and 80 in the GPi) and patients treated with optimal medication management ON medication ($n = 116$), Rothlind et al. [47] reported significantly greater mean reductions at 6 months in performance on multiple measures of processing speed and working memory in the combined DBS group, as well as higher rates of decline in neuropsychological test performance in this group [47]. Decline by multiple indicators in two or more cognitive domains was seen in 11% of the DBS patients and 3% of the medically managed patients. This multidomain cognitive decline was associated with less beneficial change in subjective ratings of everyday functioning and quality of life. However, the authors noted that the majority of individual patients receiving DBS did not display changes on individual measures or combinations of measures that would clearly distinguish them from patients treated with optimal medication management and in fact showed,

for most of them, a balance of isolated declines and improvements in test performance similar to the pattern observed in the optimal medication management arm. In other words, worsening of some neuropsychological tests after DBS was observed at a population level but was unlikely to affect individual patients in the majority of the cases.

However, Hilker et al. [37] reported significant improvement in verbal and nonverbal long-term memory 4 months after surgery in 8 bilateral STN DBS PD patients compared to 10 healthy matched controls suggesting STN DBS might in fact improve memory circuits. The study was not corrected for multiple analyses and a post hoc correction was not possible due to the lack of reported p value, making it unclear if such a correction would have made the reported improvement statistically not significant.

In summary, 10 of the 20 available controlled studies reported statistically significant worsening on some cognitive measures after bilateral STN DBS and 2 reported improvement in some and worsening in other cognitive measures. Different subtypes of fluency (semantic, phonemic, and category) worsened in some studies but not others. Worsening of attention was also reported in more than one controlled study. On the other hand, one controlled study reported improvement and 7 did not detect any cognitive difference between STN DBS and non-DBS PD patients.

3.3. Target Selection. Currently, most DBS centers prefer to implant in the GPi in PD patients with mild cognitive impairment, out of fear that STN DBS would cause more cognitive side effects. There is indeed more data in the literature reporting cognitive worsening after STN DBS than GPi DBS, but this data is markedly imbalanced as the studies detailed above have evaluated 1,777 STN DBS patients but only 165 GPi patients. It is important therefore to look more attentively at head-to-head comparison between the 2 targets.

Head-to-head comparison of the cognitive impact of STN and GPi DBS was reported in 9 studies to our knowledge, with a total of 581 STN and 617 GPi patients [26, 34, 47, 50–55] (Table 4). Only one of these [51] reported correction for multiple analyses. After corrections were applied when needed, the following studies revealed a difference between the 2 groups.

Weaver et al. [53] followed 159 patients for 3 years after surgery and reported worsening of one out of 4 memory measures after STN DBS compared to GPi DBS. The authors suggested that this difference might be secondary to a larger decrease in dopamine replacement doses in the STN group. Although Rothlind et al. [47] reported slightly greater reductions in some aspects of processing speed in the STN group and greater reductions in verbal learning and recall in participants in the GPi group, the 2 groups were deemed similar overall. Odekerken et al. [54] reported a bigger negative change in the STN group 12 months after surgery, in 4 out of 11 measures of attention, out of the 24 cognitive measures assessed. However, the frequency of cognitive decline and the quality of life were similar between the 2 groups. Of note, the authors also reported that an older age at surgery was associated with a higher risk of cognitive decline (62.4 versus 58.4 years). On the other hand, in a 36-month follow-up to this study, Odekerken et al. [34] reported no difference between the 2 groups on a composite score for cognition, mood, and behavior but reported better OFF drug motor symptoms and functioning in the STN group, as well as bigger medication reduction in that group and a higher rate of repeat surgery in the GPi group.

In summary, and after correction for multiple analyses, only 2 out of 9 studies [53, 54], totaling 126 STN and 145 GPi patients, reported worse outcome in the STN group in some measures of attention or memory. However, quality of life was similar in the 2 groups. Interestingly, these studies did not report any worse decline in language, fluency, or executive function in the STN group, as would have been expected from the open label and controlled studies. Overall, these data do not support favoring GPi over STN for fear of cognitive complications from the latter [80] in properly screened PD patients.

4. Discussion

Studies on cognitive changes after DBS in PD patients have reported different and sometimes opposite results. However, any change revealed by cognitive tests is likely subtle as detected cognitive worsening on specialized tests was usually not reported by patients, caregivers, or healthcare providers [25, 81]. In addition, quality of life measures in these patients showed improvement, even when cognitive worsening was detected [33, 53, 54, 58, 82].

Our findings confirm results from a recently published meta-analysis by Combs et al. [81] including 38 articles with an aggregated sample size of 1622 patients. The authors searched keywords and had selection criteria similar to ours, with the exception of needing sufficient report of study results to allow for an effect size to be calculated. These additional criteria might explain the lower number of studies included in the meta-analysis compared to our current review. Among the articles reviewed, 30 included STN DBS patients only, 5 reported on GPi DBS only, and 3 compared GPi and STN DBS. Combs et al. reported a small decline in psychomotor speed, learning and memory, fluency, attention/concentration, executive functions, and general cognition after STN DBS. GPi DBS patients had small changes in attention/concentration and fluency. The authors warned against concluding that GPi DBS would be cognitively safer than STN DBS, because of the small number of GPi DBS studies included.

Kumar et al. [83] suggested that variability in lead placement inside the target might explain the variation in the results of different studies. Tsai et al. [84] suggested that an active contact anteriorly located within the ventral STN could cause the neuropsychological effects reported in chronic STN DBS. York et al. [85] suggested that, in addition to the precise location of the active electrode inside the STN, a surgical trajectory through the frontal lobe might also influence the cognitive outcome. Indeed, Witt et al. [41] reported a higher risk of decline in working memory performance and global cognition associated with a trajectory intersecting the caudate nucleus. On the other hand, Smith et al. [86] could

Table 4: Studies comparing cognitive outcomes between GPi and STN DBS in PD patients.

Author, year	*N* STN/GPi	Laterality	F/u (mo)	Status of stimulation/medication at cognitive assessment	Cognitive measures assessed	Differences between GPI and STN
Boel et al., 2016 [55]	63/65	BL	36	ON/ON	GC, A/C, E, M, L	None
Follett et al., 2010 [52]	147/152	BL	24	ON/OFF	GC, L, V, E, M	None
Odekerken et al., 2013 [26]	63/65	BL	12	ON/integrated ON and OFF	Composite test	None
Odekerken et al., 2015 [54]	56/58	BL	12	ON/ON	A/C, E, M, L, V	4/11 measures of A/C worse with STN
Odekerken et al., 2016 [34]	43/47	BL	36	ON/ON	A/C, E, M, composite score	None
Okun et al., 2009 [51]	22/23	UL	7	ON/OFF	L	None
Rothlind et al., 2007 [50]	19/23	UL	6	ON/ON	A/C, E, L, V, M	None
Rothlind et al., 2007 [50]	14/15	BL	21	ON/ON	A/C, E, L, V, M	None
Rothlind et al., 2015 [47]	84/80	BL	6	ON/ON	A/C, E, GC, L, M	None overall, E worse with STN, M worse with Gpi
Weaver et al., 2012 [53]	70/89	BL	36	ON/OFF	GC, L, V, E, M	M worse with STN

PD: Parkinson's disease; GPi: globus pallidus interna; STN: subthalamic nucleus; *N*: number of patients; mo: months; UL: unilateral; BL: bilateral; A/C: attention/concentration; E: executive; GC: global cognition; L: language; M: memory; V: visual. Adapted from Mehanna [101] with permission from the author.

not find any correlation between decline in verbal fluency and any of age at surgery, number of intraoperative microelectrode penetrations, coordinates of the lead tip, or active stimulation site in a series of 28 STN DBS patients. Larger series have yet to duplicate these results. Trépanier et al. [87] also suspected variations in the characteristics of the patients selected for surgery between different centers (age, preoperative cognitive status, and comorbidity with other conditions such as psychiatric disorders) to explain conflicting conclusions from different studies.

In addition, outcome can also be influenced by stimulation parameters. Wojtecki et al. [88] reported a frequency-dependent modulation of cognitive circuits involving the STN, with low frequency (10 Hz) STN DBS improving verbal fluency compared to no stimulation and high frequency (130 Hz) STN DBS causing a nonsignificant trend towards worsening of fluency compared to no stimulation. Schoenberg et al. [89] reported improvement in cognitive test scores with increased amplitude and pulse width of the stimulation in 20 bilateral STN PD patients.

The respective contribution of lead implant and stimulation to post-DBS cognitive change is difficult to ascertain. The COMPARE trial [51] reported worsening of letter verbal fluency that persisted even when DBS was turned OFF, suggestive of a surgical rather than a stimulation-induced effect. On the other hand, Tröster et al. [35] reported worsening of measures of language and attention even before DBS was tuned ON, with further worsening after activation.

Studies assessing cognitive change after DBS for PD can have the following limitations. First, most the available studies lack a control arm of non-DBS treated PD patients, and a reported cognitive decline might thus be caused by the natural evolution of PD rather than DBS. Second, a reported cognitive improvement may stem from practice effect in the case of repeated cognitive assessment [58]. Using parallel forms of cognitive tasks might mitigate this practice effect, but it may be logistically difficult. Alternatively, cognitive assessments could be repeated at relatively long intervals [58]. Third, all studies did not assess patients in the same pharmacological condition, with most studies assessing patients ON antiparkinsonian medications, some studies assessing them OFF antiparkinsonian medications [38, 51–53, 63, 67, 75], and some other studies assessing them in a nonhomogenous way [25]. Some authors did not specify the medication and/or stimulation status of the patients at the time of cognitive evaluation [27, 28, 35]. Finally, cognitive worsening after DBS might be at least partially secondary to a postoperative reduction in antiparkinsonian medications, which is seen more after STN DBS than GPi DBS [9, 34]. A uniform assessment ON stimulation and OFF medications could minimize this confounding factor. However, severity of symptoms OFF medications might render such a preoperative assessment impossible in some patients.

5. Conclusion

After reviewing the available studies assessing cognitive changes after STN and GPi DBS in PD patients, we arrive at the following suggestions. (1) In PD patients who are adequately screened for surgery, worsening of one or more cognitive functions is rare after DBS, with available studies reporting conflicting results. (2) Any change revealed by cognitive tests is likely subtle as a detected cognitive worsening on specialized tests is usually not reported by patients,

caregivers, or healthcare providers. Furthermore, there is an improvement in quality of life after DBS, even when cognitive worsening is detected. (3) Worse cognitive outcome after STN DBS compared to GPi DBS was reported only in 2 out of 9 randomized trials. As such, fear of cognitive worsening should not systematically exclude STN as a potential DBS target. (4) Ideally, future studies on this topic should include controls for the natural evolution of PD. This can be done by using nonsurgically treated PD patients matched for all clinical and demographic variables. In addition, DBS patients should be assessed ON and OFF stimulation, thus providing direct comparison of the stimulatory effects while controlling for the effects of surgery. (5) Additional reports on anatomo-clinical correlation of cognitive worsening after DBS would help improve surgical planning to avoid sensitive structures.

Abbreviations

DBS: Deep brain stimulation
STN: Subthalamic nucleus
GPi: Globus pallidus interna
PD: Parkinson's disease
LID: Levodopa induced dyskinesias
DLPFC: Dorsolateral prefrontal cortex.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

DBS Programming: An Evolving Approach for Patients with Parkinson's Disease

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Deep brain stimulation (DBS) surgery is a well-established therapy for control of motor symptoms in Parkinson's disease. Despite an appropriate targeting and an accurate placement of DBS lead, a thorough and efficient programming is critical for a successful clinical outcome. DBS programming is a time consuming and laborious manual process. The current approach involves use of general guidelines involving determination of the lead type, electrode configuration, impedance check, and battery check. However there are no validated and well-established programming protocols. In this review, we will discuss the current practice and the recent advances in DBS programming including the use of interleaving, fractionated current, directional steering of current, and the use of novel DBS pulses. These technological improvements are focused on achieving a more efficient control of clinical symptoms with the least possible side effects. Other promising advances include the introduction of computer guided programming which will likely impact the efficiency of programming for the clinicians and the possibility of remote Internet based programming which will improve access to DBS care for the patients.

1. Introduction

Deep brain stimulation (DBS) therapy was approved by the US Federal Drug Administration (FDA) in the year 2002 for treatment of motor symptoms in Parkinson's disease [1]. The efficacy of DBS has been well established through randomized controlled studies involving several hundreds of Parkinson's disease patients [2]. DBS is effective for control of tremors that are refractory to dopaminergic medications, motor fluctuations, and levodopa induced dyskinesia that are bothersome to patients. The success of DBS is dependent on many factors including selection of appropriate patients, accurate placement of DBS lead, and a thorough programming process to identify the optimal stimulation parameters [3]. Selection of appropriate patients is based on many factors including the age of the patient, disease stage, disease duration, comorbidities, and responsiveness to levodopa medication. These factors are discussed by an interdisciplinary team consisting of neurologist, neurosurgeon, psychiatrist, neuropsychologist, rehab specialist, and sometimes a social worker. Once the DBS lead is placed in an appropriate target using standard surgical technique, DBS programming is initiated which in most cases is a time and labor intensive manual process involving multiple patient visits [4]. DBS programming is generally performed by movement disorder neurologists (including fellows in training), neurosurgeons, nurses, nurse practitioners, or physician assistants who have acquired training and experience for this procedure. Although there are general guidelines available for programming, there are no clear, validated, and established programming protocols. An inefficient programming can result in suboptimal clinical outcomes and lead to side effects

which becomes a source of frustration for Parkinson's disease patients and caregivers as well as healthcare providers [3]. These patients are then referred to as "DBS failures" and referrals are placed to advanced DBS centers for consideration of a lead revision surgery. In a retrospective analysis of 41 patients who presented to two academic DBS centers for management of "DBS failures," over a period of two years, 15 patients (37%) were identified as inadequately programmed and they improved significantly after reprogramming. There were 6 additional patients (15%) who benefitted partially from expert reprogramming, and 21 patients (51%) failed to improve despite a detailed reprogramming. There were also seven (17%) patients who did not demonstrate clinical improvement due to poor access to programming [5]. Thus lead revision is potentially avoidable when a careful and systematic algorithm based programming is employed.

2. Current Approach to DBS Programming

2.1. Initiation of Programming. In Parkinson's disease, a successful DBS programming is usually accomplished over a period of three to six months. Programming is usually not initiated immediately after the placement of a lead; instead a time frame of 2–4 weeks is allowed for the microlesion effects to fade away. These microlesion effects are believed to arise from the trauma of the DBS lead implantation rather than from the stimulation of the targeted brain structure. As a result, there is temporary improvement in clinical symptoms. Thus, for an accurate assessment of stimulation benefits, it is recommended that DBS programming gets initiated only when the initial benefits fade away [6]. In a large randomized controlled DBS study, the mean medication "on" time in patients randomized to receive delayed stimulation therapy was observed to improve at three months after surgery attributed to the microlesion effects. Nearly 40% of this group responded with an improvement of more than 2 hours of "on" time compared to the case before surgery [7]. There are some DBS centers that advocate initiation of programming at an earlier stage while the patients are still hospitalized as this method is more patient convenient and avoids an extra programming visit [8]. In addition to the microlesion effect confounding the initial results, impedance fluctuations in the tissue surrounding the DBS lead can also contribute to inaccurate assessment. Impedances are observed to be increased immediately after placement of a lead, as a consequence of edema, and they tend to decrease and stabilize over the first few weeks [9]. In these situations, DBS therapy delivered through constant-voltage stimulation is avoidable as the current delivered depends on the impedance. Instead, a constant-current stimulation that allows the current to adapt to changes in the impedance is recommended.

2.2. Lead Type, Impedance Check, Programming Thresholds, and Battery Check. In order to utilize effective stimulation parameters at the bedside, it is important for the DBS programmer to be aware of the lead type which refers to the size of the contacts and the distance between them. With the Medtronic system, the commonly used lead models are the 3387 and the 3389. The 3387 model is a 40 cm long and 1.27 mm wide cylindrical lead with 4 cylindrical electrodes that are 1.5 mm in length each and placed 1.5 mm apart. The 3389 model carries the same specifications except for electrode spacing of 0.5 mm. The Boston Scientific DBS lead has 8 cylindrical contacts that are 1.3 mm in diameter and 1.5 mm in length, placed 2 mm apart and covering a span of 15.5 mm. The Boston Scientific DBS system also offers a directional lead in which the middle two levels are split into three segments spanning approximately 120 degrees and the highest and the lowest level contain ring shaped electrodes. The Boston Scientific system is currently not FDA approved; however trials are underway. The St Jude Infinity DBS system (now called Abbott's Infinity DBS system) that has segmented electrodes and a wireless mobile platform for programming recently received FDA approval.

It is also necessary to confirm the location of the DBS lead prior to initiation of programming. At our center, we routinely obtain a postoperative CT brain that is coregistered with the preoperative MRI scan. Another important step is to gather intraoperative records for review of stimulation parameters used for testing immediately after the implantation. Once these steps are completed, the programming healthcare professional records the impedance at each of the contacts to establish a baseline for future reference. Compared to intraoperative parameters (influenced by edema), the impedance recorded is often different. If an impedance recording suggests a short circuit or an open circuit then the impedance is rechecked at higher voltages to ensure accuracy of the reading. The older Soletra® and Kinetra® Medtronic models require the provider to manually select the higher voltage for the repeat impedance check, whereas the Activa® SC/RC/PC will automatically check at 1.5 V and 3.0 V if open circuit is noted at 0.7 V stimulation. If there is a short circuit (which is extremely low impedance < 250 ohms) then the provider is not required to check at higher voltages. When a short circuit is identified, it is recommended to avoid the involved contacts as these are not dependable. There is generally faster battery depletion or there is sometimes a sudden loss of benefit. A common reason identified for short circuit has been anchoring of DBS lead with a miniplate [10]. High impedance, for example, 2000 ohms for the Soletra and 4000 ohms for the Kinetra, should be in general seen concurrently with unipolar and bipolar review. If the impedances are high in the bipolar contacts but normal in the unipolar contacts then there may not be an open circuit. Decisions regarding open circuit findings need to be evaluated on a case-by-case basis. The high impedance (open circuit) will be generated in the Activa SC/PC/RC when >10000 ohms in unipolar and bipolar configuration is noted [11]. The St Jude DBS system will show a message of "high" (read as 31 with older version and with newer one as >3000) when there is an open circuit. Lead fractures are common reasons for open circuits with an overall incidence of 5.1%, clinically presenting as electrical shocks reported by patients or lack of a therapeutic benefit. In the context of Parkinson's disease, it is also important to consider head jerking from cervical dystonia or a twiddler's syndrome, in which the patients who have developed dopaminergic medication induced impulse

control disorder subconsciously spin the neurostimulator in the chest wall which results in lead fractures [12]. In a series of 226 DBS patients, three patients identified to have a twiddler's syndrome presented with reemergence of Parkinson's disease symptoms and pain along the path of the hardware. In these patients, twisting/fracture of DBS extension was identified radiographically and was treated surgically by securing the neurostimulator in the chest wall [13, 14].

Once the electrical intactness of the system is established, thresholds of stimulation parameters that elicit benefits and induce side effects are determined. Initially, each electrode contact on the lead is tested in a monopolar configuration with the electrode as negative (cathode) and the neurostimulator case as positive (anode), a process referred to as monopolar review. The main stimulation parameters include the voltage, the frequency, and the pulse width. Amplitude controls the intensity of the stimulation, pulse width refers to the duration of each electrical pulse delivered, and frequency is the rate of stimulation employed in programming. The Medtronic system for the Soletra and Kinetra is only available in amplitudes of voltage (V). The Medtronic system for the Activa SC/RC/PC is available in either amplitudes of V or milliamps (mA). The St Jude and Boston Scientific systems are available only in amplitudes of mA. With a fixed frequency and pulse width, each of the electrode contacts is separately examined with amplitude delivered at increasing increments of 0.5 V or mA until there is elicitation of adverse effect (objective or subjective) that stays persistent with continued stimulation. This establishes a stimulation threshold for the adverse effects. Then the efficacy of stimulation at this contact is examined using an amplitude reduction by 0.1–1.0 V or mA below the stimulation threshold for side effects [15]. As the amplitude is reduced, the lowest threshold for inducing the best clinical benefits is determined. On the other hand, some centers first identify the threshold for clinical benefit and then increase the amplitude to identify the threshold for side effects. The electrode contact with the widest therapeutic window (wider difference between the threshold for inducing side effects and the threshold for clinical benefits) is selected for chronic stimulation. Both clinical effects and side effects depend on the direction of spread of current stimulating the anatomical structures as described in detail in the Table 1. If there is inadequate control of motor symptoms with single monopolar configuration, the next choice is to employ double monopolar stimulation with the two stimulation contacts as negative and the neurostimulator case as positive. There is no fixed time interval on taking this decision but most programmers wait few weeks or couple of programming sessions before switching to a bipolar configuration. Alternate method is to stay in monopolar stimulation but adjust the frequency or the pulse width. Bipolar configuration (most effective contact is negative and the adjacent contact is positive) is sought if side effects with monopolar configuration are induced at low amplitudes. With bipolar configuration, higher stimulation intensities are sometimes required to achieve the same clinical benefit.

In theory, DBS programming for a Medtronic device involves thousands of possible parameter combinations considering the range of programmable amplitudes (>90 possible), pulse widths (>10 possible), frequencies (>25 possible), interleaving settings, and configuration of anodes and cathodes. However since the recommended limit for charge density is 30 mC/cm^2 which is calculated by dividing the product of the voltage and the pulse width by the product of the impedance and the geometric surface area of the DBS electrode (0.06 cm^2) it limits the number of possible combinations [16]. There is a wide variation in the final stimulation parameters selected for DBS programming which is driven by multiple factors such as patient characteristics, the specific Parkinson's disease phenotype, and the lead position. In Parkinson's disease, the stimulation parameters used with a Medtronic system consist of a range of pulse widths (60 to 450 μs), frequencies (60 to 160 Hz), and voltages or currents (1 V to highest tolerated value). In most clinical DBS studies for Parkinson's disease, voltage in the range 2.4 to 4.4 V, frequency in the range 143 to 173 Hz, and pulse width in the range 67 to 138 μs have been found to effectively control the motor symptoms [17]. For efficient management of motor symptoms few published algorithms are available. In one study from Grenoble, France, with several combinations of stimulation settings that were systematically evaluated in patients with Parkinson's disease, the most important factors for alleviation of motor symptoms were identified as the voltage followed by the frequency [18]. In a recent study, an algorithm was proposed to specifically address the speech issue, gait impairment, and stimulation induced dyskinesia. The authors suggested lowering of stimulation frequency once other considerations including reduction of voltage, stimulation with bipolar configuration, and interleaving pattern had been tried with no clinical improvements. Caution should be exercised while using low frequency DBS as there is a possibility of worsening of appendicular rigidity, bradykinesia, and tremor [3].

2.3. Programming Visits. The initial programming visit can be often long lasting nearly 60–90 minutes. During this visit, it is important to provide patient education on several matters that are pertinent for a successful DBS programming. These include the knowledge on potential stimulation induced side effects, the use of the patient programmer (how to turn on and turn off the stimulator or go between patient group settings or programs if provided or adjusting parameters provided to the patient), and the safety precautions that need to be followed such as avoidance of strong magnetic fields and the use of diathermy during surgical procedures. Thus, family and friends are encouraged to accompany the patients during this initial programming visit. The programming is usually performed in the morning in an off-dopaminergic medication state. The rationale for holding medications is that dopaminergic medications can potentially obscure the stimulation induced benefits. Patients are instructed to hold the medications overnight or to miss at least a couple of doses so that they present to clinic in the "off-" medication state. If off-medication symptoms are intolerably severe or there is a lack of family support for outpatient management, inpatient programming is recommended. Alternately, patients are allowed to present in an on-medication state and they are

Table 1: Clinical effects of stimulating individual targets employed in Parkinson's disease depend on spread of current.

	Optimal location stimulation	Medial spread of current	Lateral spread of current	Anterior spread of current	Posterior spread of current	Dorsal or superior spread of current	Ventral or inferior spread of current
Subthalamic nucleus							
Anatomical structure stimulated	Dorsolateral aspect of subthalamic nucleus (motor territory)	Cranial nerve III Red nucleus Limbic aspect	Corticospinal tract/internal capsule Frontal eye field fibers of internal capsule	Corticospinal tract/internal capsule Hypothalamus	Medial lemniscus	Internal capsule Thalamus Zona incerta	Substantia nigra reticulata Internal capsule fibers
Clinical effects	Control of tremors, bradykinesia, and rigidity	Diplopia, eye deviation, dizziness Sweating, nausea, paresthesia, warm sensation Personality change Depression, impulsivity	Facial pulling Limb contraction contralateral side Contralateral deviation of gaze	Facial pulling Limb contraction contralateral side Autonomic symptoms Sweating, nausea	Paresthesia (tingling, electrical sensation, numbness)	Contralateral muscle contraction Improvement of dyskinesia/tremor Improvement of dyskinesia/tremor	Mood changes Depression Muscle contractions
Globus pallidum							
Anatomical structure stimulated	Posteroventral aspect of globus pallidum	Internal capsule posterior limb	Globus pallidum externus Putamen	Globus pallidum externus Putamen	Internal capsule posterior limb	Globus pallidum externus	Optic tract
Clinical effects	Reduction of bradykinesia, rigidity, and dystonia	Contralateral muscle contractions	No effect	No effect	Contralateral muscle contractions	Putamen No effect	Phosphenes
Thalamus							
Anatomical structure stimulated	Ventral intermedius nucleus located in the middle of thalamus	Medial aspect of nucleus, centromedian nucleus/parafascicular nucleus	Internal capsule posterior limb	Ventral oralis anterior Ventral oralis posterior	Ventral caudalis nucleus	Dorsal aspect of thalamic nucleus Internal capsule fibers	Zona incerta Medial lemniscus Brachium conjunctivum
Clinical effects	Tremor control	Dysarthria	Dysarthria Contralateral muscle contractions	No effect Reduction of tremor	Paresthesia	No effect Dysarthria	Improvement of tremor/dyskinesia Paresthesia ataxia

examined once the medications effects show signs of wearing off (suboptimal on-medication) [17]. Standardized motor tasks of the Unified Parkinson's Disease Rating Scale are used for clinical assessment. Amongst all the cardinal motor symptoms of Parkinson's disease, tremors and rigidity are found to respond very quickly, usually within seconds to minutes of stimulation, whereas there is a variable time delay for improvement in bradykinesia. The clinical response to DBS depends on several factors such as disease characteristics, DBS lead position, stimulation parameters, and individual patient profile. Since patient participation is critical, factors such as patient fatigue, patient comfort, patient anxiety, and training contribute significantly to the outcome.

Once the off-medication state programming is completed, patients are given their usual dopaminergic dose to further determine stimulation parameters for control of levodopa induced dyskinesia. It is noteworthy that levodopa induced dyskinesia does not necessarily emerge immediately after the first dose of medication, sometimes requiring the cumulative effects of two or three doses to develop, and is most often seen in the afternoon. The best electrode configuration is the one that adequately improves off-medication parkinsonism and reasonably suppresses on-medication dyskinesia. A challenge that arises in relation to subthalamic nucleus DBS is stimulation induced dyskinesia when the DBS lead is well-positioned in the motor territory. In these circumstances, a gradual reduction of stimulation voltage is recommended to achieve balance between control of parkinsonism and control of dyskinesia. On the other hand, stimulation of the dorsal globus pallidum may show differential effects on control of dyskinesia based on the specific anatomical region stimulated. There are reports that stimulation of dorsal globus pallidus internus induces dyskinesia which may be confused with medication related dyskinesia. When stimulation contact is shifted ventrally, dyskinesia becomes suppressed and bradykinesia tends to worsen [19].

DBS programming requires multiple patient visits. During the initial six months after surgery, patients are followed every month. Once the optimal programing settings are determined, patients are then followed on an annual basis for clinical performance, troubleshooting, and battery checks. An earlier follow-up is scheduled if the disease status worsens at a faster pace.

2.4. Battery and Programming. During the follow-up of DBS patients, estimation of battery life is critical. Battery drain is dependent on many factors including manufacturing tolerances, battery usage, battery chemistry, and variations in tissue impedance. The electrode surface area (small surface areas result in larger impedances) and the number of contacts used for stimulation affect the tissue impedance [20, 21]. With the Medtronic Soletra system, the battery life starts at a voltage of 3.69–3.74 V with an end of life (EOL) reached when the battery drains to about 2.5 V. In general with Soletra battery the voltage stays the same over a period of time; however as the battery nears the end of longevity, a slow drop in voltage may occur followed eventually by a more rapid depletion. Some patients notice worsening of symptoms when the battery is depleting and thus waiting to reach 2.5 V is not necessary to plan replacement of the DBS battery. With the Medtronic Kinetra system, the starting battery voltage is 3.2 V and the EOL is reached around 1.97 V. The Kinetra battery voltage reading slowly decreases over time; sometimes the Kinetra battery will stop showing a decline in the battery voltage for several visits; however if the patient complains of return in symptoms then it is important to make plans to replace the DBS battery. The current consumption with Kinetra is linear, unlike Soletra where the voltage doubler or tripler circuit is activated once the voltage parameter delivered for clinical stimulation increases to 3.6 V leading to a faster drain of battery [22]. In addition to the battery status indicator available in each device, battery life can be estimated through helplines/website made available locally or through Medtronic Inc [20]. Newer generation DBS systems offer rechargeable neurostimulators such as the Activa RC through the Medtronic (expected lifespan of about 9 years) or Vercise® system through the Boston Scientific (expected lifespan of about 25 years). The Abbott Infinity® system has a battery life of 3–5 years (Saint Paul, MN, USA) [23]. Medtronic Activa RC, Boston Scientific Vercise (not approved by FDA yet), and Abbott Brio all offer rechargeable DBS batteries. The Abbott Infinity 5 and Infinity 7 batteries show a status of either "battery okay," "battery low," or "battery depleted." Further details on battery life and impedance details are provided in Table 2. Future advances in DBS technology such as closed loop DBS will increase battery life and advances in DBS programming like remote and Internet based programming will increase patient comfort and convenience [24].

3. Recent Advances in DBS Programming

The electrical field delivered through the DBS contact in monopolar configuration is spherical with intensity of field decreasing in proportion to distance from the electrode. Large diameter myelinated axons have the lowest threshold for activation compared to dendrites and soma and also respond to shorter pulse widths. With bipolar configuration, the intensity of field decreases to one-quarter when the distance from electrode doubles. The intensity of electrical field increases as the distance between cathode and anode increases with wider bipolar configuration giving higher intensity field compared to narrow configuration. The conventional DBS however has limited capabilities with regard to modulating the shape of electrical field and tailoring the intensity of stimulation to maximally stimulate the neuronal pathways of interest and minimize the unintended spread to anatomical structures leading to side effects. Over the last few years, several novel technologies have developed in the field of DBS therapy. Current-based programming, interleaved programming, fractionated current, and directional current steering are important examples. The following sections will discuss these recent developments which are important advances in the field of DBS programming.

3.1. Interleaved Programming. Interleaving strategy is applied when conventional programming techniques, such as bipolar, double monopolar, or tripolar settings, and use of alternative pulse widths and frequencies fail to achieve desired clinical

Table 2: DBS system battery life and impedance limit.

DBS system company model	Battery type	Battery life (average)	Impedance limit for open circuit in ohms.	Impedance limit for short circuit in ohms
Medtronic Soletra™ (no longer manufactured)	Single chamber Nonrechargeable battery	3 to 5 years	If it is >2,000 ohms for bipolar and corresponding monopolar configurations and current is less than 10 uamps then it is likely open circuit.	<250 ohms
Medtronic Kinetra™ (no longer manufactured)	Dual chamber Nonrechargeable battery	3 to 5 years	If it is >4,000 ohms for bipolar and corresponding monopolar configurations and current is less than 10 uamps then it is likely open circuit.	<250 ohms
Medtronic Activa SC	Single chamber Nonrechargeable battery	3 to 5 years	If it is 5000–9000 ohms for bipolar and corresponding monopolar configurations suspect possible threatened open circuit. If it is >10000 ohms for bipolar and corresponding monopolar configurations then there is high suspicion of open circuit. If it is >40000 likely there is fracture in system.	<250 ohms
Medtronic Activa PC	Dual chamber Nonrechargeable battery	3 to 5 years	Same as Activa SC.	<250 ohms
Medtronic Activa RC	Dual chamber Rechargeable battery	8 years	Same as Activa SC.	<250 ohms
St Jude Libra™ (no longer manufactured)	Single chamber Nonrechargeable battery	3 to 5 years	High (31) is an open circuit.	
Abbott Infinity 5™	Dual chamber Nonrechargeable battery	3 to 4 years	>3000 Ohms.	
Abbott Infinity 7™	Dual chamber Nonrechargeable battery	4 to 5 years	>3000 Ohms.	

results. Interleaving is also useful when stimulation induced side effects are elicited at lower voltages. Interleaving consists of a rapid and alternate activation of two electrode contacts with two distinct voltages and pulse widths but with an identical frequency, up to maximum of 125 Hz in the Medtronic Activa system (interleaving not available with St Jude and Boston Scientific). Thus a limitation in modulation of frequency potentially interferes with simultaneous control of tremors and other motor symptoms as tremors tend to respond to a higher frequency [25]. Interleaving is not the same as simultaneous double monopolar stimulation as the pulses at each of the two contacts could be potentially offset by 4 ms (125 Hz equals 8 ms interpulse interval). With interleaving, an area of overlap that receives stimulation from both the electrical fields at double the frequency is seen and this area is speculated to contribute to stimulation induced chronic side effects. Interleaving is also useful when two contacts require different voltages for control of two different symptoms. For example, interleaving allowed treatment of tremors and bradykinesia through stimulation of the subregions of subthalamic nucleus and the adjacent zona incerta [26]. In another case, interleaving was used to deliver pulses to the ventral intermedius nucleus of the thalamus as well as the subthalamic nucleus region in a patient who presented with coexisting diagnosis of essential tremor and Parkinson's disease [27]. The main drawback of interleaving to keep in mind is the possibility of an increased battery drain which is a concern if Parkinson's disease patient symptoms of dystonia require high stimulation voltages and pulse widths [25].

3.2. Directional Stimulation. With the advent of directional lead technology, it is now possible to steer different shapes of current at the stimulation contact instead of providing the conventional spherical shape of current. A major advantage of this technology is steering current to the desired structures and avoidance of unintended stimulation of the neighboring anatomical structures. This new technology facilitates achievement of greater efficacy and fewer side effects [28]. This is especially desirable when small and complex brain regions are targeted [29], such as the pedunculopontine nucleus [30], or other fiber bundle targets, such as the medial forebrain bundle. Direct STN Acute (Aleva Neurotherapeutics SA) that incorporates six directional contacts with three directional contacts on each of the two levels was investigated in a recent pilot study of Parkinson's disease patients who underwent subthalamic nucleus lead implantation. This lead also had two omnidirectional electrodes proximal to the directional contacts. The directional contacts were each 1 mm × 1 mm in dimension, with a longitudinal spacing of 0.5 mm. The investigators compared the effects of directional stimulation to omnidirectional stimulation in an intraoperative setting, focusing specifically on the volume of tissue activated. They found that the volume of tissue activated with directional stimulation (4.2 mm^3) was substantially lower compared to the omnidirectional stimulation (10.5 mm^3). As a consequence, the therapeutic window was significantly wider (43% wider) and the side effects were much lower with directional stimulation [28]. Another parallel study tested a novel 32 contact lead (formerly Sapiens Steering Brain Stimulation BV, Eindhoven, the Netherlands, now called Medtronic Eindhoven Design Center). These contacts could be activated independently in clusters, allowing for directional steering of the stimulation field and directional recording of local field potentials. In this study, thresholds for therapeutic benefit and side effects determined intraoperatively in 8 patients with Parkinson's disease were noted to be increased and the therapeutic window widened [31]. Recently Vercise directional lead (Boston Scientific, Valencia, CA), which has eight-contact leads and a pulse generator capable of multiple independent current source, was tested in seven Parkinson's disease patients. This novel lead with four electrode levels had two middle level electrodes split into three segments spanning approximately 120 degrees each and ring shaped electrodes in the highest and the lowest level. An extended monopolar review session was performed during the first week after the placement of leads. The current thresholds for control of rigidity and stimulation induced adverse effects were determined using either directional or ring-mode settings. Similar to the previous two studies, the investigators reported an expansion of the therapeutic window with this novel system [32]. The benefits of directional stimulation were best appreciated when the lead was suboptimally placed and the therapeutic window was narrow, for example, when the subthalamic nucleus lead was laterally placed close to the internal capsule. While these results are promising, larger studies are warranted for further confirmation.

3.3. Current-Based Programming and Fractionalization of Current. For several years, DBS therapy involved the use of voltage based programming. However the fluctuations in the impedance at the level of electrode-tissue interface were noted to contribute to an instability of voltages delivered to the target neural tissue [33]. As a result, stimulation parameters required frequent adjustments especially during the initial programming period after the DBS lead has been placed. These undesirable fluctuations also led to the understimulation or overstimulation of the intended target. These factors prompted the development of current-controlled DBS that regulated the current delivered to the targeted neural tissue regardless of the impedance. With a constant-current device, the need for programming adjustments was expected to reduce and the outcomes of DBS programming were expected to be more reliable. In a randomized multicenter controlled study, a constant-current device was examined in Parkinson's disease patients who underwent bilateral subthalamic nucleus implantation [7]. Subjects participating received either immediate stimulation or a delayed stimulation which was initiated three months after surgery (control group). The primary outcome of the study was the mean increase in the amount of medication ON time, and it was significantly increased in the immediate stimulation group (4.27 h versus 1.77 h, $p = 0.003$). The immediate stimulation group also performed better than the control group in the off-medication/on-stimulation assessment of Unified Parkinson's Disease Rating Scale motor score (40% improvement in the immediate stimulation group). The study was not primarily designed to determine the frequency

of programming adjustments or compare constant-current with constant-voltage neurostimulation. In another crossover study of 8 Parkinson's disease cases, patients were randomized to constant-current and constant-voltage setting at about two years after subthalamic nucleus DBS surgery [33]. In both groups, the improvements in the motor scores, the reduction in levodopa dose, and the quality of life improvement were equivalent. The study concluded that constant-current stimulation programming was not necessarily superior to constant-voltage stimulation.

An accurate DBS targeting is critical for successful control of motor symptoms, and a slight error in lead location can sometime significantly impact clinical outcomes. In these circumstances, the delivery of small amounts of stimulation to multiple contacts is desirable. Until now, the DBS system consisted of a single source stimulation device. In the recent VANTAGE study, a multiple source delivery of fractionalized currents (Vercise DBS system, Boston Scientific) was examined in 40 Parkinson's disease patients who underwent bilateral subthalamic nucleus DBS surgery [23]. The Vercise DBS lead consisted of 8 contact rings one above the other on each side; each contact was 1.5 mm in length with 0.5 mm spacing between the contacts. A fractionated current with a well-defined shape of the electrical field allowed an enhanced and reliable motor response with minimized stimulation induced side effects. Once the healthcare programmer identified the contact that provided the best clinical benefits, the current was fractionalized between the best and the next best contact. Patients were then sent home with an ability to make adjustments at a preset stimulation range. In this open label study, Parkinson's disease patients were noted to improve by nearly 60% when comparing the baseline UPDRS motor scores (37.4 ± 8.9) with the six months postoperative scores (13.5 ± 6.8). There were also improvements in the quality of life, increase in the time spent in the medication on state, and reduction of the overall dose of dopaminergic medications. These outcomes were regarded better in comparison to other DBS trials and the incidence of adverse effects was in the acceptable range. Thus fractionalization of current is an important contribution to advanced DBS programming that will be soon applied in many more clinical studies.

3.4. Closed Loop DBS. There is an increasing enthusiasm for the use of closed loop DBS or adaptive DBS which represents a real-time change of DBS parameters in response to underlying physiological signals. The real-time change enables a more efficient control of clinical symptoms and at the same time there is a lesser use of battery [34]. However several questions have been raised over the best possible underlying physiological signal. In Parkinson's disease, these signals could be potentially recorded from the cortex, basal ganglia, and the skin surface over the affected body part (e.g., surface EMG) [35]. Local field potentials (LFPs) recorded from the basal ganglia are promising markers. LFPs indicate the oscillatory activity of a neuronal population surrounding the recording electrode and are usually clustered into specific frequency bands. The beta band frequency (11–30 Hz) is regarded as antikinetic, contributing to the bradykinesia and freezing of gait [36], whereas gamma band frequencies (>60 Hz) have a prokinetic role [37]. Beta band oscillations recorded from the subthalamic nucleus are found to be modulated by dopaminergic medication [38] and electrical stimulation [39]. They have been found to correlate with movement preparation and execution [40], akinesia [41], and the freezing of gait [42]. In a proof-of-principle study, LFP-based adaptive DBS was investigated in 8 patients with advanced PD who underwent subthalamic nucleus DBS [43]. The investigators applied an arbitrary threshold to the LFP power recorded from the subthalamic nucleus with DBS programmed to switch off if the beta power fell below threshold. Adaptive DBS was found to lead to a 30% greater motor improvement compared to continuous DBS therapy. Another source of physiological signals for adaptive programming is the cortex. Cortical signals recorded with electrocorticography have been frequently used for detection of seizures. In a primate model of Parkinson's disease, there was alleviation of akinesia when short stimulation trains (130 Hz) were delivered to the globus pallidus internus at fixed latency following an action potential recorded from the primary motor cortex area [44]. In another example of Parkinson's disease patient, there was improvement in rigidity when the phase amplitude coupling between beta and gamma oscillations of the cortical signals was observed to be decreased [45]. Closed loop stimulation will be increasingly utilized as the clinical advantages become established in patients with Parkinson's disease.

3.5. Applying Novel DBS Pulse for Programming. The conventional DBS therapy is a continuous delivery of charge-balanced, square waveform, cathodic pulse at specific voltages, and pulse widths that are within the limits of FDA recommended safety guidelines ($30\,\text{mC/cm}^2$). The square waveform DBS pulse has an active high-amplitude, short-duration stimulation phase, and an exponential passive low-amplitude, long-duration recharge phase that prevents tissue damage. However Hofmann et al. found that when the initial cathodic phase was followed by a short gap of time prior to introduction of an anodic phase, the neural activation and entrainment became more effective [46]. Foutz and McIntyre examined the effects of novel pulse shapes such as Gaussian, exponential, triangular, and sinusoidal pulses in both intracellular and extracellular environment to find that neural effects were elicited at lower energy consumption [47]. However, using biphasic pulse DBS therapy in which charge-balanced square-wave pulse with active recharge was used for patients with Parkinson's disease led to greater clinical benefits but at the cost of an increased battery drain [48]. Nevertheless, these applications of novel pulse shapes are promising and warrant further testing in a clinical population.

4. Guided Programming

4.1. Computer Guidance. Until now, DBS programming is mostly a time consuming and labor intensive manual process. DBS programming is also inconvenient to many patients as the DBS centers are few for meeting the needs of an increasing number of patients (more than 140,000 DBS surgeries performed worldwide) and often far away from a patient's

home [5]. The complexities involved in clinical programming are perceived as burdensome by many healthcare providers [49]. Therefore, there are growing efforts to develop computer guided programming in conjunction with a sensor-based technology for feedback. Motion sensor-based feedback has been found to result in a better clinical outcome compared to subjective assessment [50]. The feasibility of computer guided DBS programming and automated motion sensor-based assessment, requiring minimal physician involvement, has been examined in a pilot study [5]. In this study, once the software performed the initial monopolar review, multiple iterations were conducted based on the automated feedback. The software then applied an algorithm to determine the final stimulation settings required to achieve control of symptoms and at the same time minimize the side effects and the battery usage [49]. The investigators concluded that significant improvement in tremors and bradykinesia could be achieved with minimal clinician involvement. Even though these findings are promising, they will require further confirmation in the clinical settings.

4.2. Visual Guidance. DBS programming is regarded as an "empirical" and "blind" technique. The clinician empirically inputs the electrical parameters and awaits the patient response as the output. Over the last few years, computational models have been developed that incorporate individual patient neuroanatomy to facilitate visual programming. Recently, these models were tested with an iPad application interface (ImageVis3D Mobile) that provided a mobile environment for a visual feedback on the interaction of the stimulation parameters with the surrounding anatomy [51]. Aside from clear advantage in visual feedback, programming time reduced from over 4 hours to less than 2 minutes (>99% saving in time) with computational model [51]. Diffusion tensor imaging and other advanced MRI sequences can potentially contribute to improved visually guided programming. Commercial programming platforms available through the Boston Scientific (Boston Scientific Guide DBS) and Medtronic (Medtronic Optivise) should be soon available for visually guided programming [24].

In summary, the success of DBS is dependent on numerous factors including appropriate selection of patients, appropriate patient expectations, accurate placement of DBS lead, and a thorough programming to identify the optimal stimulation parameters. Although there are general guidelines available for programming, there are no protocols that are validated and clearly established. Identifying the lead type, electrode configuration, impedance in the electrical system, and battery check are key elements for programming visits. There are growing efforts to advance the current approach to DBS programming. With the advent of fractionated current technology, it is now possible to distribute current to electrodes in fractions for a broader capture of motor symptoms. Directional lead steers different shapes of current to stimulate the desired structures and avoid unintended stimulation of the neighboring anatomical structures. Since DBS programming is a time consuming and labor intensive manual process, there is increasing interest to develop computer and visually guided protocol. Programming is also not a comfortable experience for the patient as it requires frequent clinic visits and programming facilities may not necessarily be close to the patient home. However remote and Internet based programming are likely to resolve these issues in the near future.

Conflicts of Interest

All authors have no conflicts of interest regarding the publication of this paper.

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Review Article

Earlier Intervention with Deep Brain Stimulation for Parkinson's Disease

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Neuromodulation of subcortical areas of the brain as therapy to reduce Parkinsonian motor symptoms was developed in the mid-twentieth century and went through many technical and scientific advances that established specific targets and stimulation parameters. Deep Brain Stimulation (DBS) was approved by the FDA in 2002 as neuromodulation therapy for advanced Parkinson's disease, prompting several randomized controlled trials that confirmed its safety and effectiveness. The implantation of tens of thousands of patients in North America and Europe ignited research into its potential role in early disease stages and the therapeutic benefit of DBS compared to best medical therapy. In 2013 the EARLY-STIM trial provided Class I evidence for the use of DBS earlier in Parkinson's disease. This finding led to the most recent FDA approval in patients with at least 4 years of disease duration and 4 months of motor complications as an adjunct therapy for patients not adequately controlled with medications. This following review highlights the historical development and advances made overtime in DBS implantation, the current application, and the challenges that come with it.

1. Introduction

Idiopathic Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder in the western world. Dopaminergic neuronal loss begins as early as 10 years before motor symptoms appear. Diagnosis is still clinical and relies on the United Kingdom Brain Bank Criteria [1]. Currently there is no therapy to stop disease progression and management is directed primarily at motor symptoms relief. PD has a substantial economic impact on the healthcare system with an estimated cost of drug treatment calculated to be between $1,000 and 6,000 per year and annual healthcare cost between $2,000 and 20,000 per year [2, 3]. A multitude of dopamine enhancing agents are available as therapeutic options and usually employed as the first line of treatment. Although they are very effective in early disease stages there is an increasing awareness of refractory symptoms and well described motor complications related to chronic therapy [4]. These aspects have helped to establish a window of optimal therapeutic benefit for pharmacological approaches. As a result, neuromodulation by DBS arose as an adjunctive therapy for the management of dopamine-responsive patients with advanced disease. Initial use of DBS in advanced disease was heralded as a safe, cost-effective, and adjustable procedure that can be programmed to maximize motor benefits while minimizing side effects [5]. In the past few years the concept of earlier DBS therapy emerged as a therapeutic tool to prevent the development of motor complications and prolong quality of life for PD patients.

2. Historical Review

Before the discovery of dopaminergic agents, ablative surgical intervention was the main treatment for the motor symptoms of PD. The origins of the surgical interventions for movement disorders date back to the early twentieth century when the basal ganglia was considered a potential target for surgical intervention. Dr. E. Jefferson Browder at the State University of New York described improvement of Parkinsonian symptoms with caudate nucleus extirpation; and almost two decades later in 1947 neuroscientist Ernest A. Speigel and

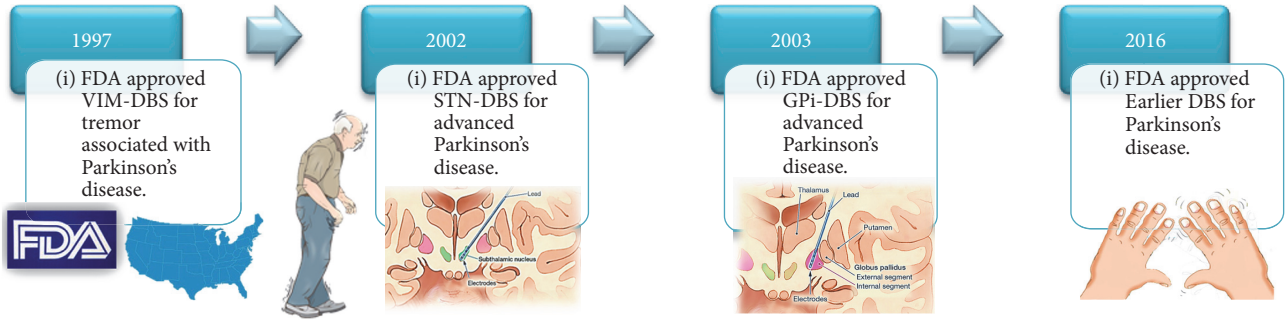

Figure 1: DBS FDA approval timeline.

neurosurgeon Henry T. Wycis at Temple University developed the first stereotaxic frame for humans. In parallel, the Neurophysiologist Jose Delgado at Yale University performed several experiments of deep electrical stimulation in animals and humans for behavioral control.

In 1953 Dr. Cooper made an accidental ligation of the anterior choroidal artery that resulted in a reduction of the contralateral tremor and rigidity in a PD patient [6]. He then proposed that this was due to an infarction of the globus pallidus interna (GPi), and as a consequence pallidotomies became a surgical treatment for PD [7]. Later, other structural lesions were studied leading to the identification of specific thalamic nuclei as a second anatomical target for therapy [8].

The next decade was notable for an expansion of ablative surgery [9] as a reflection of stereotaxic refinement and surgical procedures focused on thalamotomies and pallidotomies. In 1961 W. Watson Alberts at the Institute for the Study of Human Neurophysiology at Mount Zion Hospital studied stimulation thresholds in various parts of the globus pallidus interna and the ventrolateral thalamus. This was followed by a breakthrough discovery by neuroscientist Albe-fessard at Pierre and Marie Curie University who reported that ventralis intermedius (VIM) stimulation between 100 and 200 Hz suppressed tremor in Parkinson's patients.

The first description of chronic thalamic stimulation was made in 1965 by Carl Wilhelm Sem-Jacobsen, a Norwegian neurophysiologist and psychiatrist. However, the introduction of levodopa in 1967 by Cotzias et al. [10] temporarily ended the era of ablative surgery and neuromodulation; dopaminergic agents became the preferred treatment for PD. Dopaminergic therapy revolutionized PD treatment, but over time the limitations and side effects of taking levodopa for more than 5 years emerged. Once the limitations of motor fluctuations and dyskinesia were recognized as a consequence of long-term and high dosage levodopa therapy, there was a renewed interest in surgical therapies.

The idea of using chronic subcortical stimulation as a permanent therapy was developed in the 1970s by Dr. Natalia Petrovna Bechtereva at the Institute of Experimental Medicine and the Academy of Medical Sciences in Leningrad. Dr. Petrovna implanted electrodes into the ventrolateral and centromedian thalamic nuclei and administered intermittent high frequency pulses over several sessions. Unfortunately, since most of her articles were written in Russian and not further translated, her work was not widely disseminated.

The DBS golden era for PD was introduced to neurologists and neuroscientists by work from Dr. Benabid and his colleagues in 1987 at the Grenoble University. Their original paper highlighted the use of the traditional approach of VIM thalamotomy combined with chronic stimulation of the contralateral VIM, resulting in similar suppression of tremor in both affected sides. Afterwards, high frequency stimulation was used on 26 PD patients demonstrating improvement in tremor and rigidity, while dopaminergic medication dosage was reduced by 30% in 10 of these patients [11]. The same group eventually proved subthalamic nuclei stimulation (STN) to be not only a superior target but also the preferred intervention compared to pallidotomy [12] and thalamotomy for PD [13]. Thereafter, in 1994, the neurosurgeon Jean Siegfried at the Klinik Im Park in Zurich reported improvement of multiple symptoms of PD by stimulation of the globus pallidus interna (GPi) [14].

In 1997, the FDA approved for the first time the use of DBS as therapy in movement disorders, establishing the practice of VIM-DBS to treat essential tremor and tremor associated with Parkinson's disease (Figure 1; DBS FDA approval timeline). The first clinical trials of DBS for PD were done in 1998 by the Grenoble group. They demonstrated sustained improvement of motor fluctuations, dyskinesia, and a decrease of medication dose requirement in patients with PD and bilateral STN-DBS [15]. Simultaneously, Anthony Lang's group at the University of Toronto reached similar conclusions after completing a double-blind study [16]. Okun et al. at the University of Florida reported a retrospective review showing greater motor improvement with STN-DBS compared with GPi-DBS [17].

Three years later a large prospective double-blind study comparing STN versus GPi for PD showed a greater motor benefit from STN-DBS [18]. Collectively, these findings established the basis for how we use DBS therapy today. The level of evidence prompted eventual support by the FDA for STN-DBS in PD in 2002 [19]. Thereafter, the first long-term follow-up study of STN-DBS in PD showed sustained improvement in motor symptoms and activities of daily living

[20]. Since then, tens of thousands of patients have undergone DBS implantation [21], and numerous case reports and randomized controlled trials (RCT) have confirmed the long-term efficacy of STN and GPi targeting for the treatment of PD symptoms [17, 22–27]. The current practice parameter guidelines for DBS in PD published by the American Academy of Neurology in 2006 suggest the use of STN-DBS for PD, graded as level C evidence for improving motor function and reducing motor fluctuations, dyskinesia, and antiparkinsonian medication usage [23].

3. DBS in the Contemporary Era

Several theories have been proposed to explain the neuroprotective effect of DBS in PD. Despite the vast surgical experience with DBS, its mechanism of action and neuroprotective effects are still poorly understood [28]. DBS has electrical, chemical, and neural network effects. Computational studies have shown a possible simultaneous cell body inhibition with axonal excitation [29]; this decoupling phenomenon resulted in a network activity modification, influencing multiple thalamocortical circuits. The electrical stimulation disrupts pathological basal ganglia activity by changing firing rate [30] and increasing blood flow to the midbrain [31]. At the same time DBS triggers astrocytes to release calcium and neurotransmitters (adenosine and glutamate) and also stimulates neurogenesis [32, 33].

Class III evidence supports DBS therapy as beneficial for nonmotor symptoms such as improving sleep, mood/cognition, pain, and urinary and gastrointestinal symptoms [34–37]. This can be partially explained by increased mobility after surgery and overall improvement in quality of life, in addition to decreased medication needs. The combination of these effects may explain the associated reduction in anxiety and impulse control disorder [38]. However, there is a widely described detrimental effect on phonemic and semantic verbal fluency after the procedure [26].

The paradigm shift for DBS intervention came from two redefining concepts: (1) DBS in addition to best medical treatment (BMT) is more effective than BMT alone and (2) an earlier intervention could preserve functional capacity. Randomized controlled trials (RCT) have shown that DBS plus BMT can be superior to BMT alone, not only for improving motor function during the "off" state measured by UPDRS-III (motor subscale), but also by increasing quality of life (PDQ-39 self-reporting survey), maintaining activities of daily living (ADL), decreasing levodopa requirements, and expanding time spent in the "on" state without troublesome dyskinesia. Table 1 summarizes the main studies that proved this concept. With the exception of Charles et al. [39], all studies showed significant improvement in DBS patients when compared with BMT alone, ranging from 41% to 71% in the UPDRS-III. The Charles et al. study was designed as a safety study and was not powered to generate efficacy conclusions.

Given the robust response to DBS in PD and the quest to maintain quality of life, multiple studies have addressed the issue of functional capacity and symptoms reduction with the long-term use of DBS. Nonrandomized studies have shown sustained reduction of motor symptoms and levodopa induced dyskinesia after a five-year follow-up [20], motor scores improvement remained present after eight years [45], and medication reduction was still present at ten years after implantation. These studies were limited due to their nonrandomized design. In 2011, Parent et al. published a retrospective study with a subgroup analysis divided by age and disease duration, showing that there was an improvement in rigidity after a one-year follow-up in patients with disease onset less than 10 years versus. longer than 10 years. Similar results were seen in other prospective studies [46].

Thereafter, studies by Schuepbach et al. [44] and Charles et al. [39] explored the innovative concept of off-label early stage DBS. The pioneer study was done by a group from Vanderbilt University that published a pilot case of their early intervention in 2011 [47]. 30 patients between the ages of 35 and 75, Hoehn and Yahr stage II, and dopamine response for more than 6 months but less than 4 years were randomized to receive BMT or DBS plus BMT. The primary endpoints were the time to reach a 4-point change from baseline scores in the UPDRS-III off therapy and the change on levodopa equivalent dose from baseline to 24 months. Final results were published in 2014 [39]: the mean motor scores were not significantly different for on or off therapy and the DBS group required less medication than the BMT group at all time points with a maximal difference seen at 18 months. Two serious adverse effects occurred in two subjects, one subject had a perioperative basal ganglia infarct, and another had a traumatic scalp infection requiring removal of the device. A posterior post hoc analysis was conducted in 2015 [48] including all subjects from the pilot and a subset of subjects taking PD medications 1–4 years at enrollment which showed that DBS plus optimal drug therapy subjects experienced a 50–80% reduction in the relative risk of worsening after two years. Total UPDRS, complication of therapy, and PDQ-39 scores significantly worsened in the BMT group ($p < 0.003$); finally the DBS + BMT group significantly improved in the motor score (UPDRS-III) compared to the BMT ($p = 0.02$). Currently the group is preparing to launch a phase III clinical trial on early stage PD STN-DBS.

In 2012, a German-French group published a paper theorizing three phases of PD progression [49]. The first phase, the honeymoon period, is when the disease is well controlled with medications. The second phase, the intermediate phase, is when patients develop motor complications such as "on/off" fluctuations as a result of chronic dopaminergic therapy; this phase is variable in duration and is determined by individual biological/physiological factors. The third one is the levodopa resistant phase, when physicians struggle to find a trade-off between maximizing motor symptoms control and minimizing the presence of motor complications as a side effect.

The concept of PD phases prompted the initial hypothesis that the use of DBS as an adjunctive therapy in the early stage second-phase disease could maintain quality of life and social adjustment in PD patients, leading to the EARLY-STIM trial [44], an early interventional study in PD. Patients

Table 1: Randomized controlled trials for DBS versus BMT in PD.

Study	Target/number	Mean age (yrs)	Baseline characteristic in the "off" state	Mean disease duration (yrs)	Follow-up (mos)	Outcome/conclusion
Deuschl et al. 2006 [40]	STN + BMT: 78 BMT: 78	STN + BMT: 60.5 BMT: 60.8	*H & Y* STN + BMT: 3.7, BMT: 3.8 *UPDRS-III* SNT + BMT: 48.0, BMT: 46.8	>5	6	(i) UPDRS-III: 41% improvement in DBS versus 0% in the BMT ($p < 0.001$). (ii) PDQ-39: STN resulted in 14 % improvement.
Schüpbach et al. 2007 [41]	Bilateral STN + BMT: 10 BMT: 10	Bilateral STN + BMT: 48.4 BMT: 48.5	*H & Y* <3 *UPDRS-III* Bilateral STN + BMT: 32.7 BMT: 25.3	Bilateral STN + BMT: 7.2 BMT: 6.4	18	(i) UPDRS-III: 69% improvement in DBS versus worsening in BMT ($p < 0.05$). (ii) PDQ-39: 24% improvement in DBS versus 0% in BMT ($p < 0.05$). (iii) Levodopa dose: reduced by 57% in the DBS versus 12% in the BMT ($p < 0.001$).
Weaver et al. 2009 [42]	Bilateral STN/GPi: 121 BMT: 134	Bilateral STN/GPi: 62.4 BMT: 62.3	*H & Y* Bilateral STN/GPi: 3.4, BMT: 3.3 *UPDRS-III* Bilateral STN/GPi: 43 BMT: 43.2	Bilateral STN/GPi: 10.8 BMT: 12.6	6	(i) UPDRS-III: 71% of DBS patients experienced clinically meaningful motor function versus 32% of BMT patients ($p < 0.001$). (ii) PDQ-39: DBS group had significant improvement ($p < 0.001$).
Williams et al. 2010 [43]	Bilateral STN/GPi: 183 BMT: 183	DBS: 59 BMT: 59	*H & Y* DBS: 3.1, BMT: 3.2 *UPDRS-III* DBS: 47.6, BMT: 48.6	DBS: 11.5 BMT: 11.2	12	(i) UPDRS-III: 36% improvement in the DBS group versus 2% in BMT ($p < 0.0001$). (ii) PDQ-39: mean improvement compared with baseline was 5.0 for the DBS group versus 0.3 points in the BMT ($p = 0.001$).
Schuepbach et al. 2013 [44]	SNT + BMT: 124 BMT: 127	SNT + BMT: 52.9 BMT: 52.2	*H & Y* <3 *UPDRS-III* STN + BMT: 33.2 BMT: 33	STN + BMT: 7.3 BMT: 7.7	24	(i) UPDRS-III: 56% improvement in the DBS group versus 4% in BMT ($p < 0.001$). (ii) PDQ-39: 26% improvement in the DBS group versus no improvement in the BMT group ($p = 0.002$). (iii) Levodopa induced motor complications: 61% improvement in the DBS group versus no improvement in the BMT group ($p < 0.001$).
Charles et al. 2014 [39]	STN + BMT: 15 BMT: 15	STN + BMT: 60 BMT: 60	*H & Y* STN + BMT: 2, BMT: 2 *UPDRS-III* STN + BMT: 25.3 BMT: 25.6	STN + BMT: 2.2 BMT: 2.1	24	(i) UPDRS-III: mean scores were not significantly different on or off therapy. (ii) Medication requirements in the DBS + BMT group were lower at all time points.

DBS: Deep Brain Stimulation; SNT: subthalamic nucleus; GPi: globus pallidus interna; BMT: best medical therapy.

included in this trial were 60 years of age or younger and had onset of PD for 4 years or more, but less than 3 years of motor complications. The initial sample size included 251 patients, who were then randomized to either receive BMT or STN-DBS. The authors of the EARLY-STIM study [44] chose quality of life as their primary outcome measured by the 39 items of Parkinson's disease questionnaire for quality of life (PDQ-39), mainly because it evaluates the influence on quality of life by both motor and nonmotor symptoms of PD. After two years of follow-up the final results were published in the New England Journal of Medicine in 2013: a total of 226 of the 251 patients recruited were analyzed; the others were excluded due to deviation from the protocol or adverse events. Results showed that the PDQ-39 score improved by 26% in the neurostimulation plus BMT group but worsened in the BMT group. UPDRS-III scores improved by 53% in the neurostimulation group versus 4% in the BMT group. Medication dose was reduced 39% in the neurostimulation group but increased 21% in the BMT group. No significant cognitive changes were found between groups. Importantly, depression was more frequent in the neurostimulation group. In addition the study showed decreased progression of motor complications in a selected population between ages 19 and 60 with less than 4 years of disease duration as well as no more than 3 years of motor complications. Summarily, this pivotal study demonstrated additional Class I evidence of sustained motor and quality of life improvement after two years of DBS compared to BMT alone.

These two studies are the backbone of earlier intervention in PD; furthermore there were two Japanese prospective publications that reported significant improvement in ADLs and UPDRS-III with early STN-DBS implantation after 3- and 6-month follow-up [50, 51].

Moreover a base-case analysis showed that the incremental cost-utility ratio for STN-DBS versus BMT was 22.700 euros per quality adjusted life year gained, showing that STN-DBS at earlier stages of the disease is cost-effective in patients below the age of 61 [52]. Likewise a decision analysis model of early versus. delayed bilateral DBS implantation showed that early intervention results in superior cost-effectiveness due to a greater quality adjusted life expectancy by reduction in pharmaceutical cost, therapy, and specialist consultations [53]. Similarly, DBS offered earlier provided substantial long-term reduction in medication cost by maintaining a simplified, low dose medication regimen [54].

The above findings led to the recent FDA approval of DBS in PD levodopa-responsive patients with at least 4 years of disease duration and 4 months of motor complications not adequately controlled with medications [55].

The implementation of this new criterion of early intervention based on the EARLY-STIM criteria requires a complete evaluation of the limitations of this study and has been the subject of extensive ethical discussion [56, 57]. Despite a strong design, the inclusion criteria excluded patients older than 60 years, an age group that has a high risk of rapid development of motor complications. Therefore, clinical decisions in this age group are limited. In addition, long-term expectations for the procedure effect are difficult to predict due to the short follow-up period of only 2 years. This time frame could be considered insufficient when observing a progressive chronic illness such as PD [58]. Future follow-up data from the EARLY-STIM study will help to answer these concerns.

The lack of a double-blinded design with sham surgery raised the concern for placebo effect in this trial. Some authors state that the placebo effect in PD trials can be as high as 39% [59]. However, this number has been extrapolated from PD trials that do not have a DBS surgery therapy component. Motor and quality of life improvement was sustained for two years and the motor assessment was performed with on/off stimulation and rated blindly by a movement disorder specialist. The two-year follow-up reduces the probability of a placebo effect that would prevail for such a long time given the natural history of disease progression [60].

The rate of progression in PD is variable [61–63] but an important concept in order to determine when to offer DBS. PD progression is influenced by many aspects including but not limited to age at diagnosis, gender, genetics, motor subtype, presence of certain symptoms at diagnosis [64], life style, and treatment. There is evidence from two 5-year follow-up studies suggesting that motor complications derived from therapy remain relatively mild in the early years after their onset in dopamine naïve patients [65, 66]. Angeli et al. [67] found in a retrospective review of patients who underwent DBS that Parkin mutation carriers reached motor complications earlier but had a less prolonged course; likewise glucocerebrosidase mutation carriers reached the threshold for DBS earlier and had more cognitive impairment after the procedure. Deciding when to undergo an elective surgical procedure requires a careful consideration of motor complications, rate of progression, and additional therapeutic options and it should be done on a case-by-case basis including a risk versus benefit evaluation by a multidisciplinary team [68].

The motor and nonmotor benefit obtained in the earlier intervention studies is at least as good as or even better than what RCTs have shown in advanced Parkinson's disease. Earlier DBS extends the possibility of maintaining functional capacity and improving the patient's quality of life earlier in the disease course.

4. Earlier DBS Intervention Challenges

Within the movement disorders field, the concept of earlier DBS intervention has been a matter of debate among neurologists and there have been multiple challenges to implement it in the clinical scenario.

4.1. Patient Selection. For patients to be considered for early DBS implantation, they require a diagnosis of at least 4 years of disease duration and after 4 months of motor complications, which are not adequately controlled with medication. This 4-year time window has been established to avoid DBS implantation in patients with Parkinson's plus syndromes. This is supported by the literature which shows that most Parkinson's plus syndromes receive correct diagnoses within 4-5 years [69]. In this regard, it is important to keep in mind that diagnostic accuracy performed by MD experts range

from 79.6% after the initial assessment to 83.9% after the follow-up [70]. Using the MDS 2015 task force diagnostic criteria for PD, the specificity reaches 90% [71]. This explains why the UK Brain Bank criteria and an on/off trial assessment administered by experienced MD specialist is still the most important outcome predictor for DBS success [72] and avoids implantation of patients with atypical Parkinsonism.

4.2. Predictors of Outcomes after DBS. Preoperative indicators for good outcomes in DBS for PD include younger age, short disease duration, robust levodopa-response, few axial motor symptoms, absence of dementia, and stable psychiatric conditions [23]. The EARLY-STIM trial showed motor and quality of life improvement greater than BMT sustained for 2 years.

Patients who will most likely benefit from early DBS intervention according to the EARLY-STIM trial subgroup analysis [73] are patients with baseline poor Hoehn and Yahr scores (stages 4-5) and fluctuating disease (even if only mild) and patients who report poor mobility during a large part of the day.

4.3. Adverse Events. The benefit to risk ratio is an important consideration; the use of earlier DBS should be considered in specific patients if the benefits of the surgical therapy are weighed against the procedure risks and the lifelong need for specialized care [73]. DBS complications have been widely reported in advanced Parkinson's patients [40, 74]; these can be categorized as surgery related, hardware related, and stimulation dependent. The most common ones are cerebral hematoma (0–5%), infection (0–15%), skin erosion (1–2.5%), and mental status/behavioral changes (9–18%).

To the best of our knowledge there is no data available regarding a difference in the incidence of these adverse events with an earlier intervention. However, a recent report of the Implantable Systems Performance Registry (ISPR), a prospective, long-term multicenter registry supported by Medtronic® compared adverse events in the overall DBS cohort versus early PD-DBS patients (<7.5 years disease duration) showing no significant differences of the adverse event profile between the Earlier PD Subset and the Overall Cohort [75]. Adverse event rates in the two aforementioned RCT studies were similar to what has been reported in the literature for advanced PD with the exception of a substantial increase in suicidal ideation, attempts, and complete suicides. Evidence from retrospective studies has shown the safety of DBS [76], and RCT of advanced Parkinson disease interventions revealed no elevated suicide behaviors in the 6-month period after DBS surgery [24, 77]. A multicenter retrospective survey of fifty-five movement disorder centers around the world revealed 0.45% suicides and 0.90% suicidal attempts in the following 4 years after STN-DBS [78]. These findings raised the need for psychiatric assessment and close follow-up that may only be successfully performed by an interdisciplinary highly experienced center [79].

4.4. Prognosis. Little has been described of the impact of DBS on survival, and it is still a topic of debate that requires further studies. Schupbach et al. published a retrospective study on a historical comparison of 118 operated patients with 39 nonoperated patients from a different population; survival among operated patients was not different compared to 118 nonoperated patients with overlapping ages at PD onset (HR = 1.2; 95% CI = 0.7–2.1) [41]. In addition, Lilleeng et al. compared mortality over time in two matched groups of PD patients with and without DBS and found that survival was similar in the two groups during long-term follow-up (HR = 1.76, CI = 0.91–3.40, $p = 0.091$) [80]. In contrast, Ngoga et al. conducted a controlled trial and concluded that age matched patients that underwent STN-DBS had significantly longer survival and were significantly less likely to be admitted to a residential care home than those managed purely by a medical regimen (survival: $p = 0.002$, HR 0.29 [95% CI: 0.13 to 0.64]) [81].

4.5. Neuroprotection. Several animal models have raised the possibility of DBS as a neuroprotective therapy. Multiple studies of STN-DBS on 6-OHDA lesioned rodents showed that rats with DBS had less dopaminergic cell loss compared with controls [82–85]. Another study in a MPTP primate model reported that up to 24% of dopaminergic cells were preserved following STN-DBS compared with controls [86]. On the other hand clinical studies have not been able to prove the same concept; a multicenter international DOPA-PET-study did not show any reduction in the loss of dopaminergic terminals [87] and multiple clinical trials reported an increase in motor symptoms over time with DBS. Nonetheless, the animal studies best represented a moderate stage of disease and not the extreme nigral cell loss seen in a dvanced PD [88].

5. Conclusion

Deep Brain Stimulation for Parkinson's disease was developed based on findings from ablative surgical procedures. Research into its use decreased with the advent of levodopa but resumed in the early 1990s due to frequent motor complications and symptoms refractory to dopaminergic therapy. In 2002, DBS was approved for late stage PD with motor complications. Even more recently in 2016 Class I evidence led to the approval for earlier intervention in patients who were diagnosed for at least 4 years and exhibited at least 4 months of motor complications. Early interventions require the assessment and follow-up of an interdisciplinary and highly experienced team. Due to the recent approval of earlier intervention, we are missing knowledge regarding the patient progression and the long-term outcomes of the early DBS patients. Nonetheless, extensive education of the healthcare community, especially neurologists, is crucial in order to provide the intervention for appropriately selected candidates. Earlier DBS intervention offers the opportunity to impact PD patients' quality of life and functional ability, providing potential significant symptomatic relief over a longer period of time.

Conflicts of Interest

Drs. Suarez-Cedeno and Suescun have no conflicts of interest to be reported. Dr. Mya Schiess is a consultant for Medtronic.

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Research Article

Predictors of Functional and Quality of Life Outcomes following Deep Brain Stimulation Surgery in Parkinson's Disease Patients: Disease, Patient, and Surgical Factors

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Objective. The primary objective was to evaluate predictors of quality of life (QOL) and functional outcomes following deep brain stimulation (DBS) in Parkinson's disease (PD) patients. The secondary objective was to identify predictors of global improvement. *Methods*. PD patients who underwent DBS at our Center from 2006 to 2011 were evaluated by chart review and email/phone survey. Postoperative UPDRS II and EQ-5D were analyzed using simple linear regression adjusting for preoperative score. For global outcomes, we utilized the Patient Global Impression of Change Scale (PGIS) and the Clinician Global Impression of Change Scale (CGIS). *Results*. There were 130 patients in the dataset. Preoperative and postoperative UPDRS II and EQ-5D were available for 45 patients, PGIS for 67 patients, and CGIS for 116 patients. Patients with falls/postural instability had 6-month functional scores and 1-year QOL scores that were significantly worse than patients without falls/postural instability. For every 1-point increase in preoperative UPDRS III and for every 1-unit increase in body mass index (BMI), the 6-month functional scores significantly worsened. Patients with tremors, without dyskinesia, and without gait-freezing were more likely to have "much" or "very much" improved CGIS. *Conclusions*. Presence of postural instability, high BMI, and worse baseline motor scores were the greatest predictors of poorer functional and QOL outcomes after DBS.

1. Introduction

Although deep brain stimulation surgery (DBS) has been established as a superior treatment option for advanced Parkinson's disease (PD) [1], there has been a discrepancy between motor and functional/quality of life (QOL) outcomes after surgery [2, 3]. While motor outcomes are believed to improve significantly in the majority of patients following DBS compared to medical therapy alone [2], QOL outcomes are not as consistent with only about 50% of patients showing some improvement in QOL after surgery [3]. This has led to a recent shift of focus in DBS research from motor outcomes to functional and QOL outcomes. In recent years, an increasing number of studies attempted to find new clinical predictors of these outcomes to complement or replace traditional motor predictors with the goal of ultimately translating into better

selection of surgical candidates [4–7]. In addition to commonly studied factors such as age and disease duration, our group and others explored less conventional outcome predictors like socioeconomic status [8], mood and psychosocial factors [3, 9], and preoperative cognitive patterns [10]. In this study, we look at the effect of several disease, patient, and surgical factors on QOL, functional, and global measures.

2. Methods

We performed a retrospective review of consecutive PD patients who underwent DBS implantation (subthalamic or internal globus pallidus) at our center from 2006 to 2011 and had near-complete charting. We collected two health status measures (HSM), the European Quality of Life 5-Dimension Questionnaire (EQ-5D) and the Unified Parkinson's Disease Rating Scale, part 2: activities of daily living (UPDRS II) [the Movement Disorders Society-Unified Parkinson's Disease Rating Scale or MDS-UPDRS II was used for visits after 2008], for the following time points when available: latest preoperatively (within one month prior to surgery), 6 months postoperatively (range: 3–9 months), and 12 months postoperatively (range: 9–15 months). The EQ-5D is a standardized instrument for measuring health-related QOL in terms of five dimensions (5D), mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, producing a single index value for overall health status. In addition, we also conducted a one-item Patient Global Impression of Change Scale (PGIS) via phone/email survey using an IRB-approved phone/email script for all study subjects to provide additional long-term global outcome specific for this study. The PGIS aims at determining the patient's global impression of his/her current state compared to the state prior to DBS surgery with the following possible answers: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. The PGIS survey was distributed in mid-2011 (1 to 5 years from date of first surgery). To match our patient-perceived outcomes to clinicians' perception of overall outcome after surgery, we also conducted a one-item Clinician's Global Impression of Change Scale (CGIS) survey for study subjects. The CGIS aims at determining the clinician's impression of the overall clinical change in each patient after surgery using the same 7-point anchor as the PGIS. The CGIS scores were retrospectively determined based on the full information derived from patients' medical records and postoperative office visits during the same time periods when the PGIS was obtained.

The following potential clinical predictors were collected for all patients from their preoperative visits and operative reports:

(i) Disease factors: disease duration, dopaminergic burden (based on levodopa equivalent daily dose [LEDD] conversion), preoperative UPDRS part III motor subscale (MDS-UPDRS part III after 2008) in the ON state, presence of tremors, dyskinesia, freezing of gait (FOG), and falls/balance dysfunction. Clinical symptoms were based on the patients' major complaints when presenting for DBS evaluation. Although these complaints were matched to their UPDRS III/MDS-UPDRS III subscores on exam, no formal score cutoffs were used for quantification. This was based, in part, on the difficulty of developing unified cutoff scores for the two different versions of the motor scale. More importantly, since this study was geared towards patients' experience, we meant to put more emphasis on patient-reported symptoms rather than motor subscores as potential predictors of QOL and functional outcomes

(ii) Patient factors: age, marital status, and body mass index (BMI)

(iii) Surgical factors: surgery type (i.e., unilateral, staged bilateral, or simultaneous bilateral) and number of intraoperative microelectrode passes

2.1. Statistical Analysis. To determine short-term and intermediate predictors of improved functional state and QOL, we created simple linear regression models where the 6-month and 12-month postoperative UPDRS II/MDS-UPDRS II score or EQ-5D index was the dependent variable. For each of these models, we adjusted for the preoperative score by including it in the model as a covariate. For each of the clinical predictors listed in Methods, we created a separate model where that predictor was the independent variable. The effect of each predictor on outcome is provided through estimated beta coefficients and associated 95% confidence intervals. Patients with missing data for certain time point were not included in the analysis for that time point.

To determine predictors of global outcomes based on patient's and clinician's perceptions, we dichotomized the responses in the PGIS and CGIS into "much improved" or "very much improved" versus all other responses. For categorical predictors, we computed the proportion and percent of patients with PGIS or CGIS of "much improved" or "very much improved." Fisher's exact tests were used to determine statistical significance. For continuous predictors, we created logistic regression models. We estimated odds ratios and computed 95% confidence intervals for each. Due to the exploratory nature of this study, we did not correct for multiple comparisons.

All analyses were conducted using R, version 3.0.1, and P values less than 0.05 were considered statistically significant. This study was approved by Cleveland Clinic's institutional review board.

3. Results

3.1. Predictors of Functional and QOL Outcomes. There were 130 patients in the dataset. Overall, patients had an average age at time of surgery of 63.0 (±9.1) years, had PD for 10.7 (±5.1) years, had an average BMI of 27.5 (±5.2) kg/m^2, and had an average LEDD of 1190 (±666). The cohort was more predominantly male (70.8%), white (86.9%), and married (66.9%). Of the 130 patients, 55 (42.3%) had unilateral surgery, 50 (38.4%) had bilateral staged surgery, and 25 (19.2%) had bilateral unstaged surgery. Most patients were implanted in the STN, 124 (95.3%).

Table 1: Beta estimates for health status measures collected at 2 follow-ups.

		6 months postop.			1 year postop.		
		N	Estimate (95% CI)	*P* value	*N*	Estimate (95% CI)	*P* value
UPDRS II	Age	39	−0.05 (−0.34, 0.23)	0.7058	32	0.03 (−0.3, 0.36)	0.8438
	Disease duration	38	−0.45 (−1.00, 0.11)	0.1127	31	0.21 (−0.56, 0.97)	0.5859
	BMI	37	0.49 (0.04, 0.94)	**0.0332**	32	0.68 (−0.002, 1.37)	0.0507
	Laterality (versus unilateral)						
	Staged bilateral	39	1.16 (−4.58, 6.89)	0.6849	32	0.53 (−6.75, 7.82)	0.8819
	Simultaneous bilateral	39	−3.68 (−12.69, 5.32)	0.4118	32	−5.46 (−14.34, 3.42)	0.2179
	Electrode passes (right)	29	2.09 (−0.41, 4.60)	0.0978	24	1.96 (−1.77, 5.69)	0.2876
	Electrode passes (left)	35	−1.21 (−4.29, 1.87)	0.4300	30	−2.18 (−6.14, 1.78)	0.2681
	Electrode passes (total)	36	0.31 (−1.15, 1.76)	0.6731	30	0.00 (−1.96, 1.97)	0.9963
	% equivalent levodopa dose	37	1.83 (−3.93, 7.58)	0.5233	30	0.89 (−6.15, 7.94)	0.7967
	On UPDRS III	39	0.09 (−0.21, 0.38)	0.5535	31	0.22 (−0.10, 0.54)	0.1709
	Tremor	39	−0.95 (−5.78, 3.88)	0.6909	32	1.35 (−4.41, 7.12)	0.6345
	Dyskinesia	39	−2.46 (−7.28, 2.36)	0.3072	32	−2.06 (−7.86, 3.74)	0.4736
	Freezing	39	2.32 (−2.97, 7.62)	0.3792	32	3.85 (−2.55, 10.26)	0.2284
	Falls/balance	39	6.48 (1.11, 11.84)	**0.0193**	32	6.45 (−0.38, 13.28)	0.0634
	Marital status	38	−1.86 (−7.35, 3.63)	0.4958	31	2.74 (−3.88, 9.36)	0.4041
EQ-5D index	Age	45	0.00 (−0.01, 0.00)	0.3403	36	0.00 (−0.01, 0.01)	0.9897
	Disease duration	43	0.01 (0.00, 0.02)	0.1810	35	−0.01 (−0.02, 0.00)	0.0696
	BMI	45	0.001 (−0.009, 0.011)	0.8450	36	−0.002 (−0.014, 0.011)	0.7983
	Laterality (versus unilateral)						
	Staged bilateral	44	0.08 (−0.02, 0.19)	0.1252	36	−0.01 (−0.14, 0.12)	0.9127
	Simultaneous bilateral	44	0.13 (−0.04, 0.29)	0.1351	36	0.003 (−0.15, 0.16)	0.9654
	Electrode passes (right)	33	−0.02 (−0.06, 0.02)	0.3494	28	−0.03 (−0.09, 0.04)	0.3837
	Electrode passes (left)	38	0.04 (−0.02, 0.11)	0.2006	32	0.07 (0.00, 0.14)	0.0508
	Electrode passes (total)	41	0.02 (−0.01, 0.05)	0.2458	34	0.01 (−0.03, 0.04)	0.6988
	Equivalent levodopa dose	42	−0.07 (−0.19, 0.04)	0.2000	34	0.06 (−0.06, 0.19)	0.3138
	On UPDRS III	44	−0.01 (−0.01, 0.00)	**0.0050**	35	0.00 (−0.01, 0.00)	0.6310
	Tremor	44	0.03 (−0.07, 0.13)	0.5516	36	0.07 (−0.03, 0.17)	0.1602
	Dyskinesia	44	−0.01 (−0.11, 0.09)	0.8448	36	0.02 (−0.09, 0.12)	0.7197
	Freezing	44	−0.03 (−0.13, 0.08)	0.5955	36	−0.09 (−0.19, 0.01)	0.0762
	Falls/balance	44	−0.06 (−0.17, 0.05)	0.269	36	−0.12 (−0.23, −0.02)	**0.0191**
	Marital status	44	−0.04 (−0.15, 0.08)	0.4992	35	−0.04 (−0.16, 0.07)	0.4668

Forty-five patients had both preoperative and postoperative data at 6 months and at 12 months. This group had mostly similar characteristics to the group with incomplete data except for having a younger average age (60.4 years, $P = 0.019$). Of these 45 patients, 29 patients (64.4%) had bilateral surgery. At 6 months, statistically significant improvement was seen for both the mean EQ-5D index ($P = 0.03$) and the average UPDRS II/MDS-UPDRS II score ($P = 0.002$). However, one year after surgery, no significant improvement or worsening was found for either scale.

There were 116 patients for which the CGIS could be completed from the available records. Of these, 19 (16.4%) were rated as "very much improved," 63 (54.3%) as "much improved," 23 (19.8%) as "minimally improved," 6 (5.2%) as "no change," 3 (2.6%) as "minimally worsened," and 2 (1.7%) as "much worsened."

There were 67 patients that completed the PGIS. Of these 67 patients, 29 (43.3%) reported "very much improved," 25 (37.3%) reported "much improved," 10 (14.9%) reported "minimally improved," 2 (3.0%) reported "much worse," and 1 (1.5%) reported "very much worse."

Table 1 displays results of the simple linear regression models relating different predictors to approximate 6-month and 1-year HSM. Patients that had falls/balance-dysfunction had 6-month mean UPDRS II/MDS-UPDRS II scores that were 6.48 points worse than patients that did not have falls/balance-dysfunction ($P = 0.019$). A similar estimated effect of falls/balance-dysfunction was found at the 1-year UPDRS II/MDS-UPDRS II scores, but statistical significance was not achieved (Estimated effect = 6.45; $P = 0.0634$). Similarly, patients that had falls/balance dysfunction at baseline had 1-year mean EQ-5D index scores that were 0.12 points lower than patients who did not have falls/balance dysfunction ($P = 0.019$) but this effect was not significant at 6 months ($P = 0.2690$). After adjusting for preoperative EQ-5D index, for every one-point increase in the preoperative

Table 2: Patient Global Impression of Change Scale (PGIS) and Clinician's Global Impression of Change Scale (CGIS) results by various categorical predictors.

	% PGIS much improved or very much improved (proportion)	*P* value	% CGIS much improved or very much improved (proportion)	*P* value
Tremor	76.9% (20/26)	0.7566	84.0% (42/50)	**0.0075**
No tremor	82.1% (32/39)		60.0% (42/70)	
Dyskinesia	83.7% (36/43)	0.5167	64.2% (52/81)	**0.0380**
No dyskinesia	75.0% (18/24)		83.7% (36/43)	
Freezing	78.8% (26/33)	0.7591	61.9% (39/63)	**0.0315**
No freezing	82.4% (28/34)		80.3% (49/61)	
Falls/balance	75.0% (21/28)	0.3688	66.1% (41/62)	0.3218
No falls/balance	84.6% (33/39)		75.8% (47/62)	
Left unilateral	75.0% (6/8)	1.0000	63.6% (7/11)	1.0000
Right unilateral	77.8% (14/18)		67.6% (23/34)	
Unilateral	76.9% (20/26)	0.7906	66.7% (30/45)	0.7741
Two-stage bilateral	81.5% (22/27)		73.1% (38/52)	
Unstaged bilateral	85.7% (12/14)		73.1% (19/26)	

UPDRS III/MDS-UPDRS III score in the ON state, the 6-month EQ-5D index worsened by 0.01 units ($P = 0.005$). However, no relationship between UPDRS III/MDS-UPDRS III score in the ON state and the EQ-5D index was seen at 1 year. Moreover, no relationship was found between the UPDRS III/MDS-UPDRS III and the UPDRS II/MDS-UPDRS II scores at either 6 months or 1 year.

The BMI distribution in the patient group was as follows: underweight, 0 patients; normal weight, 12 patients; overweight, 16 patients; and obese, 15 patients. After excluding 2 outliers, the estimated effect of BMI on 6-month UPDRS II/MDS-UPDRS II score was significant ($P = 0.033$). For every one-unit increase in BMI, the UPDRS II/MDS-UPDRS II score at 6 months worsened by 0.49 points on average. There was also evidence of a similar but weaker association at 1 year ($P = 0.0507$). However, at both six months and one year after surgery, no significant associations were found between BMI and EQ-5D index.

3.2. Predictors of Global Outcomes. Table 2 displays the results relating categorical predictors to the PGIS and CGIS. While the majority of the patients in our cohort were rated to be "very much" or "much" improved in the PGIS and CGIS, of patients that had tremor, 84.0% showed "much" or "very much" improvement on the CGIS, whereas only 60.0% of patients without tremor showed "much" or "very much" improvement ($P = 0.0075$). Patients without dyskinesia and patients without freezing were more likely to show "much" or "very much" improvement on the CGIS ($P = 0.038$ and $P = 0.0315$, resp.). There were no statistically significant results when correlating continuous predictors to the CGIS and the PGIS. There was also no correlation between global outcomes and the cognitive and mood predictors included in our previously reported cognitive study [10].

3.3. Noninfluential Factors. There was no significant association between QOL, functional, or global outcomes and patients' age, disease duration, laterality of surgery (unilateral versus bilateral), number of intraoperative electrode passes, LEDD, or marital status. However, some interesting trends were observed including a trend between shorter disease duration and more improvement in EQ-5D index at 1 year ($P = 0.0696$) and a PGIS of "much" or "very much improvement" ($P = 0.0683$). There was also a trend between higher number of intraoperative microelectrode passes on the left and less improvement of EQ-5D index at 1 year ($P = 0.0508$).

4. Discussion

In this study, we looked at predictors of functional and QOL outcomes of DBS in a cohort of PD patients who underwent DBS under a standardized protocol. We explored a large number of potential predictors including several disease, patient, and surgical factors. We have previously reported the socioeconomic and cognitive data of the same cohort [8, 10]. In the current study, we found that the baseline presence of falls/balance dysfunction was associated with worse 6-month functional outcome after DBS with a trend towards a similar poor outcome at 1 year after surgery. Falls/balance dysfunction were also predictive of poor QOL outcome at 1 year. In addition, the presence of FOG and absence of tremors, other indicators of predominantly axial disease, predicted poorer CGIS. These relationships are in agreement with findings by Welter and colleagues who reported poor functional outcomes 6 months after surgery in patients with axial motor symptoms preoperatively [4]. On the same note, Maier and colleagues reported an association between higher axial motor score and worse subjective perceived outcome after DBS [11]. Patients with predominantly axial disease are known to attain less motoric benefit from DBS [12] and our results suggest that this might extend into functional, QOL, and global outcomes after surgery.

The presence of dyskinesia preoperatively was associated with somewhat poorer long-term global outcome in our

study as represented by the CGIS. In 2011, Daniels and colleagues reported similar findings showing that patients with lower preoperative dyskinesia scores did better on QOL measures after surgery as represented by the Parkinson's Disease Questionnaire-39 (PD-Q39) and the 36-Item Short Form Health Survey (SF-36) [5]. Although the presence of dyskinesia is considered a classical indication for DBS and patients often experience reduction of dyskinesia after surgery especially when the dose of levodopa is successfully reduced [13], this does not necessarily translate into improvement in QOL or global perceivable outcome [5]. It is well known that, in many occasions, dyskinesia is more bothersome to patients' families than the patients themselves and is not detrimental to the QOL of PD patients [14]; in addition, the loss of levodopa peak-dose euphoria after dose reduction postoperatively may explain why patients with preoperative dyskinesia report less improvement in QOL after surgery when their dyskinesia improves as suggested by Daniels and colleagues [5]. Other possible explanations include the fact that the presence of dyskinesia, in general, indicates more advanced disease and that some patients may rarely experience worsening dyskinesia with stimulation [15].

Our results agreed with both Welter's and Daniels' studies in confirming a role for preoperative UPDRS III motor score in predicting functional/QOL outcomes following DBS, with higher scores indicating worse outcomes, perhaps as a general indication of more advanced disease [4, 5]. Soulas and colleagues confirmed the finding by Welter which demonstrates that age and disease duration are predictors of poorer outcome after surgery [6], but these factors were noninfluential in our study, although longer disease duration showed a weak trend towards poorer EQ-5D and PGIS in our group. In a study by Floden and colleagues from our group utilizing a different QOL scale (PDQ-39), preoperative episodic memory, depression, and bilateral surgery were the most influential predictors [3]. Table 3 displays a summary of the studies that looked at predictors of functional, QOL, and global DBS outcomes since the early 2000s.

In addition to disease characteristics, our study suggests that certain patient characteristics, regardless of disease severity, may also influence functional and QOL outcomes after DBS. In addition to the impact of socioeconomic status, which we previously reported [8], BMI seems to have a similar effect on DBS outcomes. Higher preoperative BMI predicted worse functional outcomes at 6 months and, to a lesser extent, at 1 year after surgery. This finding could be another reflection of poorer socioeconomic status where obesity is more prevalent [16] but it may also be related to further weight gain incurred after surgery. Weight gain after DBS has been frequently reported in literature and is thought to be secondary to reduction in the metabolic rate after resolution of tremor/dyskinesia and/or a direct stimulation effect on appetite centers [17–20]. Adding more weight after DBS in patients who are already overweight or obese can translate into patient perception of a suboptimal functional outcome. A post hoc analysis of our patient group revealed that the BMI increased in 55% of the patients at 1 year after surgery with an increment higher than $1\,kg/m^2$ in 35% and higher than $2\,kg/m^2$ in 17%. In a recent study, preoperative obesity was associated with poor axial and cognitive outcomes after DBS [21] but our study is the first to test the effect of BMI on functional and QOL outcomes. This is an important area that warrants further study. Exploring the role of dieting and/or exercise prior to DBS on motor and nonmotor outcomes may be of value.

There are several limitations to our study. In addition to the retrospective nature of the study, the sample size was fairly small for the number of comparisons and the study may have been underpowered, especially for the functional and QOL outcomes. Nonetheless, the demographic features of the subset of patients with complete data versus the entire cohort showed largely similar demographics; therefore, we believe that this subset still represented the PD population who underwent DBS surgery. The slight difference in age between the two groups is probably attributed to the fact that younger patients are more familiar with technology and therefore more likely to complete computer-based surveys and assessment scales. Further studies utilizing larger patient cohorts are needed to better study predictors of functional and QOL outcomes following DBS. We did not look into other QOL measures that are more specific for PD such as the PDQ-39 due to limited availability of data in this cohort; however, PDQ-39 data were available in a more recent patient cohort and were recently published by our group in a separate paper as discussed earlier [3]. Also we did not study functional/QOL outcomes beyond 1 year after surgery which, although consistent with other similar studies, does not account for how the benefit from surgery holds up against disease progression over the years. The absence of statistically significant difference in QOL and functional scores one year after surgery compared to preoperative scores was inconsistent with the results of previous DBS randomized trials [22]. However, the majority of our patients rated their overall global outcome as much or very much improved on the PGIS survey that was distributed to the patients 1 to 5 years after the date of surgery. This indicates that DBS still exerted a very positive impact on patients' global outcome many years after surgery even if not reflected on the EQ-5D and UPDRS II scores. In addition, there was also no significant worsening of the QOL and functional scores one year after surgery despite the progressive nature of the disease. This means that DBS still had a relative positive impact on QOL and functional outcomes one year after surgery in this real-life patient cohort though understandably less pronounced than what was seen in the more carefully selected cohorts in randomized trials. Although the CGIS was completed for most of the patients, the scoring was done retrospectively by our investigators exploiting data from patients' charts. The scoring system relied on documentation made by the first-hand clinicians, a method that has not been validated in other studies. The effect on caregiver burden was also not addressed. Finally, we did not correct for multiple comparisons due to the exploratory nature of the study and since we were looking at predetermined predictors prior to data collection [23]. Still, the relatively large number of comparisons in absence of such correction may have confounded the results to some degree; therefore the results of our study should be interpreted with caution in view of the limitations related to sample size

Table 3: Studies of functional, QOL, and global impression outcomes after DBS in PD.

Study	Functional, QOL, or global impression scale	Significant predictors	Number of patients	Time lapse since surgery
Welter et al., 2002	UPDRS II	(i) Age (ii) Disease duration (iii) UPDRS III (iv) Axial motor score (v) LED	41	6 months
Daniels et al., 2011	PD-Q39 SF-36	(i) Daily off time (+ve) (ii) Lower dyskinesia score (+ve) (iii) Improvement in UPDRS III (+ve) (iv) Improvement in psychiatric scales (+ve) (v) Reduction of dyskinesia (−ve)	61	6 months
Soulas et al., 2011	PD-Q39 SF-36	(i) Age (ii) Disease duration (iii) Depression (iv) Less use of social support coping	41	6 months and 12 months
Smeding et al., 2011	PDQL	(i) L-dopa response at baseline (+ve)	105	12 months
Maier et al., 2013	Subjective perceived outcome	(i) Depression (ii) Apathy	30	3 months
Floden et al., 2014	PD-Q39	(i) Depression (ii) Single-trial learning (episodic memory) (iii) Preoperative PD-Q39 score (iv) Bilateral surgery (+ve)	85	8 months (average)
Genc et al., 2016	MDS-UPDRS II EQ-5D CGIS	(i) Household median income	125 (43 for MDS-UPDRS II and EQ-5D)	6 months and 12 months
Maier et al., 2016	Subjective perceived outcome	(i) Apathy (ii) Axial motor score	28	12 months
Abboud et al.	MDS-UPDRS II EQ-5D PGIS CGIS	(i) Falls/balance dysfunction (ii) Dyskinesia (iii) Absence of tremors (iv) Freezing (v) UPDRS III (vi) Preoperative BMI	130 (45 FOR MDS-UPDRS II and EQ-5D)	6 months and 12 months

UPDRS II: Unified Parkinson's Disease Rating Scale, part 2: activities of daily living; LED: L-dopa equivalent dose; PD-Q39: Parkinson's Disease Questionnaire-39; SF-36: 36-Item Short Form Health Survey; PDQL: Parkinson's Disease Quality of Life Questionnaire; MDS-UPDRS II: Movement Disorders Society-Unified Parkinson's Disease Rating Scale, part 2: motor experience of daily living; EQ-5D: European Quality of Life 5-dimension Questionnaire; CGIS: Clinician's Global Impression of Change Scale; PGIS: Patient Global Impression of Change Scale.

and methodology. Overall, the majority of the significant predictors in our study conform to prior DBS literature which increases the confidence in those results. Our novel significant predictors like BMI will need validation in other cohorts.

In conclusion, our study suggests that certain disease characteristics may influence outcomes after DBS. While the majority of the patients in our cohort were globally rated as significantly improved on global scales, falls and balance dysfunction, absence of tremors, presence of dyskinesia, freezing of gait, and preoperative motor severity as represented by UPDRS III/MDS-UPDRS III were the most influential predictors of poorer outcome. In addition, some previously underrecognized patient characteristics may also influence DBS outcomes such as higher preoperative BMI and lower socioeconomic status. By confirming known DBS outcome predictors and identifying new factors, we hope to provide new insights into the process of patient selection and risk stratification prior to DBS. Further prospective studies utilizing higher number of patients and combining both objective and subjective outcome measures should be performed to confirm or refute the results of our study.

Disclosure

This study was presented as an abstract at the 2015 International Parkinson's and Movement Disorders Congress and at the 2016 American Academy of Neurology Annual Meeting.

Conflicts of Interest

Gencer Genc, Nicolas R. Thompson, Srivadee Oravivattanakul, Faisal Alsallom, Dennys Reyes, Kathy Wilson, Russell Cerejo, Xin Xin Yu, Darlene Floden, Ayman Ezzeldin, Hazem Marouf, Ossama Y. Mansour, Anwar Ahmed, and Michal Gostkowski report no conflicts of interest. Dr. Hesham Abboud is a consultant for Biogen, Genentech, and Genzyme. Dr. Andre Machado received personal compensation from IntElect Medical/Boston Scientific, ATI, Cardionomics, and Monteris for consulting services and is a consultant for Functional Neuromodulation, Spinal Modulation, and Icahn. He holds distribution rights from intellectual property in ATI, Cardionomic, and Enspire; fellowship support from Medtronic; and research funding from the National Institutes of Health. Dr. Hubert H. Fernandez has received honoraria from Advanced Health Media, Cleveland Clinic CME, Medical Communications Media, Movement Disorders Society, and Vindico Medical Education, as a speaker in CME events. Hubert H. Fernandez has received honoraria from Ipsen, Merz Pharmaceuticals, Pfizer, Teva Neuroscience, and Zambon Pharmaceuticals, as a speaker and/or consultant. Hubert H. Fernandez has received personal compensation for serving as Co-Medical Editor of the Movement Disorders Society Website. Hubert H. Fernandez has received royalty payments from Demos Publishing and Manson Ltd. for serving as a book author/editor. Hubert H. Fernandez has received research support from Abbott, Acadia, Biotie Therapies, EMD Serono, Huntington Study Group, Merck, Michael J. Fox Foundation, Movement Disorders Society, National Parkinson Foundation, NIH/NINDS, Novartis, Parkinson Study Group, Synosia, and Teva but has no owner interest in any pharmaceutical company.

Authors' Contributions

Dr. Hesham Abboud was responsible for conception and design of the study, acquisition of data, interpretation of data, literature search, writing of the first draft, and revising the manuscript. Dr. Gencer Genc was responsible for acquisition of data, interpretation of data, literature search, and reviewing/revising the manuscript. Mr. Nicolas R. Thompson performed the statistical analysis and contributed to writing of the statistical methods and results. Drs. Srivadee Oravivattanakul, Faisal Alsallom, and Xin Xin Yu were responsible for acquisition and interpretation of data. Drs Dennys Reyes, Russell Cerejo, and Kathy Wilson designed the body mass index analysis and analyzed and interpreted the data. Drs. Darlene Floden, Michal Gostkowski, Anwar Ahmed, Ayman Ezzeldin, Hazem Marouf, Ossama Y. Mansour, and Andre Machado critiqued, reviewed, and revised the manuscript. Dr. Hubert H. Fernandez was responsible for the conception and design of the study and review, revision, and final approval of the manuscript. All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content. Each author confirms that all authors have read the manuscript.

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Research Article

Bridging the Gaps in Patient Education for DBS Surgery in Parkinson's Disease

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Introduction. Improvements in quality of life, tremor, and other motor features have been recognized as superior in patients with advanced Parkinson's disease (PD) treated with deep brain stimulation (DBS) surgery versus best medical therapy. We studied a group of patients with PD after undergoing DBS surgery in regard to expectations and satisfaction with DBS outcomes to determine gaps in patient education. *Methods*. This study was a retrospective, single academic center chart review and outcome questionnaire sent to patients with PD who had undergone DBS surgery between 2007 and 2014. *Results*. All patients surveyed indicated that benefit from DBS surgery met their overall expectations at least partially, but only 46.4% (*SE: 9.6*%) were in complete agreement. 3.6% (*SE: 3.6*%) of participants strongly disagreed that preoperative education prepared them adequately for the procedure and 17.9% (*SE: 7.4*%) only somewhat agreed. *Conclusions*. Our findings demonstrate that patients' expectations of DBS surgery in PD were at least partially met. However, there was a considerable percentage of patients who did not feel adequately prepared for the procedure. A structured, multidisciplinary team approach in educating PD patients throughout the different stages of DBS surgery may be helpful in optimizing patients' experience and satisfaction with surgery outcomes.

1. Introduction

Parkinson's disease (PD) is a progressive neurological disorder in which the cardinal signs are resting tremor, bradykinesia, rigidity, and loss of postural reflexes [1]. In 2002, the FDA approved deep brain stimulation (DBS) in the subthalamic nucleus (STN) for patients with levodopa-responsive PD [2]. The proposed mechanisms that explain the therapeutic benefit of DBS include local and network-wide electrical and neurochemical effects of stimulation, modulation of oscillatory activity, synaptic plasticity, neuroprotection, and neurogenesis [3–8]. Motor benefits have been documented as long as 10 years after implantation [9].

A good DBS surgical candidate is considered to be a patient with idiopathic PD and good response to levodopa, who is experiencing motor fluctuations, dyskinesias, or refractory tremor despite the best medical therapy and does not suffer from significant cognitive impairment. Prospective DBS candidates need to have an adequate understanding of expected benefits and possible adverse effects from DBS. This is best accomplished through a thorough educational process that spans the pre- to postoperative period. Few studies have been specifically conducted to explore the patient expectations and satisfaction from DBS surgery in relation to the education received by the multidisciplinary treatment team (neurosurgeon, movement disorder specialist, nurses, and neuropsychologists).

Multiple studies have addressed both motor and nonmotor quality-of-life issues after DBS surgery (see Appendix 1 in the Supplementary Material available online

at https://doi.org/10.1155/2017/9360354) [10–15]. While motor aspects of PD consistently show improvement with DBS, changes in quality of life (QoL) and mental health are less frequently documented in the literature. Montel and Bungener [12] conducted a study comparing patients undergoing DBS surgery with the best medical therapy alone. The authors found that depression and anxiety were not significantly impacted by the type of therapy received. Those with DBS therapy scored higher in coping techniques, with no particular strategy showing significant differences. The DBS treatment group also experienced decreased QoL measures related to dysarthria.

Ferrara et al. [11] looked at health-related quality of life (HRQoL) and health satisfaction (HS) following DBS surgery. The findings revealed improvements in various HRQoL issues, especially motor function and independence measures. Life satisfaction following DBS did not improve perceived function at work, personal relationships, leisure activities, or living conditions. Social, emotional, and cognitive factors tended to be better predictors of quality of life. Following DBS, energy level and life enjoyment improved significantly. The authors suggested studying HRQoL and HS in subsequent studies, focusing on the enhancement of the patient selection process and consideration of predictive clinical variables.

In a study by Lezcano et al. [13], patients were followed up for five years following DBS surgery. The overall QoL was found to be significantly improved one year after surgery but regressed back to baseline at five years in most measures. Floden et al. [10] retrospectively studied the predictability of QoL measures in 85 patients after STN DBS. They found that QoL improved on 39-item PD questionnaire (PDQ-39) measures for motor function, mood, and self-consciousness but not for speech, cognitive function, and hallucinations. Patients who reported reduced QoL before surgery did not experience a significant increase in QoL after surgery. The authors concluded that DBS increases or preserves QoL in most patients. Hasegawa et al. [16] studied the correlation between patient expectations with satisfaction and outcomes in STN DBS for PD and concluded that pre- and postoperative expectations may play an important role in patient satisfaction and overall success of STN DBS.

The goal of our study was to determine the degree to which patients' expectations from DBS surgery were met postoperatively. Additionally, we sought to gain information that could aid in improving patient education for DBS and creating a patient-centered experience.

2. Methods

A retrospective, single academic center study was conducted to evaluate patients' postoperative expectations of DBS. The study was IRB-approved and followed ethical guidelines. A twenty-seven-item questionnaire was developed (Appendix 2 in the Supplementary Material) and administered to patients and a retrospective chart review was performed. Study subjects were identified by using billing codes for PD and DBS from 2007 to 2014. Fifty-two patients were contacted. Patients who had devices removed for any reason were included, regardless of whether they had been reimplanted or not. Initially, patients were recruited via mail. The questionnaire was designed to evaluate patients' expectations, preoperative education, and overall satisfaction with DBS surgery. Most items were evaluated using a Likert scale, but several free response questions were included. Patients' charts were reviewed to identify documentation about DBS education. Additional information gathered included gender, date of birth, education level, ethnicity, age at symptom onset, age at PD diagnosis, age at implant(s), most troublesome symptom(s) prompting DBS, and implanted target area of the brain. Analysis of data was done with STATA, version 12.

Table 1: Patient demographics and clinical characteristics.

Gender	21 M/8 F
Race	100% Caucasian
Disease duration (mean ± SD)	15.1 ± 8.59 years
Age at surgery (mean ± SD)	66.8 ± 10.8 years
Education	43% high school/GED 43% associates degree or higher
DBS targets	STN bilateral 62.1% STN unilateral 17.4% GPi bilateral 13.8% VIM unilateral 6.9%

3. Results

Among the 52 questionnaires mailed, 32 were returned and 29 were included in the analysis, yielding a response rate of 55.8%. One survey was returned unanswered. One subject was excluded from analysis as chart review revealed a diagnosis of essential tremor, rather than PD. The age at DBS surgery ranged from 36 to 86 years with a mean of 66.8 (SD: 10.8) years (Table 1). The majority of patients were males (71%) and the range of disease duration was 2–32 years with a mean of 15.1 (SD: 8.6) years.

The most commonly cited symptoms from the patients' perspective prompting consideration for DBS were tremor (79.3%), dyskinesias (24.1%), and rigidity (13.8%). Another 6.9% of patients reported inadequate on-time and complex medication schedules. Other reasons cited for seeking DBS surgery included walking problems (10.3%), reduced quality of life (10.3%), balance problems (3.4%), freezing of gait (3.4%), and impaired handwriting (3.4%). When participants were asked to identify their sources of DBS education, 96.4% indicated having received information from the provider managing their PD, 60.7% from the neurosurgeon, 46.4% from industry device representatives, 14.3% from nurses or other ancillary staff members, 46.4% from the Internet, and 14.3% from other sources (i.e., support groups, seminars).

71.4% of the participants reported having been asked about their expectations from DBS prior to surgery; however, a discussion of patient expectations was only documented in medical charts in 48.3%. Postoperatively, 100% of subjects were in at least some agreement that their expectations

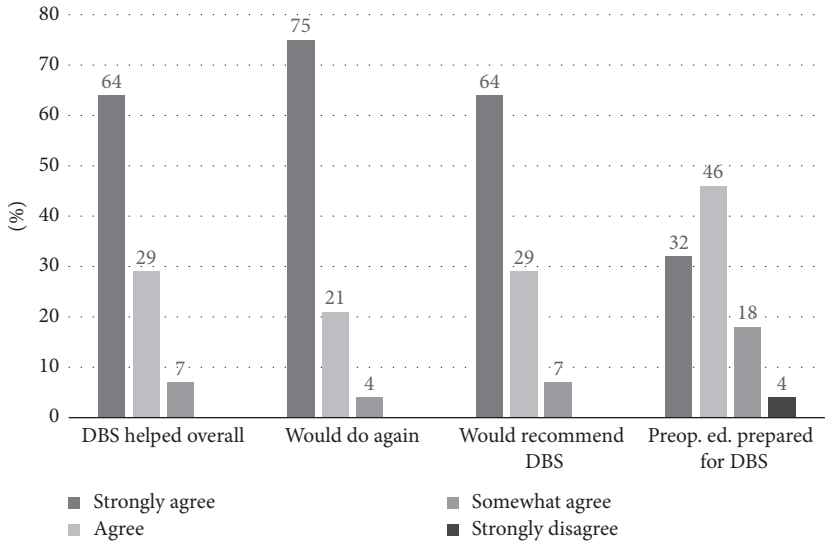

Figure 1: Patient satisfaction with DBS outcomes and preoperative education.

Table 2: Percentage of patients having their motor expectations met after DBS surgery.

Symptom (% of any agreement)	*Strongly agree* % *(SE)*	*Agree* % *(SE)*	*Somewhat agree* % *(SE)*	Neither agree nor disagree % (SE)	Somewhat disagree % (SE)	Disagree % (SE)	Strongly disagree % (SE)	N/A % (SE)
Tremor $N = 29$ (82)	*61 (9.0)*	*14 (7.0)*	*7.0 (5.0)*	0	0	0	0	18 (7.0)
Rigidity $N = 29$ (82)	*32 (9.0)*	*29 (9.0)*	*21 (8.0)*	4.0 (4.0)	4.0 (4.0)	0	0	10 (6.0)
Slowness $N = 29$ (75)	*29 (9.0)*	*21 (8.0)*	*25 (8.0)*	7.0 (5.0)	4.0 (4.0)	7.0 (5.0)	0	7.0 (5.0)
On-time $N = 28$ (85)	*39 (9.0)*	*25 (8.0)*	*21 (8.0)*	11 (1.1)	0	0	0	4.0 (4.0)
Dyskinesia $N = 29$ (82)	*36 (9.0)*	*25 (8.0)*	*21 (8.0)*	7.0 (5.0)	0	0	0	10 (6.0)
Dystonia $N = 29$ (62)	*21 (8.0)*	*29 (9.0)*	*18 (7.0)*	7.0 (5.0)	0	0	0	25 (8.0)

from DBS surgery were met. More specifically, 46.4% (*SE: 9.6%*) strongly agreed, 39.3% agreed (*SE: 9.4%*), and 14.3% (*SE: 6.7%*) somewhat agreed. Furthermore, 100% of patients surveyed agreed that DBS was overall helpful with 64.3% (*SE: 9.2%*) in strong agreement, 28.6% (*SE: 8.7%*) in agreement, and 7.1% (*SE: 5%*) somewhat in agreement. 100% of participants would elect to undergo DBS surgery again, with 75% (*SE: 8.3%*) in strong agreement, 21.4% (*SE: 7.9%*) in agreement, and 3.6% (*SE: 3.6%*) in some agreement. Similarly, 100% of participants would recommend DBS to someone else with PD, with 64.3% (*SE: 9.2%*) in strong agreement, 28.6% (*SE: 8.7%*) in agreement, and 7.1% (*SE: 5%*) in some agreement. When asked whether preoperative education prepared them adequately about the limitations of DBS, 32.1% (*SE: 8.9%*) strongly agreed, 46.4% (*SE: 9.6%*) agreed, 17.9% (*SE: 7.4%*) somewhat agreed, and 3.6% (*SE: 3.6%*) strongly disagreed (Figure 1).

We also investigated the level to which DBS outcomes met patients' expectations for improvement of various PD symptoms. Expectations were defined as met if the participants strongly agreed, agreed, or somewhat agreed. Overall, patients felt their expectations of symptom improvement were met by DBS (Table 2). Specifically, 82% of patients agreed that their expectations were met for improvement of tremor, rigidity, and dyskinesias, 75% for improvement of bradykinesia, 85% for improvement of "on-time," and 68% for dystonia.

Table 3 shows data on pre- and postoperative patient expectations across all symptoms and the degree to which expectations were met. Reduction of tremor was identified as the expected outcome by 75% of participants, yet this was only documented in 34.5% of reviewed charts. 79.3% of the participants reported that their expectation for tremor improvement was met. Medication reduction was documented as an expected outcome in 31% of chart reviews,

Table 3: A comparison of pre- and postoperative patient expectations from DBS surgery. Expectations listed under "A" are deemed realistic expectations with good chances for improvement following DBS surgery. Reducing PD medications ("B") following DBS surgery is a realistic expectation depending on the target for electrode placement. Symptoms listed under "C" may or may not improve following DBS surgery.

	Feature	Preop. expectation documented $N = 14$ % (SE)	Desired expectation for having DBS $N = 29$ % (SE)	Expectation met $N = 28$ % (SE)	Expectation somewhat met $N = 28$ % (SE)	Expectation not met $N = 28$ % (SE)
A	Tremor	35 (9.0)	75 (8.3)	79 (7.7)	3.4 (3.4)	—
	Rigidity	10 (5.8)	8.8 (7.4)	10 (5.8)	—	3.4 (3.4)
	Slowness	—	7.1 (5.0)	3.4 (3.4)	3.4 (3.4)	—
	On-time	21 (7.7)	21 (7.9)	17 (7.1)	3.4 (3.4)	—
	Dyskinesias	17 (7.1)	18 (7.4)	21 (7.7)	3.4 (3.4)	—
	Dystonia	3.4 (3.4)	7.1 (5.0)	3.4 (3.4)	3.4 (3.4)	—
B	Reduce medications	31 (8.7)	21 (7.9)	14 (6.5)	3.4 (3.4)	3.4 (3.4)
C	Sleep	10 (5.8)	3.6 (3.6)	3.4 (3.4)	—	—
	Freezing of gait	6.9 (4.8)	3.6 (3.6)	—	—	—
	Speech	—	3.6 (3.6)	—	—	3.4 (3.4)
	Balance	3.4 (3.4)	3.6 (3.6)	—	—	3.4 (3.4)
	Walking	6.9 (4.8)	14 (6.7)	6.9 (4.8)	—	10 (5.8)
	Writing	—	11 (6.0)	14 (6.5)	—	—
	QoL	—	21 (7.9)	17 (7.1)	—	3.4 (3.4)
	Reduce pain	—	7.1 (5.0)	—	3.4 (3.4)	3.4 (3.4)
	Eat w/utensils	—	3.6 (3.6)	6.9 (4.8)	—	—
	Use tools	—	—	—	3.4 (3.4)	—
	Improve PD	—	11 (6.0)	6.9 (4.8)	3.4 (3.4)	—
	Ride bike	—	3.6 (3.6)	3.4 (3.4)	—	—
	Use of arm	—	3.6 (3.6)	3.4 (3.4)	—	—
	Normal life	—	3.6 (3.6)	3.4 (3.4)	—	—
	Other	24 (8.1)	3.6 (3.6)	3.4 (3.4)	—	—

while 21.4% identified this as a desired expectation of DBS on the questionnaire. This expectation was met in 13.8%, whereas 3.4% reported that the expectation was somewhat met, and 3.4% did not have their expectation met. Other patient expectations were felt to be more problematic (C in Table 3), such as improvements in sleep which was cited by 10.3% of participants. In summary, we identified considerable discrepancies in documentations of expected symptom improvements per chart review with patient self-reported expectations on retrospective questionnaire as well as the absence of consistent documentation of patient expectations in medical charts.

4. Discussion

The aim of this study was to determine whether patient expectations from DBS surgery in PD were met and to identify gaps in patient education. Data from patient outcome questionnaires showed that a majority of patients (79%) listed tremor as the main reason for pursuing DBS, a symptom that is highly associated with improvement after surgery [17]. Over 96% of the study participants noted that they received DBS education by a PD specialist, but far fewer (61%) recalled having received education from a neurosurgeon. Frequently, patients sought education on their own, with 46% reporting education from Internet sources. While the lower reported rate of education by neurosurgeons may be related to less time spent with the patient throughout the process, it highlights an area for improvement, especially considering the possibility of surgical complications [18]. The large portion of patients receiving information from the Internet highlights the need for providers to guide patients towards reliable sources for information online. A considerable discrepancy between documentation of preoperative patient expectations in charts compared to patient reports of having discussed expectation with providers indicates a need for improvements in documentation of DBS education and following a standard format for this purpose.

Overall, patients had high satisfaction with DBS outcomes and 100% of the participants in our study were in at least partial agreement that their postoperative expectations for DBS surgery were met. Although 96% of the participants were in at least partial agreement when asked whether preoperative education prepared them for DBS surgery, 3.6% strongly disagreed, suggesting a need to optimize the educational process for DBS surgery.

Breit et al. [19] described unmet patient expectations as adverse DBS effects, negatively affecting the stimulation therapy. This is of special concern if the primary patient goals from surgery are not deemed realistic. Family members may also have unrealistic expectations that should be addressed whenever possible. Some patients or families may have unrealistic goals sparked as a result of media depictions of DBS or making generalizations from outcomes observed on other patients [20, 21].

Clinical practice guidelines state that patient education should begin early in the preoperative evaluation process. What can realistically be expected from surgery should be described [17]. Thorough preoperative education should be mandatory, including potential surgical complications [18]. Patients and medical providers should clearly document patient expectations, so that this can be reviewed postoperatively for a more meaningful assessment of goal attainment [22].

As well documented in the literature, most motor symptoms show improvement after DBS surgery. In our sample, 62 to 82% of patients had their expectations of motor-symptom improvements met. Of note, "slowness," for which 11% of patients disagreed about any improvements postoperatively, is a broad encompassing symptom that may have different meanings. It may be interpreted both in a psychosocial context and in relation to axial signs, which have been documented to relate to dissatisfaction with DBS, especially if present preoperatively [23]. Medication reduction, which often can be accomplished especially after STN-DBS [9, 13, 18, 24], was an expectation that was met for the majority of patients. Expectations for improvement in nonmotor symptoms such as sleep, gait freezing, and handwriting were relatively infrequently mentioned in our survey which likely reflects adequate patient education about the uncertainty of expected benefits from DBS for these symptoms.

Our study has several limitations. This is a retrospective study with a relatively small sample size collected over a seven-year period. Our survey instrument was not evaluated for reliability or validity and was developed as there are currently no established scales to measure patient expectation and satisfaction from DBS surgery. Different practitioners provided the patient with education and documentation in charts was lacking in many instances. There was no protocol in place for a standardized approach to patient education on DBS surgery. The study was performed at a single institution and may not reflect experience with DBS patient education at other centers.

5. Conclusions

Despite overall satisfaction in our patient sample with outcomes from DBS, patient expectations should be further explored in a systematic manner. We found considerable discrepancies of documented patient education versus patient reported education on expected symptom improvement. Patient education on DBS should be improved and follow a standardized protocol, ideally involving a multidisciplinary team. Involvement of a nurse educator, a DBS support group, and tailored information over several visits may assist patients in reaching realistic expectations about surgery outcomes and improving their overall satisfaction with DBS surgery. Additional longitudinal studies are needed to further understand the patient-centered experience.

Disclosure

This study has previously been presented as a poster presentation at Ochsner Medical Center and was the capstone project for the doctoral degree in nursing for Colleen D. Knoop, DNP, APRN.

Conflicts of Interest

Dr. Michael C. Park is a listed faculty for the University of Minnesota Educational Partnership with Medtronic, Inc., Minneapolis, MN. He received research support from Medtronic, Inc., Boston Scientific and Advanced Neuromodulation Systems, Inc., and St. Jude Medical. Dr. Kathrin LaFaver received research support for participation in multicenter studies from the Parkinson's Study Group, Huntington's Study Group, and Vaccinex, Inc. Drs. Colleen D. Knoop, Robert Kadish, Kathy Hager, and Paul D. Loprinzi declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Deep Brain Stimulation in Parkinson's Disease: New and Emerging Targets for Refractory Motor and Nonmotor Symptoms

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Parkinson's disease (PD) is a progressive neurodegenerative condition characterized by bradykinesia, tremor, rigidity, and postural instability (PI), in addition to numerous nonmotor manifestations. Many pharmacological therapies now exist to successfully treat PD motor symptoms; however, as the disease progresses, it often becomes challenging to treat with medications alone. Deep brain stimulation (DBS) has become a crucial player in PD treatment, particularly for patients who have disabling motor complications from medical treatment. Well-established DBS targets include the subthalamic nucleus (STN), the globus pallidus pars interna (GPi), and to a lesser degree the ventral intermediate nucleus (VIM) of the thalamus. Studies of alternative DBS targets for PD are ongoing, the majority of which have shown some clinical benefit; however, more carefully designed and controlled studies are needed. In the present review, we discuss the role of these new and emerging DBS targets in treating refractory axial motor symptoms and other motor and nonmotor symptoms (NMS).

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative condition. Many successful pharmacological therapies and strategies have been developed to treat both the motor and nonmotor manifestations of PD; however, as PD progresses it often becomes intractably difficult to treat, typically as a result of motor complications related to treatment. Since the seminal study by Benabid et al. targeting the ventral intermediate nucleus (VIM) of the thalamus [1], deep brain stimulation (DBS) has emerged as a key player in the treatment of PD. Multiple randomized controlled studies have demonstrated subthalamic nucleus- (STN-) and globus pallidus interna- (GPi-) DBS to be superior to medical treatment alone in treating a number of the cardinal symptoms and motor complications from therapy [1–3]. The benefit of DBS on axial symptoms is less clear. Several reports have indicated improvement of posture, gait, and balance control after STN- or GPi-DBS, when these symptoms were responsive to levodopa treatment before DBS surgery [4–9]; however, the benefit on postural instability (PI) and gait is not sustained [4]. Moreover, it has been noted that a significant number of patients report postoperative worsening of gait, despite concurrent improvement in motor scores and global outcomes after bilateral STN-DBS. Further, fall risk has been demonstrated to increase and levodopa-resistant freezing of gait (FoG) persists or worsens [10–16]. The axial domains of speech [17–19] and swallowing [20, 21] have also shown to be impacted by DBS. To complicate matters further, stimulation parameters (i.e., high frequency stimulation) can also lead to adverse axial effects in patients. These disparities in outcome have fueled the exploration for novel DBS targets that may prove beneficial at treating the axial motor symptoms of PD. In addition to refractory axial motor symptoms, it is clear that nonmotor symptoms (NMS) can also become particularly troublesome [22], as PD progresses and increases in severity. NMS have a significant impact on prognosis and quality of life [23], again highlighting the need for alternative DBS targets that will have therapeutic benefit not only for refractory motor symptoms, but for NMS in PD as well.

In the present review, we discuss new and emerging DBS targets currently being investigated for the treatment of refractory motor symptoms and NMS in PD. These targets include the pedunculopontine nucleus (PPN), the caudal zona incerta (ZI), the substantia nigra (SN) pars reticulate (SNr) (Figure 1), the motor cortex, and other less explored targets.

2. New and Emerging DBS Targets for Refractory Motor Symptoms

2.1. Refractory Tremor. For tremor-dominant PD, where severe and disabling tremor is refractory to treatment, VIM-DBS has been shown to suppress tremor effectively. In addition, STN- and GPi-DBS both provide sustained benefit for PD resting tremor. For severe tremor and coexisting essential tremor, DBS leads implanted in the posterior aspect of the GPi or STN (i.e., ZI region bordering the STN) appear to be of benefit [23].

2.1.1. Caudal Zona Incerta. The ZI is a small heterogeneous cellular nucleus that lies within the anatomical location termed the posterior subthalamic area (PSA) [24, 25]. The borders of the PSA include the posterior border of the STN anteriorly, the dorsal SN inferiorly, the ventral thalamic nuclei superiorly, the anterolateral red nucleus posteromedially, the medial lemniscus posteriorly, and the internal capsule laterally [24, 25]. The rostral ZI lies along the dorsal and medial STN, while the caudal ZI (cZI) is located posteromedially to the STN [26] (Figure 1(b)). Various functions of the ZI have been postulated throughout the literature; however, it is commonly held that the ZI plays a role in visceral function, arousal, attention, and posture and locomotion, with the cZI mediating the latter [26]. The cZI has widespread afferent and efferent projections amongst the cerebral cortex, diencephalon, brainstem, cerebellum, and spinal cord, the majority of which are GABAergic [26]. While its circuitry remains complex and poorly understood, it is postulated that the cZI may act as an integrator within and between the basal ganglia-thalamocortical loop and the cerebellothalamocortical loop, assisting in the synchronization of oscillatory neuronal firing in both of these pathways [27]. Abnormalities in oscillatory neuronal synchronization that are generated along either of these loops or at the level of the cZI are thought to play a major role in the generation of tremor [24, 25, 27].

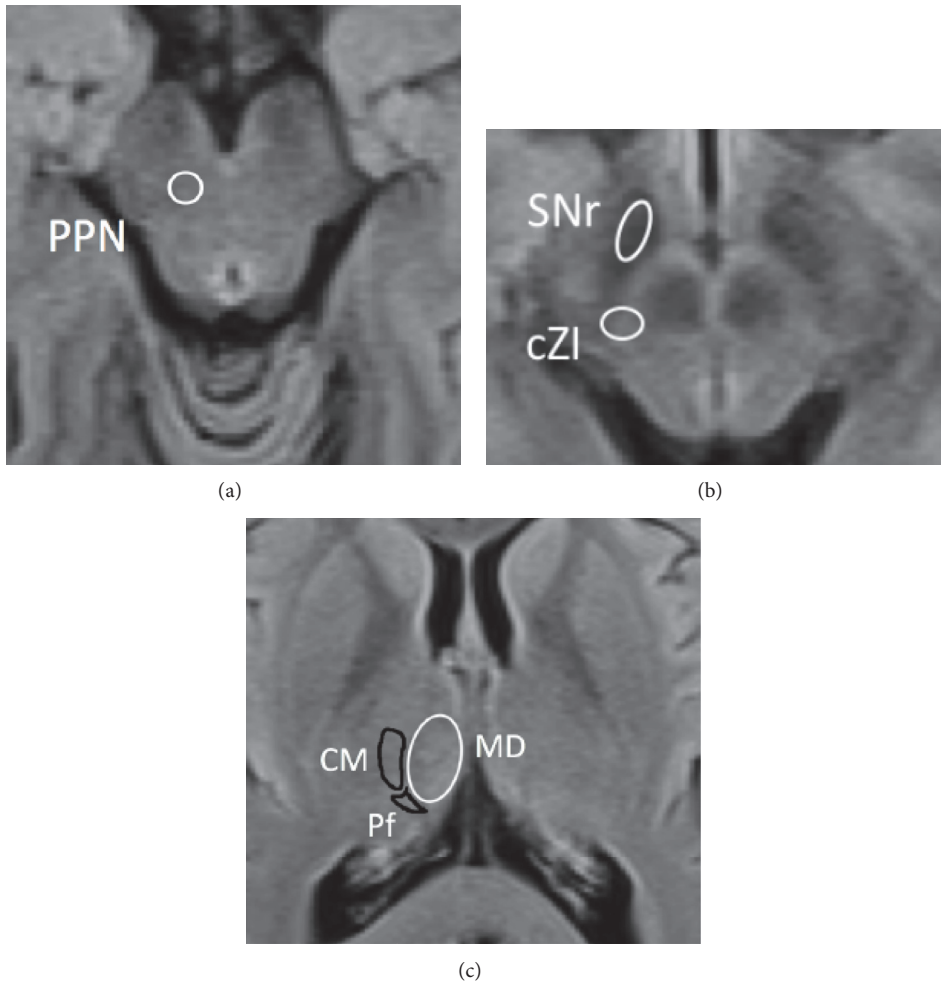
The benefit of cZI-DBS for tremor control has been well established in studies investigating its role in essential tremor [28]. In PD, the majority of information that has been gleaned regarding the cZI has come from lesional studies. It has previously been shown that subthalamotomy including the region of the ZI can lead to clinical improvement in PD [29]. Subsequent work focusing on the ZI and the cZI has led to significant discoveries regarding the promise of this structure as a DBS target in PD [24, 25]. The relevance of the cZI as a DBS target in PD was brought to the forefront by Plaha et al., in their study comparing motor outcomes amongst three DBS targets: the cZI, the posterodorsal STN, and dorsomedial/medial STN [30]. When compared to STN stimulation, unilateral cZI stimulation with mean frequency of 150 Hz led to greater improvement in tremor control and overall Unified Parkinson's Disease Rating Scale (UPDRS) motor scores.

A subsequent longitudinal, observational study by Plaha et al. again demonstrated the utility of cZI-DBS (bilateral, 145 Hz) in reducing parkinsonian tremor, as well as a variety of other tremor types, including cerebellar outflow, essential, and dystonic tremor at 12 months of follow-up [27]. Recent work by Blomstedt et al., in an open labeled study with 18 months of follow-up [23–25], echoed the results of Plaha et al. [27], demonstrating the benefit of unilateral cZI-DBS with mean frequency of 160 Hz in the treatment of contralateral, severe parkinsonian tremor. The benefit on rigidity and bradykinesia was not as profound as in STN-DBS; however, a number of studies have suggested that cZI-DBS has a lower incidence of speech deterioration and is associated with better neuropsychological outcomes [27, 31]. That being said, cZI-DBS is not as well established as STN- or GPi-DBS in PD. Further larger scale studies are required to guide future target selection.

2.1.2. Centromedian and Parafascicular Nuclei. The centromedian and parafascicular nuclei (CMPf) (Figure 1(c)) are the two main constituents of the intralaminar nucleus of the thalamus and have several connections within the basal ganglia, with projections to the STN, substantia nigra (SN), and GPi [32]. It has been postulated that CMPf-DBS affects other thalamic components [ventralis oralis anterior (VOA) and VIM] whose role in tremor control has been well established [33, 34].

Interest in the CMPf as a DBS target resurfaced following the observation by Krauss et al. that stimulation of CMPf appeared to abolish resting tremor in 1 patient and involuntary choreoathetotic and dyskinetic movements in 2 others [35]. In subsequent reports, it was observed that CMPf stimulation, independent of STN stimulation, led to reduction of tremor-related muscle activity in 2 patients with PD [36, 37]. Additionally, they demonstrated better tremor control compared with STN-DBS alone. Mazzone et al. [38] demonstrated that combination of CMPf- and GPi-DBS reduced UPDRS III scores by 49.9%, a value significantly different when compared to CMPf or GPi stimulation alone. Unfortunately, tremor control was not specified within the study. Further studies should help clarify whether CMPf stimulation is superior to VIM-DBS for tremor control in PD.

2.2. Refractory Axial Motor Symptoms-Gait and Balance. FoG, in addition to other gait disturbances such as decreased stride length and gait variability, is associated with increased fall risk in patients with PD [50]. These symptoms are typically refractory to therapy, including STN- and GPi-DBS [51, 52], and are thus a significant source of morbidity in PD [53]. The pathophysiology and neuropathological substrates underlying FoG remain largely unknown. FoG may be due to a failure to adequately scale amplitudes for the intended movement [54] and/or defective motor programming by the supplementary motor area (SMA) and its maintenance by the basal ganglia, leading to a mismatch between intention and automation [54].



(a) (b)

(c)

Figure 1: Axial MRI imaging at the level of the midbrain and thalamus, demonstrating the anatomical locations of DBS targets described in the review. CMPf, centromedian-parafascicular nuclear complex; cZI, caudal zona incerta; PPN, pedunculopontine nucleus; SNr, substantia nigra pars reticulata.

2.2.1. Pedunculopontine Nucleus. The mesencephalic locomotor region (MLR) appears critical for normal gait function [61]. The PPN is a key component of the MLR [62] (Figure 1(a)). Widespread projections involving the PPN include direct glutamatergic inputs from the motor cortex and GABAergic inputs from SNr, GPi, STN, and deep nuclei of the cerebellum. Ascending efferent projections target GPi, SN pars compacta [63], and thalamus. Descending efferent projections target pontine and medullary reticular formations, as well as spinal cord structures vital to the control of muscle tone and locomotion. The PPN appears to play a key role in the initiation, acceleration, deceleration, and termination of locomotion through connections to the basal ganglia and higher cortical regions [61]. PPN neuronal loss is evident in PD [64]. Ways to modulate PPN connectivity and activity have proven elusive. Acetylcholinesterase inhibitors may affect the PPN but effects are likely modest.

Jenkinson et al. were the first group to demonstrate the efficacy of PPN-DBS, in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) exposed macaque [65]. Following MPTP exposure, unilateral PPN stimulation was equivalent to levodopa in improving motor activity scores [65]. In 2005, 2 case studies were the first to establish the safety and efficacy of PPN-DBS in humans [39, 40] (Table 1), demonstrating improvements in UPDRS motor scores. Subsequently, a study by Plaha and Gill was the first to show the role of PPN-DBS in improving gait dysfunction and PI in PD [40]. Multiple open labeled PPN-DBS studies have demonstrated clinical improvement in patients with PD, although results have been variable [41, 42, 45, 47] (Table 1). Additional open labeled studies from Thevathasan et al. [45, 46, 66, 67] demonstrated that PPN stimulation (20–35 Hz) improved frequency of falls in PD patients with severe FoG and PI during the "on" state [45]. One study showed improvement in gait and falls questionnaire score but not UPDRS III score in 5 patients with PD implanted with bilateral PPN electrodes [46]. The first double-blinded assessment of PPN-DBS was performed by Ferraye and colleagues [43], demonstrating improvement in FoG but not PI or overall UPDRS scores. The lack of improvement in global motor function and axial symptoms, other than FoG, was in opposition to previous studies (Table 1) [39–41, 46, 48]. Moro

Table 1: Summary of studies on PD patients implanted with PPN-DBS for gait and balance impairment.

Study	Number of Patients	Inclusion criteria	Study design	Stimulation target	Stimulation parameters	Outcomes	Adverse events	Comments
Mazzone et al. [39]	2	FoG	Open label	Bilateral PPN	Bipolar; 10 Hz	Intraoperative improvement of UPDRS III score	NR	First human study to demonstrate the potential efficacy of PPN-DBS in PD
Plaha and Gill [40]	2	FoG, PI, and frequent falls	Open label	Bilateral PPN	Bipolar; 20–25 Hz	UPDRS improved by 53%; UPDRS III by 57%	Certain stimulation frequencies can exacerbate gait	Short follow-up, 42 days for patient 1 and 16 days for patient 2
Stefani et al. [41]	6	FoG, 3 had "on" FoG, UPDRS-III > 70, and levodopa-induced dyskinesias	Open label	Bilateral STN and PPN	Bipolar; 25 Hz at PPN	PPN stimulation showed more benefit on posture and gait items compared to STN stimulation; UPDRS III improved by 32%; axial symptoms (UPDRS 27–30) by 60%	Paresthesia	Total length of study was 6 months; noted decline in motor benefit; trend of improved UPDRS scores with both STN and PPN stimulation
Strafella et al. [42]	1	Advanced PD, FoG, PI	Open label	Unilateral PPN	70 Hz	UPDRS improved by 19%, mainly in relation to gait, tremor, and bradykinesia	NR	PET studies showed increased rCBF in different subcortical areas, most notably in the thalamus bilaterally
Ferraye et al. [43]	6	Severe FoG unresponsive to levodopa and STN stimulation	Double-blinded assessment	Bilateral STN and PPN	Bipolar; 15–25 Hz	Only FoG showed clear improvement; gait and PI scores did not improve; falls unrelated to FoG were unchanged in 5/6	Seizure in 1 patient; stimulation frequency dependent oscillopsia; paresthesias; limb myoclonus	The total length of the study was 1 year; objective improvement of FoG in 2 patients
Moro et al. [44]	6	Age < 70, severe "off" FoG and PI; no dementia	Double-blinded assessment	Unilateral PPN	Bipolar; chronic stimulation frequency of 67 Hz	Improvement in UPDRS item 13 (falling) by 75% at 3 and 12 months	Stimulation frequency dependent oscillopsia and paresthesias	First double-blinded study to investigate unilateral PPN stimulation; total study length was 1 year
Thevathasan et al. [45]	11	Severe FoG and PI, in addition to falls both in the "on" and "off" states	Open label	Bilateral PPN in 8 patients, bilateral PPN and ZI in 2 patients, and unilateral PPN and bilateral ZI in 1 patient	Bipolar; 20–35 Hz	Improvement in frequency of falls and gait	NR	Follow-up 3–38 months
Thevathasan et al. [46]	5	Severe FoG and PI, in addition to falls persisting in the "on" state	Open label	Bilateral PPN	Monopolar; 35 Hz; PPN target more caudal than previous	Improvement in all by FoG and falls questionnaire at 3 months and 2 years	Stimulation frequency dependent decline in motor function and gait; oscillopsia	Total study length was 2 years; assessments at 3 months and 2 years
Khan et al. [47]	7	PD patients with severe FoG, PI, falls during "on" and "off" states	Open label	Bilateral PPN, in combination with cZi stimulation	Bipolar; 60 Hz (PPN)	Improvement in UPDRS III score (18.8%) and axial symptoms score (26.3%)	Akinesia in 2 patients	Follow-up 12 months; similar benefit with ZI stimulation versus ZI and PPN "on"

Table 1: Continued.

Study	Number of Patients	Inclusion criteria	Study design	Stimulation target	Stimulation parameters	Outcomes	Adverse events	Comments
Thevathasan et al. [48]	7	PI, severe FoG, and falls during "on" state	Open label	5 bilateral and 2 unilateral	Bipolar; 35 Hz	Improvement in freezing of gait questionnaire, turn task duration, and cadence	NR	First study to directly compare unilateral versus bilateral stimulation; less robust result in unilateral PPN
Mazzone et al. [49]	28	24 patients had PD and 4 had PSP	Open label	Both bilateral (6) and unilateral (22) PPN	Bipolar; unilateral (40 Hz) and bilateral (25 Hz)	Improvement in UPDRS III score in "off" medication and "on" stimulation	None	The largest and longest study of PPN DBS to date with a mean follow-up of 3.8 years; included patients from prior studies

FoG, freezing of gait; NR, not reported; PD, Parkinson's disease; PET, positron emission tomography; PI, postural instability; PPN, pedunculopontine nucleus; PSP, progressive supranuclear palsy; rCBF, regional cerebral; STN, subthalamic nucleus; UPDRS, United Parkinson Disease Rating Scale; ZI, zona incerta.

et al. were the first to investigate the role of unilateral PPN-DBS in a double-blinded study of 6 patients with PD [44]. At study end period (1 year), UPDRS item 13 (falling) showed 75% improvement, with no statistically significant changes in other motor domains. Furthermore, bilateral stimulation proved more effective than unilateral stimulation [48].

The largest study with the longest follow-up of PPN-DBS in PD was reported by Mazzone et al. [49, 68, 69]. A total of 24 patients with PD and 4 with progressive supranuclear palsy (PSP) [49] were followed for a mean follow-up of 3.8 years. At study end period, they demonstrated an improvement in UPDRS III scores and in axial symptoms (UPDRS items 27–30) (off levodopa therapy); however, no difference was detected between the "on" medication and "off" stimulation state and the "off" medication and "on" stimulation state.

Connectivity to and from the MLR/PPN appears critical for normal gait function and is likely a factor in FoG as well. Structural deficits in connectivity are evident between the basal ganglia and PPN, in addition to other tracts in patients with FoG [70, 71]. Functional connectivity studies suggest that FoG patients may have significantly stronger connectivity between the PPN and supplementary motor area (SMA) [70], possibly reflecting maladaptive compensatory mechanisms. The integrity of these tracts has not been studied in patients who have undergone PPN-DBS. The variability of this deficit in structural and functional connectivity to and from the PPN may at least partially explain the variable results within the literature. In addition, the PPN tends to be spatially diffuse in humans and microelectrode recording is not helpful intraoperatively, thus making precise lead placement difficult and potentially contributing to further variability from study to study.

The experience and results with PPN-DBS are in their infancy. More precise targeting strategies with improved technology (i.e., improved imaging and programming) are required. It remains to be seen whether PPN-DBS should be an adjunct target to STN- or GPi-DBS for better overall motor control.

2.2.2. Combined Pedunculopontine Nucleus and Caudal Zona Incerta Stimulation. Khan et al. investigated the effects of bilateral PPN-DBS and caudal cZI-DBS in a blinded study of 7 patients with PD [47]. The authors demonstrated an 18.8% improvement in UPDRS III score and a 26.3% improvement in axial symptoms (items 27–30 on UPDRS III) of levodopa therapy. However, the same subscore was only significantly reduced in the "on" medication state when the PPN and cZI were stimulated in concert. This study suggested that, with these stimulation parameters, PPN stimulation alone was insufficient in improving "on" medication and resistant axial symptoms and that costimulation of cZI could provide an additive, beneficial role.

2.2.3. Substantia Nigra Pars Reticulata. The SN is a dense, laterally oriented collection of dopaminergic and GABAergic neurons located within the ventral midbrain, just dorsal to the corticospinal and corticobulbar tracts, ventral to the red nuclei, and lateral to the ventral tegmental area [72]. Its 2 components, the SNr and SNc [63], have traditionally been considered the major output and input nuclei, respectively, of the basal ganglia. While there is fair overlap, the SNr lies ventrally and laterally to the SNc in the midbrain [73]. In the classically held framework of basal ganglia circuitry, facilitation of movement was felt to be achieved through activation of a direct pathway from striatum to output nuclei (SNr and GPi), while inhibition of movement occurred through excitation of an indirect pathway (through globus pallidus externus and STN) [72]; however, recent advances in modeling of striatonigral-thalamocortical pathways have made it clear that while the classical model of basal ganglia circuitry provides a solid foundation for the understanding of its complex interconnections, it hardly captures its complete intricacies [72].

The SNr is another key player in the MLR, via its significant efferent GABAergic input to the PPN [74]. Efferents from the lateral SNr to the PPN are felt to modulate postural tone, while its medial efferents projecting to the cuneiform nucleus of the MLR influence locomotion [74]. It may not then be surprising that axial motor symptomatology, including gait impairment and PI, in patients with PD has shown favorable response to SNr stimulation in the literature [55–57, 75] (Table 2). Significant improvements in UPDRS III axial motor subscores and braking capacity, but not in distal motor symptoms (segmental akinesia, limb rigidity, and tremor), have been observed previously with SNr-DBS [55]. In contrast, one of the more recent double-blind, cross-over, randomized controlled trials with combined STN and SNr stimulation did show significant improvement in FoG, but not in other axial symptoms when compared to STN-DBS alone [56]. With SNr-DBS, one should be cautious about the possibility of worsening akinesia, as increased immobility and recurrent falls were reported in 1 patient in the same study during the last week of follow-up under combined STN and SNr stimulation [56].

While some benefit from SN stimulation has been reported, significant and variable impacts on mood and behavior can occur, likely owing to its limbic projections [76, 77]. Reports of acute depression [78, 79], hypomania [77], and mania [76, 80] secondary to high frequency SN stimulation are evident in the literature. While it is difficult to rule out STN participation in the provocation of mood symptoms, it is clear that stimulation of more ventrally placed leads within the SN and likely the SNr can preferentially elicit these symptoms.

2.2.4. Motor Cortex. Extradural motor cortex stimulation (EMCS) has been studied as another treatment modality in PD, particularly for those patients with advanced PD who are poor surgical candidates [81–86]. The primary motor cortex is a key component of corticobasal ganglia loops and thus forms a potential therapeutic target in PD [87]. Tremor and rigidity in PD can be suppressed by EMCS [58, 88], and benefit has been seen in advanced PD [82, 83]. Since initial reports, numerous studies have investigated the role of EMCS for the treatment of advanced PD, with variable results [58–60, 84, 86, 89–91] (Table 2).

Table 2: Summary of studies on PD patients implanted with novel DBS targets (SNr, motor cortex, CMPf) for gait and balance impairment.

Study	Study subjects/inclusion criteria	Study design	Effect on FoG/PI/falls	Motor effects	Comments
			SNr		
Chastan et al. [55]	7 patients with levodopa and STN-DBS. At least one contact of each electrode was located within the SNr	Open label	Significant improvements in UPDRS III axial motor subscores and in braking capacity	No improvement in motor symptoms (segmental akinesia, limb rigidity, and tremor)	No specific criteria for axial involvement
Weiss et al. [56]	12 patients, with combined STN and SNr stimulation; axial UPDRS ≥ 12; advance PD patients with gait/balance impairment; refractory to medical treatment	Double-blind, cross-over, randomized controlled trial	With combined STN and SNr stimulation improvement in FoG at the 3-week follow-up	No global effect on axial motor domains; no benefit for segmental motor functions	Immediate assessment and 3-week follow-up; long term effects unclear
Brosius et al. [57]	1 patient with advance PD, severe FoG; unilateral STN/SNr stimulation	Case report	Significantly improved FoG in a patient with advanced PD, using interleaving setting		Contralateral STN, the more severe side with STN/SNr
			Motor cortex		
Pagni et al. [58]	41 patients with advanced PD; not DBS candidates, Hoehn-Yahr III–V; unilateral lead over hand area of motor cortex	Open label	Improvement in standing, gait, and motor performance; significant improvement in UPDRS axial scores	Improved "off" medication UPDRS-III; not significant for "on" medication score	Sustained improvement of quality of life measures through 3-year follow-up
Cilia et al. [59]	5 patients with advanced PD	Open label	Subjective improvement of axial symptomatology	No quantifiable clinical benefit at 6 months	Small sample size; subjective improvement only
Fasano et al. [60]	1 patient with severe PD who was unable to stand from sitting without assistance	Case report	Able to stand without assistance, with improvement in both axial akinesia and walking		Case report; short lasting benefit (5 months)
			CMPf		
Mazzone et al. [38]	6 PD patients with disabling FoG, with GPi and CMPf-DBS	Open label	CMPf activation was more efficacious on freezing of gait	A significant amelioration of UPDRS scores was achieved	Small sample size; observation of CMPf stimulation alone may not control PD motor symptoms adequately

CMPf, centromedian-parafascicular nuclear complex; FoG, freezing of gait; GPi, globus pallidus, internal segment; PD, Parkinson disease; PI, postural instability; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus; UPDRS, United Parkinson Disease Rating Scale.

The largest study of EMCS in 41 patients with advanced PD (not eligible for DBS) showed improvement in standing, gait, and motor performance [58], though these results were not supported by other studies [59, 60, 91]. Additional studies have shown that EMCS improved quality of life parameters and modestly reduced levodopa dose but did not improve UPDRS III scores or axial symptoms [90, 92].

2.2.5. Centromedian and Parafascicular Nuclei. A single study demonstrated that CMPf stimulation alone led to significantly reduced FoG, where GPi stimulation alone did not [38]; however, this study had a sample size of only 6 patients. The authors further observed that CMPf stimulation alone may not control PD motor symptoms adequately. This observation raised the possibility of multiple-target stimulation strategy to optimize axial symptoms and overall motor control in PD.

2.3. Refractory Axial Symptoms-Speech and Swallowing. To date, no convincing evidence has demonstrated improvements in speech or swallowing in PD with STN- or GPi-DBS. Speech and swallowing can worsen with DBS surgery or programming. Research on the impact of cZI-DBS on associated motor symptomatology in PD has also taken place. Particular focus in the literature has been given to the effects of cZI-DBS on speech and its related domains. Stimulation of cZI was shown to have a deleterious effect on voice intensity when compared to STN-DBS [93], while articulatory precision of speech also worsens in patients receiving cZI-DBS [94]. Significant impairment in verbal fluency is also observed in the immediate postoperative period; however, this deficit does not maintain significance in the long term [95]. Speech intelligibility has been demonstrated to be significantly reduced in cZI-DBS patients speaking from a read-speech passage [96]; however, this effect was not reproduced when evaluated from spontaneous speech at 1 year postoperatively, suggesting that the impact of cZI-DBS on speech intelligibility may have initially been overstated [97]. While STN-DBS has beneficial effects on pitch variability and range, cZI-DBS displayed no such benefit in a small study of 16 patients with 1-year follow-up [98]. The effect of cZI-DBS on swallowing dysfunction has also been evaluated in 2 longitudinal, prospective studies of 8 and 9 patients [99, 100]. Both studies demonstrated that cZI-DBS did not have a clinically significant impact on either swallowing function or self-reported swallowing-specific quality of life at 1 year postoperatively. Further studies should help clarify the effect of cZI-DBS on both speech and swallowing dysfunction. In 1 study of EMCS in advanced PD, Pagni et al. demonstrated improved speech and swallowing in patients who are not DBS candidates [58].

Speech and swallowing symptoms following DBS have yet to be defined within the current literature. Methodology in assessing the symptoms varies from study to study. Severity of dysarthria/dysphagia preoperatively, duration and severity of disease, and positioning of the electrode(s) are all critical contributing factors in speech outcomes. Large-scale studies and systemic analyses are required.

3. Nonmotor Symptoms of PD

NMS are debilitating in PD. Robust evidence is lacking for STN- and GPi-DBS in treating NMS. A number of reports have demonstrated that PPN-DBS is capable of modulating the NMS of PD, including cognition, sleep, and attention [101–103]. The cognitive benefit of PPN-DBS has been reported in a small number of uncontrolled studies, with bilateral PPN stimulation reducing reaction time when assessing executive function and working memory and improving delayed recall and verbal fluency [101, 102]. It has been postulated that the cognitive improvement in these domains might be mediated via activation of ascending cholinergic neurons to the thalamic CMPf, subsequently leading to widespread activation via intralaminar thalamic nuclei. Indeed, functional imaging via positron emission tomography has shown an increase in fluorodeoxyglucose uptake in prefrontal areas, suggesting a modulation of thalamic metabolism after PPN-DBS [104]. Romigi was the first to identify the role of PPN-DBS in sleep, demonstrating that bilateral PPN stimulation resulted in increased rapid eye movement (REM) sleep in patients with PD [105]. Similarly, Lim et al. showed that unilateral PPN-DBS in 3 PD patients and 2 PSP patients resulted in increased nocturnal REM sleep [106]. In a subsequent study by the same group, the authors noted that bilateral, low-frequency stimulation of the PPN resulted in improved attention in 2 patients with PD [107]. No other studies to date have investigated the role of PPN-DBS in attention.

DBS targets involved in memory circuits have garnered interest in recent years. To date, only 1 human study of DBS with bilateral STN and nucleus basalis of Meynert (NBM) stimulation in PD dementia (PDD) has evaluated the potential for cognitive and/or memory improvement [108]. In this study, STN-DBS alone yielded significant improvements in motor functioning, but not in memory or cognition. The addition of NBM stimulation to STN stimulation produced significant improvements in memory and cognitive functioning, manifested as improved performance on the Rey Auditory Verbal Learning Task, Trail-Making Test A, and the Clock Drawing Test.

4. Discussion

A multitude of new developments have been made in the area of alternative DBS targets in PD treatment over the last two decades. Research has focused on novel DBS targets, with the aim of relieving motor symptoms and NMS that are usually refractory to dopaminergic agents and traditional STN-, GPi-, and VIM-DBS.

Stimulation of the cZI has shown promise in alleviating severe parkinsonian tremor, amongst other types, and its costimulation with PPN could provide an additive benefit on axial symptoms and PI. cZI stimulation is relatively new in its conception and additional studies are required to further evaluate its possible deleterious effects on speech, particularly voice intensity and articulatory precision.

Studies investigating axial motor symptomatology and PI with PPN stimulation have yielded mixed results. From

a technical aspect, considerable variability exists amongst stimulation parameters in PPN-DBS studies (Table 1) and may account for the variable degrees of success in relieving axial motor symptoms. Additionally, the PPN tends to be spatially diffuse in humans and electrophysiological recording intraoperatively is not as helpful [109] as that of the STN, GPi, or VIM. The connectivity deficit of the PPN should also be taken into account with invasive procedures like DBS. White matter tract integrity may prove fruitful with respect to patient selection. With regard to study design, a PD population with clear dopamine-resistant gait and balance deficits should be chosen. Moreover, whether or not study subjects have concurrent STN- or GPi-DBS should be considered and studied systemically to verify the therapeutic benefit of PPN stimulation. As indicated in Table 1, few studies have been randomized and double-blinded. High quality randomized studies with standardized outcomes are needed.

The SNr represents an area of great importance in the complex hierarchy of basal ganglia circuitry and studies evaluating its potential as a DBS target have yielded mixed results. While some studies of SNr-DBS have shown improvement in axial motor symptoms, the incidence of acute mania, hypomania, and depression suggests that its utility as a target in alleviating PD symptoms may be limited by these adverse changes.

EMCS and CMPf-DBS provide some benefit in PD symptomatology. However, evidence is not conclusive for either target to be superior to STN or GPi in motor control.

NMS symptoms are disabling in PD patients. Although there is some evidence that PPN-DBS improves NMS, data are as of yet too limited to consider PPN-DBS as a therapeutic option for this domain of symptomatology. PPN-DBS may prove to be a safer target in the cognitive domain, particularly when considering the possible impact of STN- and GPi-DBS on cognition.

5. Conclusions

The future of DBS in PD appears promising. The field has advanced significantly with a number of new targets to address the refractory symptoms of PD. Amongst the studies investigating these novel targets, the large majority are open-label and are not powerful enough to determine true therapeutic benefit. Future, large-scale randomized studies focusing on identifying ideal candidates, optimal targets, and stimulation parameters would certainly be of utility in triggering the DBS community to perform more robust comparisons across studies.

Abbreviations

cZI: Caudal zona incerta
CMPf: Centromedian-parafascicular nuclear complex
DBS: Deep brain stimulation
EMCS: Extradural motor cortex stimulation
FoG: Freezing of gait
GPi: Globus pallidus pars interna
MLR: Mesencephalic locomotor region
MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NBM: Nucleus basalis of Meynert
NMS: Nonmotor symptoms
PD: Parkinson's disease
PI: Postural instability
PPN: Pedunculopontine nucleus
PSA: Posterior subthalamic area
PSP: Progressive supranuclear palsy
REM: Rapid eye movement
SMA: Supplementary motor area
SN: Substantia nigra
SNc: Substantia nigra pars compacta
SNr: Substantia nigra pars reticulata
STN: Subthalamic nucleus
UPDRS: Unified Parkinson's Disease Rating Scale
VIM: Ventral intermediate nucleus
VOA: Ventralis oralis anterior
ZI: Zona incerta.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Dustin Anderson and Grayson Beecher contributed equally to this work.

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Research Article

Deep Brain Stimulation of Hemiparkinsonian Rats with Unipolar and Bipolar Electrodes for up to 6 Weeks: Behavioral Testing of Freely Moving Animals

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Although the clinical use of deep brain stimulation (DBS) is increasing, its basic mechanisms of action are still poorly understood. Platinum/iridium electrodes were inserted into the subthalamic nucleus of rats with unilateral 6-OHDA-induced lesions of the medial forebrain bundle. Six behavioral parameters were compared with respect to their potential to detect DBS effects. Locomotor function was quantified by (i) apomorphine-induced rotation, (ii) initiation time, (iii) the number of adjusting steps in the stepping test, and (iv) the total migration distance in the open field test. Sensorimotor neglect and anxiety were quantified by (v) the retrieval bias in the corridor test and (vi) the ratio of migration distance in the center versus in the periphery in the open field test, respectively. In our setup, unipolar stimulation was found to be more efficient than bipolar stimulation for achieving beneficial long-term DBS effects. Performance in the apomorphine-induced rotation test showed no improvement after 6 weeks. DBS reduced the initiation time of the contralateral paw in the stepping test after 3 weeks of DBS followed by 3 weeks without DBS. Similarly, sensorimotor neglect was improved. The latter two parameters were found to be most appropriate for judging therapeutic DBS effects.

1. Introduction

Electrical stimulation of the brain is an emerging area for the treatment of a growing number of neurological and psychiatric diseases. Deep brain stimulation (DBS) is well established for the treatment of movement disorders, such as Parkinson's disease (PD) [1]. For patients in the advanced stages of PD, DBS of the *subthalamic nucleus* (STN) is highly effective in reversing motor deficits. In addition to locomotor and sensorimotor deficits, PD patients also suffer from emotional disturbances, namely, depression and anxiety. Anxiety may result not only from the impairment of motor function but also from dysfunction in the STN [2]. More recently, DBS has also been applied at earlier stages of PD [3]. Nevertheless, STN-DBS does not always improve symptoms, and it may actually worsen them [4]. However, only limited information is available on (i) the effects of DBS on cognitive and emotional traits; (ii) the efficiency of different stimulation modes, in particular unipolar versus bipolar stimulation; and (iii) the long-term sustainability of symptom alleviation after the cessation of DBS.

The STN is one of the most important target regions for high-frequency (approx. 130 Hz) DBS in patients, especially in patients in the advanced stages of PD who are refractory to conventional therapy [5, 6]. Historically, DBS was developed as a modification of ablative surgery, in which basal ganglia, such as the STN, were irreversibly destroyed as a final treatment option in late-stage PD [7]. During surgery, electric stimulation was used to guide neurosurgeons to the precise position of the lesions. The main advantages of DBS over

surgical lesions are its reversibility and the ability to modulate the stimulation parameters [8]. It has been well documented that DBS of the STN may also improve the cardinal motor symptoms of PD in the long-term [9, 10].

Maesawa et al. [11] were the first to describe a DBS-related protection of dopaminergic neurons in the SNc by STN-DBS of 6-OHDA hemiparkinsonian rats. Later, Harnack et al. [12] described a preservation of approx. 50% of the dopaminergic nigral neurons in the SNc by STN-DBS compared to sham-stimulated and naïve rats. Spieles-Engemann et al. [13] demonstrated an increase in the levels of the brain-derived neurotrophic factor and Wu et al. [14] observed decreased apoptosis in the nigrostriatal system after STN-DBS of 6-OHDA-lesioned rats. Other authors have described the preservation of neurons or even neurogenesis by DBS in other brain regions [15, 16].

Clearly, more information is needed to explore the full therapeutic potential of DBS. For example, optimum target regions are not always known, and the basic mechanisms by which DBS acts are still poorly understood [17–22]. In addition, adverse side effects cannot always be avoided. Therefore, research on both the optimal DBS technique and its neurological mechanisms is needed. To allow for a comparison with the clinical situation, the availability of animal models for long-term examinations and behavioral testing is of the utmost importance. Many groups have reported results from animal models with external stimulators, although these used very short durations of DBS. In some cases, only anaesthetized animals were used. Long-term behavioral outcomes have not been sufficiently examined (for reviews see [23, 24]). Nevertheless, miniaturized mobile stimulators for the chronic instrumentation of freely moving mice or rats for up to five weeks have recently been developed by a few groups [11, 25–32], including our own [33]. Such animal models allow the testing of drug-induced or spontaneous behaviors as a way to quantify the effects of lesion-induced or DBS-induced changes in locomotor function and behavior.

In pioneering work on experimental DBS, stainless steel electrodes have been used to optimize the electrode position in the brain [34, 35]. However, stainless steel electrodes are obsolete and not ideal for current studies. Their use in long-term experiments is prevented because of corrosion and the detrimental effects this has on the surrounding brain tissue [36–38].

Here, we combined a revised version of our miniaturized constant-current-pulse generator [33] with new Pt/Ir electrodes to test the effects of different modes of STN-DBS on the behavioral performance of 6-OHDA-induced hemiparkinsonian rats [39]. Several tests have been developed for the detailed evaluation of spontaneous motor and sensorimotor function in rodents [40–42]. Here, we chose four different behavioral tests: (i) an apomorphine-induced rotation test [43, 44], (ii) the stepping test [45], (iii) the corridor test [46], and (iv) a modified version of the classical open field test [47]. From these tests, six quantitative parameters were determined to describe the effects of lesion- and DBS-induced changes in locomotor function, sensorimotor neglect, exploration, and anxiety-like behavior.

2. Materials and Methods

2.1. Animals. Male Wistar Han rats (240 g–260 g; Crl:WI(Han) Rattus norvegicus: RRID:RGD_2308816) were obtained from Charles River Laboratory (Sulzfeld, Germany) and housed under temperature-controlled conditions in a 12-h light-dark cycle with conventional rodent chow and water provided ad libitum. The study was carried out in accordance with the European Community Council directive 86/609/EEC for the care of laboratory animals and was approved by the local animal care committee (LALLF M-V/TSEM/7221.3-1.2-019/10).

2.2. Electrodes. Two types of microelectrodes were custom-made from round Pt/Ir alloy (Pt90/Ir10) wires, which were insulated with polyesterimide but left bare at the tips (Figure 1). The unipolar microelectrodes were purchased from Polyfil (Zug, Switzerland) and the bipolar microelectrodes were purchased from FHC (Bowdoin, ME, USA). Their distal ends were connected with biocompatible insulated wire. To avoid excessive heating from soldering, the cables were connected with conductive silver glue, covered by biocompatible heat-shrink tubing and sealed with biocompatible silicon glue (NuSil Technology, Carpinteria, USA). The unipolar electrodes were driven against a gold-wire counter electrode (length 30 mm, diameter 200 μm). The bipolar electrodes did not require the implantation of an additional counter electrode.

2.3. Surgery. The surgical procedures were performed using a stereotactic frame (Stoelting, Wood Dale, IL, USA). Rats were anesthetized by intraperitoneal injection of ketamine hydrochloride (10 mg per 100 g body weight, Ketanest S®, Pfizer, Karlsruhe, Germany) and xylazine (0.5 mg per 100 g body weight, Rompun®, Pfizer). During surgery, their eyes were protected from dehydration by Vidisic® (Bausch and Lomb, Berlin, Germany).

The skull was opened using a dental rose-head bur (Kaniedenta, Herford, Germany). To induce hemiparkinsonism, rats were lesioned with a unilateral injection of 6-OHDA into the right medial forebrain bundle. Twenty-four μg 6-OHDA dissolved in 4 μl 0.1 M citrate buffer were delivered over 4 min via a 5 μl Hamilton microsyringe. Sham-lesioned rats received 4 μl 0.1 M citrate buffer delivered in the same fashion. The stereotactic coordinates, relative to bregma, were anterior-posterior (AP: −2.3 mm), medial-lateral (ML: 1.5 mm), and dorsal-ventral (DV: −8.5 mm) ([48]; RRID:SCR_006369). After surgery, the wound was sutured and the animals received 0.1 ml novaminsulfone (Ratiopharm, Ulm, Germany) and 4 ml saline subcutaneously. To prevent hypothermia, a heat lamp was used until vital functions returned to normal. The success of the lesion procedure was evaluated with the apomorphine-induced rotation test 12–14 days after surgery.

Approximately 3 weeks after lesion induction, the electrodes were implanted with their stimulating tips localized in the STN. The tip coordinates, relative to bregma, were AP: −3.5 mm, ML: 2.4 mm, and DV: −7.6 mm ([48];

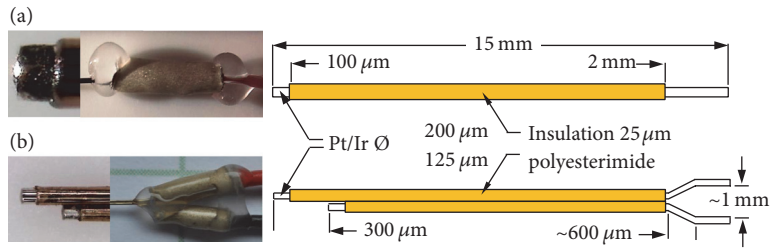


Figure 1: Photographs of tips (left), distal connections (center), and schematic drawings (right) of (a) the unipolar (200 μm wire diameter) and (b) the bipolar microelectrode (125 μm wire diameter). The electrode shafts were insulated with 25 μm polyesterimide. All electrode tips were bare for 100 μm.

RRID:SCR_006369). The shorter counter electrode tips of the bipolar electrodes were oriented so that they were lateral to the stimulating tip. The electrode shafts were fixed to the skull by an adhesive-glue bridge of dental acrylic resin (Pontiform automix 10 : 1, Müller & Weygandt GmbH, Büdingen) attached to an anchor screw fixed to the skull above the left hemisphere. Figure 2 illustrates the unipolar electrode orientation.

Following electrode implantation, the cables of the stimulating and the counter electrode contacts were implanted subcutaneously with a central dorsal outlet port (Figure 3(a)). After surgery, the rats were treated in the same manner as after the 6-OHDA injection. Rats were allowed to recover for eight days before stimulation started.

2.4. Chronic Instrumentation. One week after surgery, a plug connector (M52-040023V0545, Harwin Plc, Hampshire, UK) was crimped to the electrode cables (Figure 3(b)). The connector ensured flexibility in the use of commercial rat jackets (Lomir Biomedical, Quebec, Canada), which contained the stimulators and batteries in a custom-made fabric backpack (Figure 2(e)).

The setup allowed for the completely free movement of the animals over long periods of time. The stimulator plate was protected from mechanical strain and moisture by a custom-made polymethyl-methacrylate box and was connected to the external current-pulse battery. At the start of the stimulation, the electrode connector was plugged into the stimulator (Figure 2). The entire stimulator system was miniaturized and designed for minimum power consumption relative to our preliminary versions [33]. A separate long-lasting pulse-generator battery was inserted at the bottom of the DBS stimulator. Only the current-pulse battery (Figure 2(e)) had to be exchanged at 4 weeks.

The jacket and cables were checked daily to ensure the long-term effectiveness of the device. Cables that were torn off by the animal in exceptional cases were replaced immediately. The jackets had to be replaced every week because of wear. The stimulator signal was checked with an oscilloscope at the same time as the jackets were replaced. There has never been a problem with the batteries or the stimulator hardware.

2.5. Stimulation Conditions. The stimulator provided rectangular monophasic current pulses. Different treatment groups were stimulated for 3 days, 3 weeks, or 6 weeks. In all experiments, the stimulators were adjusted to a pulse width of 60 μsec with the negative pulse current of −200 μA applied to the stimulating unipolar electrode or to the proximal tip of the bipolar electrode. The pulse repetition frequency was 130 Hz. For sham-DBS controls, only bipolar electrodes were used because they induce more mechanical stress to the tissue during the surgical procedure.

2.6. Behavioral Tests. The effects of lesion- and DBS-induced changes in the animals' behavior were quantified using the drug-induced apomorphine-stimulated rotation test and three non-drug-induced tests (the stepping, corridor, and open field tests). Experiments were conducted at different times: (i) prior to lesion induction; (ii) 12–14 days after lesion or sham lesion induction; (iii) after 3 days of DBS or 3 days with the stimulator off (sham stimulation); (iv) after 3 weeks of DBS or 3 weeks with the stimulator off (sham stimulation); (v) ≥3 days after the cessation of DBS subsequent to 3 weeks of DBS; (vi) after 6 weeks of DBS; and (vii) 3 weeks after the cessation of DBS subsequent to 3 weeks of DBS. For details see Table 1 and Figure 4.

2.7. Apomorphine-Induced Rotation Test. For assessing drug-induced locomotor function, apomorphine (0.25 mg/kg body weight dissolved in saline) was injected subcutaneously. Rotation was quantified in a custom-made "rodent-rotometer" modified according to Ungerstedt and Arbuthnott [44]. The rate of pathological circling, in rotations per minute (rpm), contralateral to the 6-OHDA-lesion site was determined electronically over 40 min. Rotation counts of at least 2 rpm indicated successful lesions. Subsequently, animals were assigned to groups such that the groups were composed of rats that had approximately the same mean rotation values. The rotation tests were repeated after one day because the first apomorphine application did not usually result in the maximum response.

2.8. Stepping Test. The stepping test, which assesses forelimb akinesia, was essentially performed as described by Olsson et al. [45]. In brief, rats were set on a table and allowed to settle with all limbs on the table. The experimenter then lifted the lower body by grabbing the rat around neck and behind the forepaws in a way that only the forepaws were touching the

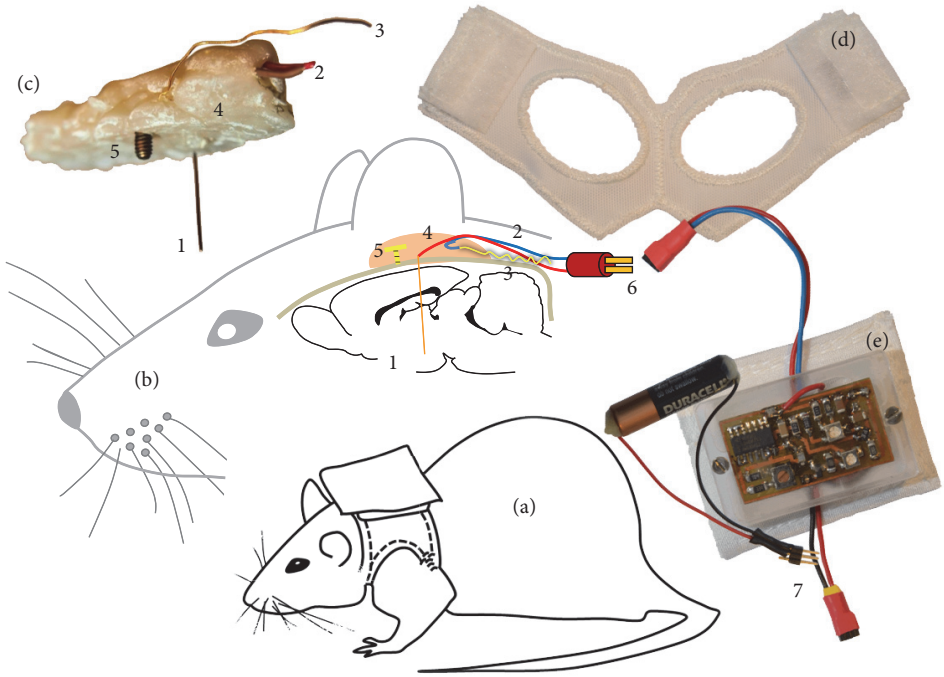
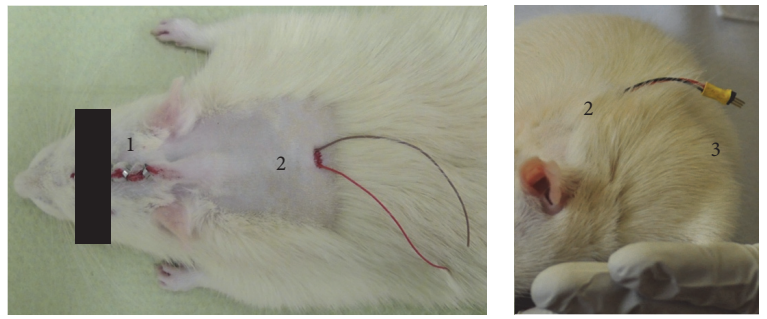


Figure 2: Schematic views of the unipolar DBS rat model. (a) Rat with stimulator in backpack; (b) sagittal view illustrating the locations of the implanted unipolar DBS electrode; (c) image of an explanted DBS mounting; (d) backpack vest with Velcro hooks; (e) stimulator in PMMA housing with pocket and current-pulse battery. 1: unipolar Pt/Ir electrode; 2: electrode cables; 3: gold-wire counter electrode; 4: biocompatible dental acrylic embedding all components; 5: anchor screw to fix the acrylic mounting to the skull; 6: electrode connector; 7: current-pulse battery connector.



(a) (b)

Figure 3: (a) Details of the outlet port for the subcutaneous cables centered at the dorsum. (b) Rat with electrode connector one week after surgery. 1: suture clips; 2: dorsal cable outlet port; 3: crimped plug connector.

Table 1: Experimental design. The number of rats refers to the group sizes at the time of the apomorphine-induced rotation tests.

Group name	6-OHDA lesion	Electrode	DBS duration	Number of animals
Naive_3 d/3 w	–	—	—	10
Naive_sham_3 w	–	Bipolar	—	9
6-OHDA_sham_3 d/3 w	+	Bipolar	—	7
Sham_bi_3 d	Sham	Bipolar	3 days	9
Sham_bi_3 w	Sham	Bipolar	3 weeks	10
Sham_uni_6 w	Sham	Unipolar	6 weeks	7
6-OHDA_bi_3 d	+	Bipolar	3 days	7
6-OHDA_bi_3 w	+	Bipolar	3 weeks	5
6-OHDA_uni_3 d	+	Unipolar	3 days	13
6-OHDA_uni_3 w/3 w + 3 d off	+	Unipolar	3 weeks	11
6-OHDA_uni_6 w	+	Unipolar	6 weeks	7
6-OHDA_uni_3 w + 3 w off	+	Unipolar	3 weeks	8

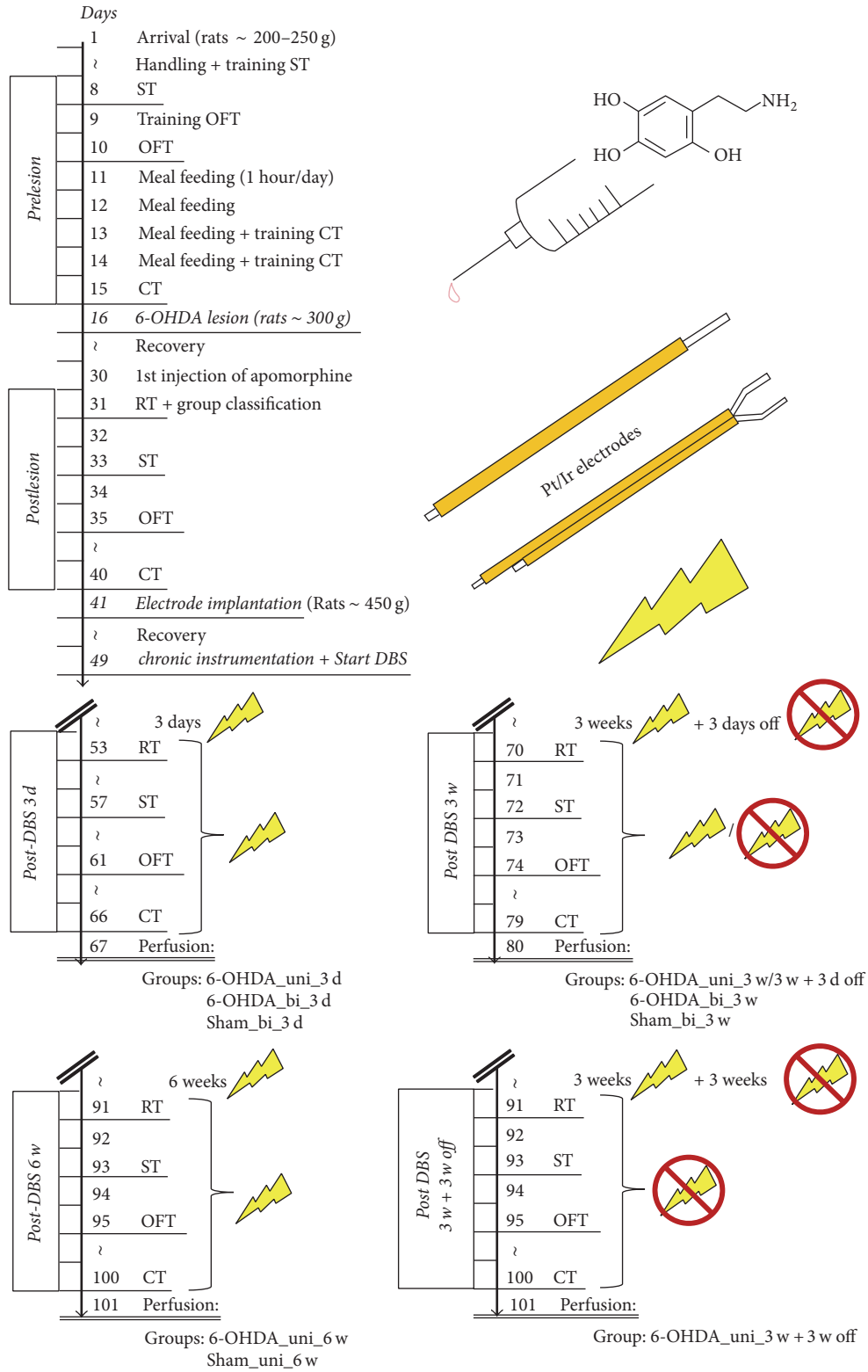


Figure 4: Schedules of the test procedures. RT, ST, OFT, and CT refer to the rotation, stepping, open field, and corridor tests, respectively.

table. Then, one forepaw was restrained, and the free forepaw, which was still touching the table, was moved sideways at a steady pace along the table surface in both directions at a rate of approximately 1 m per 5 s. The number of adjusting steps was counted manually for the movement of both forepaws in the forehand and backhand directions. For both directions, the contralateral bias was calculated as the percentage of steps of the contralateral paw with respect to the sum of the steps of both forepaws (50% was expected for control). In addition, the time needed for the initiation of the first adjusting step toward the rats' home cage was recorded for both forepaws. In the cases of an immediate response (i.e., when the initiation time was too short to be registered manually), the time was recorded as zero.

2.9. Corridor Test. To assess sensorimotor neglect, we used the corridor test [46]. A long narrow wooden corridor (240 cm long, 7 cm wide, and 23 cm high) was equipped with 14 equidistant pairs of adjacent pots (diameter: 1.2 cm) placed along both sides of the corridor. Each pot contained five sucrose reward tablets (5TUT; TestDiet®, USA). The clear plastic lid of the corridor allowed us to observe the rats during testing. Before the tests, rats were food-restricted with only 1 hour per day allowed for feeding ("meal feeding") for 4 days. Two tests were performed on two consecutive days under the same conditions. The trials started with placing the rat into one end of the corridor, where it was free to explore, turn around, and feed on pellets. One "retrieval" was counted when the animal poked its nose into a pot with sugar pellets, regardless of whether it actually retrieved or fed on any pellets. The exploration of each new pot was counted as an additional retrieval. To reduce exploration behavior of the corridor itself, rats were placed into an identical, empty corridor beforehand. The number of retrievals ipsilateral and contralateral to the side of the lesion were recorded manually over 5 min. The contralateral bias was expressed as the percentage of the retrievals made on the contralateral side relative to the total number of retrievals.

2.10. Open Field Test. Spontaneous mobility and anxiety were evaluated by placing the rats in a square open field arena (46 cm × 45 cm) inside an isolation box. The animals were kept in the dark in the examination room 1 h before the start of the test. The open field was illuminated by a white photo bulb providing 200 to 250 Lux. During testing, rats were monitored by a video camera. The open field was divided into a center area (22 cm × 22 cm) and a peripheral zone using the tracking software Ethovision XT (Noldus Information Technology, Leesburg, VA, USA; RRID:SCR_000441). This allowed for the automatic recording of the rat's movement in the two zones. Each rat was tested once for 10 minutes. After each session, the open field was cleaned to prevent odor from influencing the next animal's behavior. The total migration distances were taken as a measure of spontaneous mobility and the ratio of the migration distance within the center area to the total distance moved was interpreted as a measure of anxiety.

2.11. Statistics. Data analysis was conducted with the SAS software package, Version 9.4 for Windows (Copyright, SAS Institute Inc., Cary, NC, USA, RRID:SCR_008567). Descriptive statistics and tests for normality were calculated with the UNIVARIATE procedure using Base SAS software. Data that could be considered as approximately normal was analyzed by one-way repeated measurement ANOVA with the MIXED procedure of the SAS/STAT software module. The models for the investigated treatments contained the fixed factor "time" with different levels (prelesion, postlesion, 3 d, 3 w, 3 w + 3 d, and 6 w) for each treatment. Repeated measures on the same animal were taken into account in the REPEATED statement of the MIXED procedure using time as the repeated effect, the SUBJECT = animal option to define the blocks of the residual covariance matrix and the TYPE = CS option to define their covariance structure. Least-square means (LSM) and their standard errors (SE) were computed for each time level of each treatment and compared with the "postlesion"-LSM using the Dunnett-Hsu procedure (pairwise multiple comparisons with the control).

The investigated treatments for each time (prelesion, postlesion, 3 d, 3 w, 3 w + 3 d, and 6 w) were analyzed by one-way ANOVA with the MIXED procedure of the SAS/STAT software module. The models for the times contained the fixed factor treatment (see Table 1). LSM and their SE were computed for each treatment level of each time and were compared pairwise using the Tukey-Kramer procedure (pairwise multiple comparisons of all possible pairs). Effects and differences were considered significant for $p \leq 0.05$.

3. Results

3.1. Confirmation of Electrode Placement. The localization of electrode tips in the STN was evaluated by retrospective analyses of Nissl-stained cryosections of the STN of selected rats. It suggested a precise electrode placement in approximately 75% of the cases, analogous to the success rate of the lesion surgery (see below). A comprehensive histological evaluation is currently underway.

3.2. Locomotor Activity. The success of lesion induction was evaluated based on the apomorphine-induced rotation test results 12–14 days after surgery. The success rate (rpm ≥ 2) was approximately 75%, and the mortality rate was less than 10%. In the apomorphine-induced rotation test, reduced rotation was detected with DBS after 3 days and after 3 weeks. In these cases, unipolar stimulation was more effective than bipolar stimulation (Figure 5). However, after 6 weeks, pathological rotation was detected again, regardless of whether the DBS had been continued or discontinued after 3 weeks. As expected, no pathological rotation was detected in naïve or sham-lesioned rats.

Spontaneous locomotor activity was assessed based on the total migration distance in the open field test. 6-OHDA lesions reduced the total migration distance, whereas naïve rats showed a marginal increase in total distance with each trial, which can be explained by habituation to the open

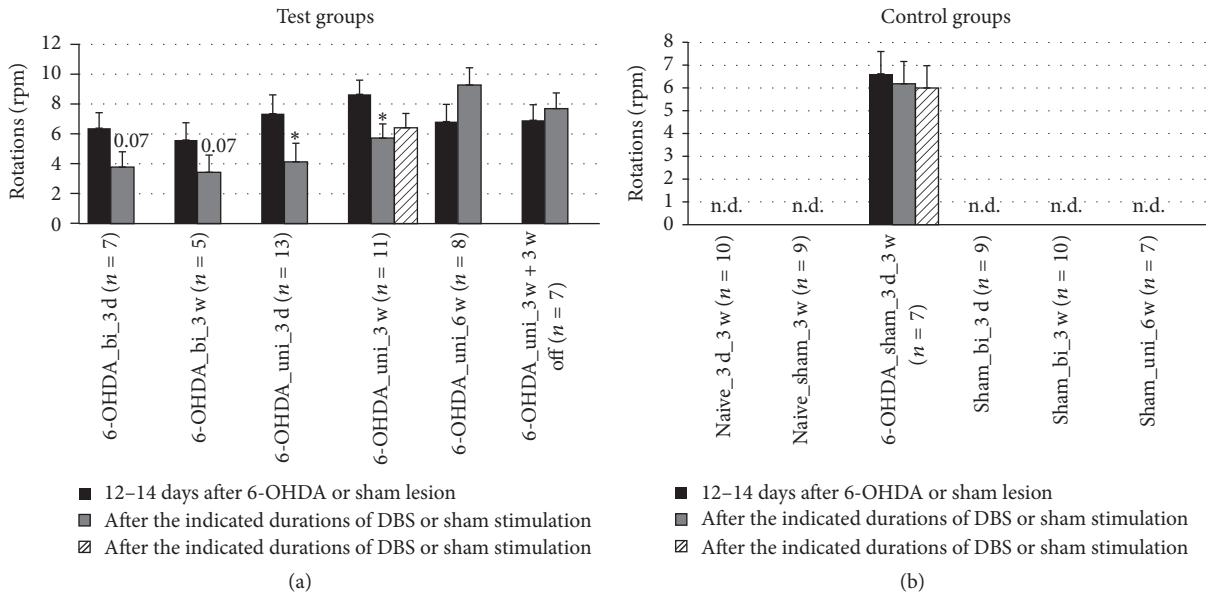


Figure 5: Short-term and long-term effects of DBS with uni- and bipolar electrodes on the apomorphine-induced rotation behavior of hemiparkinsonian rats. (a) and (b) refer to test groups and controls, respectively. Different column patterns indicate the different times of behavioral testing; black: 12–14 days after 6-OHDA or sham lesion; gray and hatched: after the durations of DBS or sham stimulation indicated in the group labels. For experimental details see Table 1. Significance levels are indicated with asterisks as follows: $^{*}p \leq 0.05$, b (borderline): $0.05 < p \leq 0.08$ according to one-way ANOVA. Asterisks refer to comparisons with corresponding black columns.

field with repeated exposure. In contrast, DBS reduced the total migration distance, in most of the groups. The total migration distance increased at 3 days after the cessation of DBS subsequent to 3 weeks of DBS with unipolar electrodes (Figure 11).

3.3. Akinesia. To assess the effects of the lesion-induced akinesia, the parameters "initiation time of paw movement" and "number of adjusting steps" were recorded in the stepping test. In rats receiving bipolar DBS, a significant reduction in the initiation time of contralateral forepaw stepping was observed after 3 days but not after 3 weeks of DBS (Figure 6). In long-term, unipolar DBS, significant improvements were found 3 weeks after the cessation of DBS subsequent to 3 weeks of DBS. A similar effect was observed after 6 weeks of continuous stimulation, although with borderline significance.

Unexpectedly, we observed an increase in the initiation time of ipsilateral forepaw stepping after 6-OHDA lesioning in one group and no beneficial effect of DBS in any of the groups. Moreover, we found an aggravating effect of DBS effect after 3 weeks that vanished 3 days after the cessation of DBS (Figure 7).

Impaired contralateral paw movement (contralateral bias) was determined based on the number of contralateral versus ipsilateral adjusting steps of the forepaws. A significant difference in the contralateral bias during forced sidestepping was found in only one case. The contralateral bias in the forehand direction worsened after 6 weeks of unipolar DBS (Figure 8). In the backhand direction, no significant effects of DBS were detected (Figure 9). Overall, the contralateral bias measured in the stepping test did not seem to be affected by DBS therapy (Table 2).

3.4. Sensorimotor Neglect. In the corridor test, DBS reduced the amount of sensorimotor neglect when applied by unipolar electrodes for 3 weeks (Figure 10). The beneficial effect persisted for at least 3 weeks after the cessation of DBS, although with borderline significance. Interestingly, 6 weeks of continuous DBS did not demonstrate the same beneficial effect, and DBS with bipolar electrodes did not show any significant beneficial effects.

3.5. Anxiety. The open field test provided information on locomotor activity and anxiety-like behavior. Although the total distance moved (Figure 11) was determined by both locomotor function and anxiety, the ratio of distances (central versus peripheral movement) predominantly reflects anxiety. In untreated naïve rats, the distance ratio generally increased with time, indicating a habituation effect, and sham DBS-treated naïve rats and DBS-treated sham-lesioned rats retained this behavior (Figure 12). However, the distance ratio significantly increased in the groups treated by DBS with unipolar electrodes after 3 or 6 weeks, but not after 3 days. In contrast, the distance ratio was increased in the groups treated by DBS with bipolar electrodes after 3 days, but not after 3 weeks. A minor increase ($p = 0.053$) in the distance ratio was also observed after 6 weeks of sham stimulation with unipolar electrodes.

Table 2 summarizes the test results for DBS-induced parameter changes.

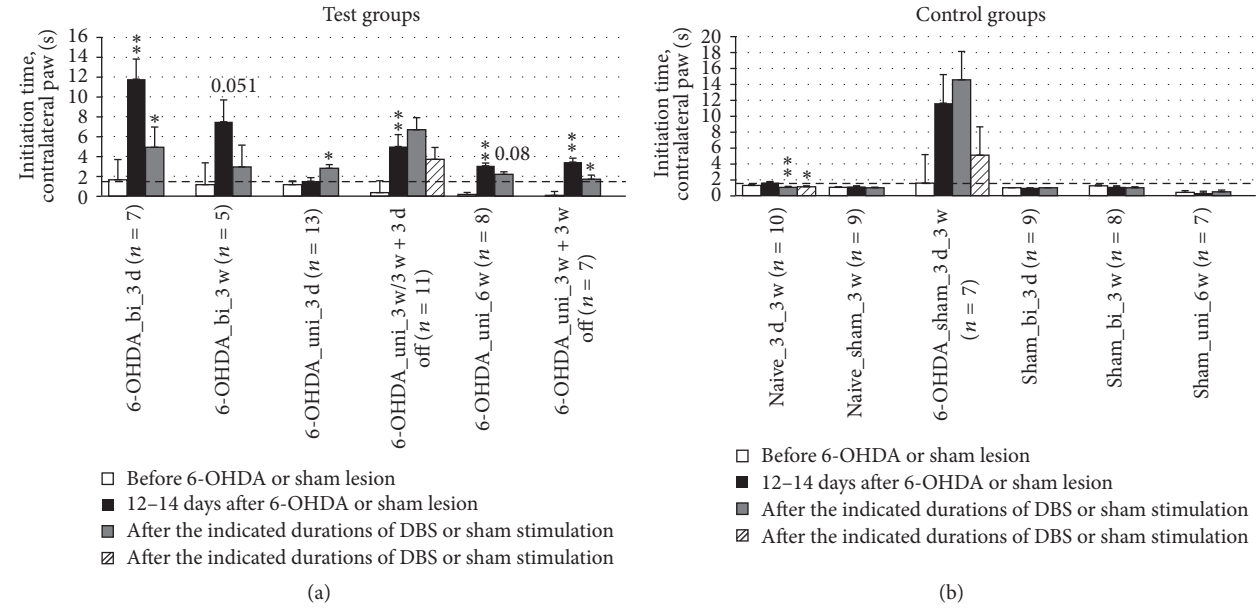


Figure 6: Short-term and long-term effects of DBS with uni- and bipolar electrodes on akinesia as measured by the initiation time of the first adjusting step of the contralateral forepaw in the stepping test. (a) and (b) refer to test groups and controls, respectively. The dashed line at 1 s allows for an easier comparison with Figure 7 and between (a) and (b). Different column patterns indicate different times of behavioral testing; white: before 6-OHDA or sham lesion; black: 12–14 days after 6-OHDA or sham lesion; gray and hatched: after the durations of DBS or sham stimulation indicated in the group labels. For experimental details see Table 1. Significance levels are indicated with asterisks as follows: $^{**}p \leq 0.01$, $^{*}p \leq 0.05$, b (borderline): $0.05 < p \leq 0.08$ according to one-way ANOVA. Asterisks above black columns refer to white columns; all others refer to black columns.

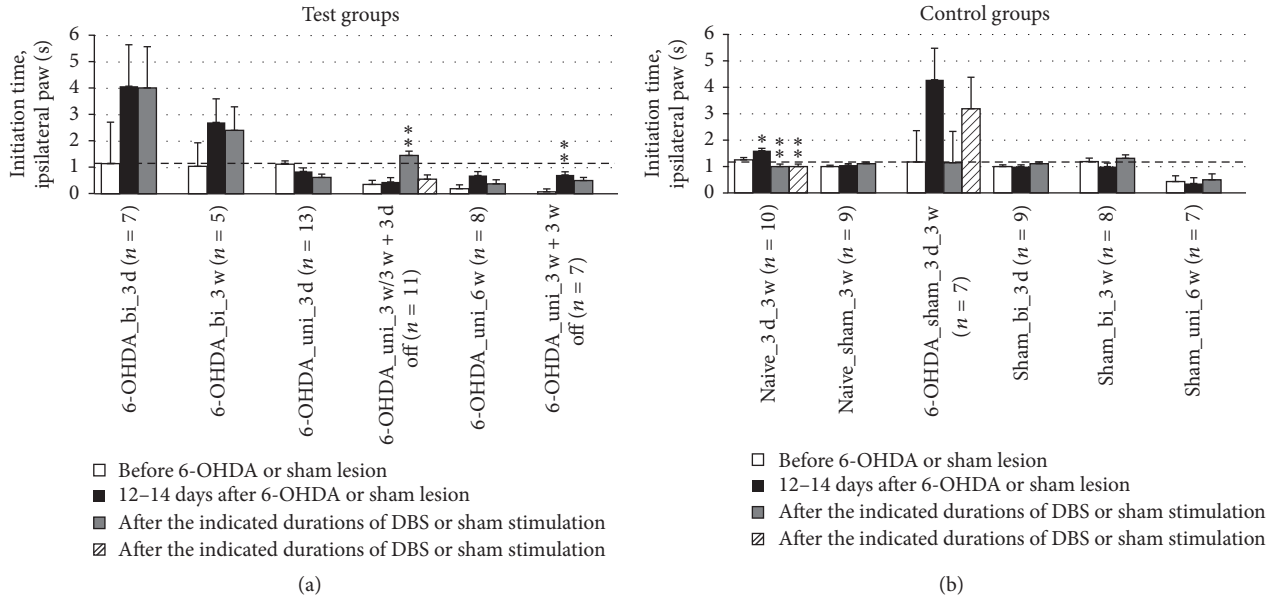


Figure 7: Short-term and long-term effects of DBS with uni- and bipolar electrodes on the akinesia of hemiparkinsonian rats as measured by the initiation time of the first adjusting step of the ipsilateral forepaw in the stepping test. (a) and (b) refer to test groups and controls, respectively. The dashed line at 1 s allows for an easier comparison with Figure 6 and between (a) and (b). Different column patterns indicate different times of behavioral testing; white: before 6-OHDA or sham lesion; black: 12–14 days after 6-OHDA or sham lesion; gray and hatched: after the durations of DBS or sham stimulation indicated in the group labels. For experimental details see Table 1. Significance levels are indicated with asterisks as follows: $^{**}p \leq 0.01$, $^{*}p \leq 0.05$, b (borderline): $0.05 < p \leq 0.08$ according to one-way ANOVA. Asterisks above black columns refer to white columns; all others refer to black columns.

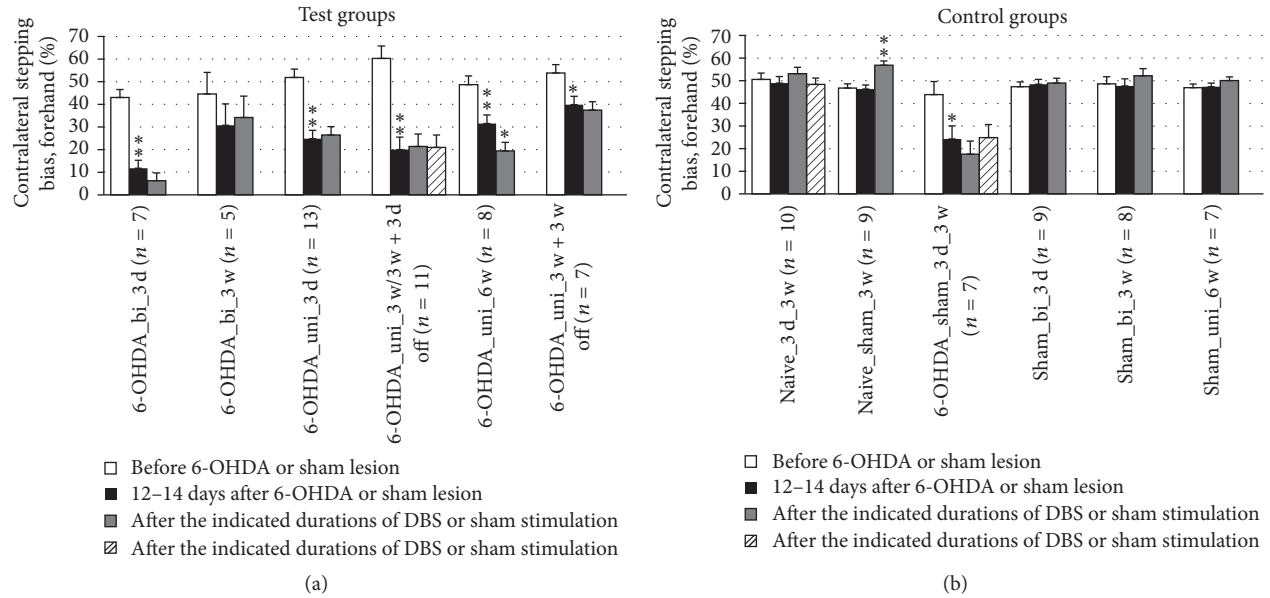


Figure 8: Short-term and long-term effects of DBS with uni- and bipolar electrodes on akinesia as measured by forced sidestepping of the forepaws in the forehand direction in the stepping tests. (a) and (b) refer to test groups and controls, respectively. Different column patterns indicate different times of behavioral testing; white: before 6-OHDA or sham lesion; black: 12–14 days after 6-OHDA or sham lesion; gray and hatched: after the durations of DBS or sham stimulation indicated in the group labels. For experimental details see Table 1. Significance levels are indicated with asterisks as follows: $^{**}p \leq 0.01$, $^{*}p \leq 0.05$, b (borderline): $0.05 < p \leq 0.08$ according to one-way ANOVA. Asterisks above black columns refer to white columns; all others refer to black columns.

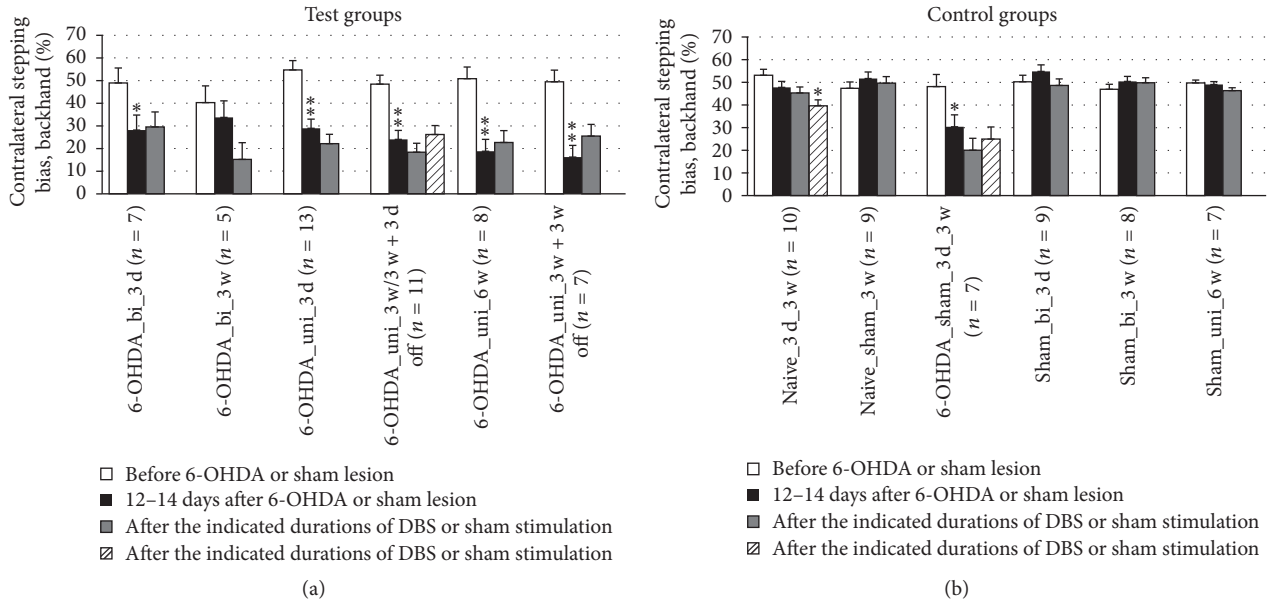


Figure 9: Short-term and long-term effects of DBS with uni- and bipolar electrodes on the akinesia of hemiparkinsonian rats as measured by forced sidestepping of the forepaws in the backhand direction in the stepping tests. (a) and (b) refer to test groups and controls, respectively. Different column patterns indicate different times of behavioral testing; white: before 6-OHDA or sham lesion; black: 12–14 days after 6-OHDA or sham lesion; gray and hatched: after the durations of DBS or sham stimulation indicated in the group labels. For experimental details see Table 1. Significance levels are indicated with asterisks as follows: $^{**}p \leq 0.01$, $^{*}p \leq 0.05$, b (borderline): $0.05 < p \leq 0.08$ according to one-way ANOVA. Asterisks above black columns refer to white columns; all others refer to black columns.

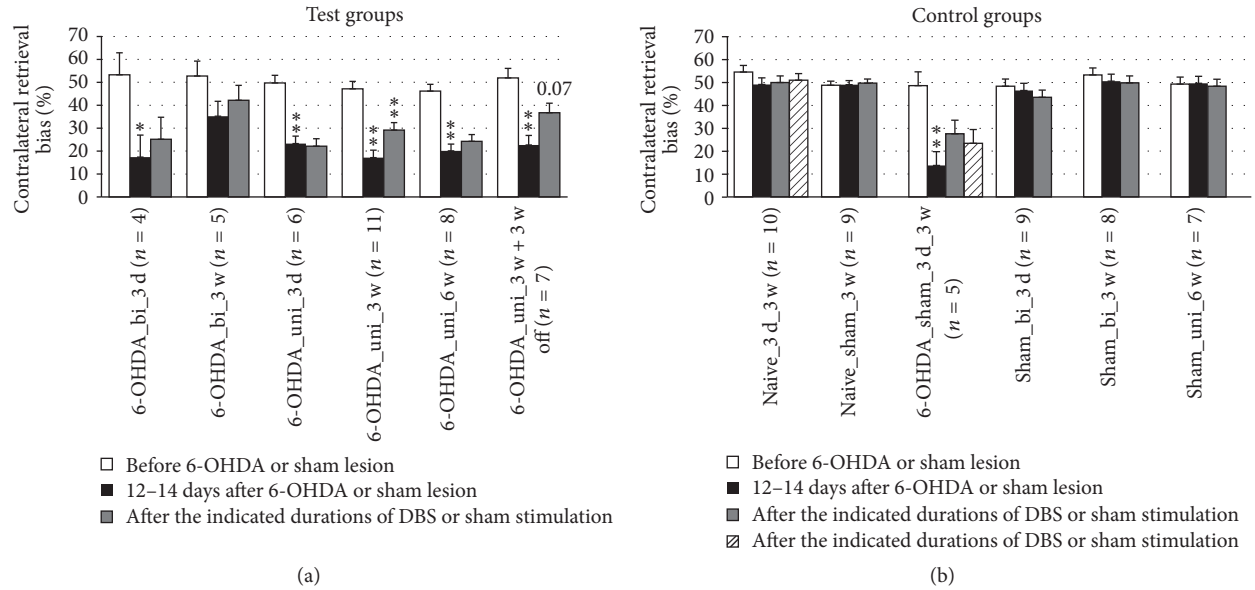


Figure 10: Short-term and long-term effects of DBS with uni- and bipolar electrodes on the sensorimotor neglect of hemiparkinsonian rats as measured by the corridor test. (a) and (b) refer to test groups and controls, respectively. Different column patterns indicate different times of behavioral testing; white: before 6-OHDA or sham lesion; black: 12–14 days after 6-OHDA or sham lesion; gray and hatched: after the durations of DBS or sham stimulation indicated in the group labels. For experimental details see Table 1. Significance levels are indicated with asterisks as follows: $^{**}p \leq 0.01$, $^{*}p \leq 0.05$, b (borderline): $0.05 < p \leq 0.08$ according to one-way ANOVA. Asterisks above black columns refer to white columns; all others refer to black columns.

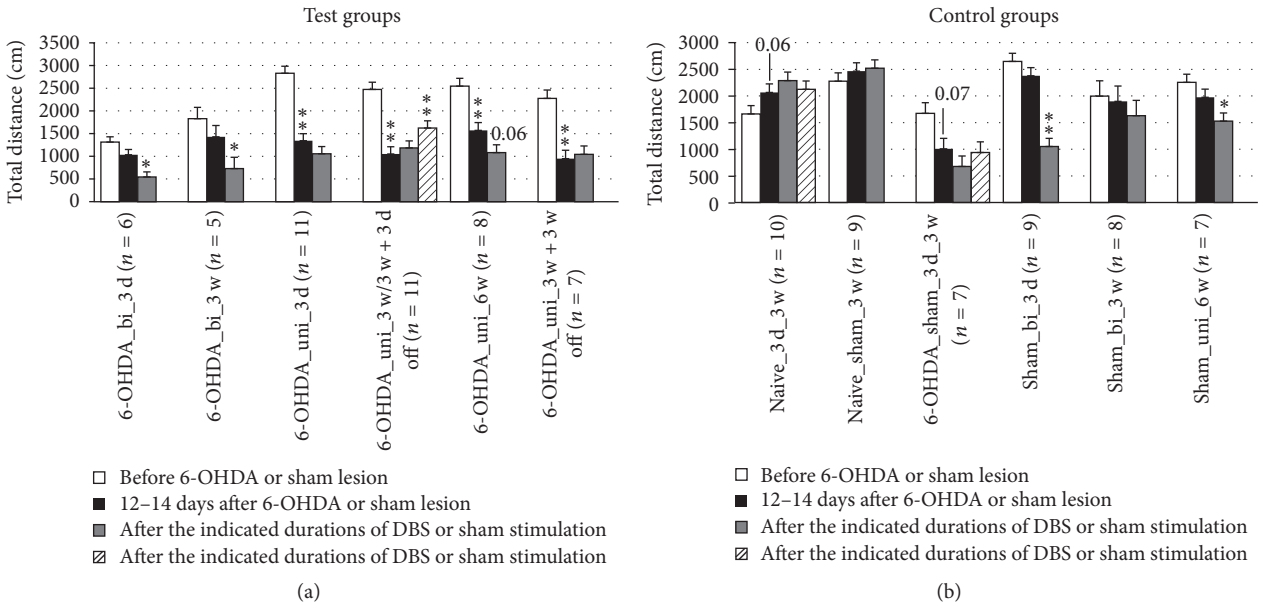


Figure 11: Short-term and long-term effects of DBS with uni- and bipolar electrodes on the locomotor activity of hemiparkinsonian rats as measured by the total migration distance in the open field. (a) and (b) refer to test groups and controls, respectively. Different column patterns indicate different times of behavioral testing; white: before 6-OHDA or sham lesion; black: 12–14 days after 6-OHDA or sham lesion; gray and hatched: after the durations of DBS or sham stimulation indicated in the group labels. For experimental details see Table 1. Significance levels are indicated with asterisks as follows: $^{**}p \leq 0.01$, $^{*}p \leq 0.05$, b (borderline): $0.05 < p \leq 0.08$ according to one-way ANOVA. Asterisks above black columns refer to white columns; all others refer to black columns.

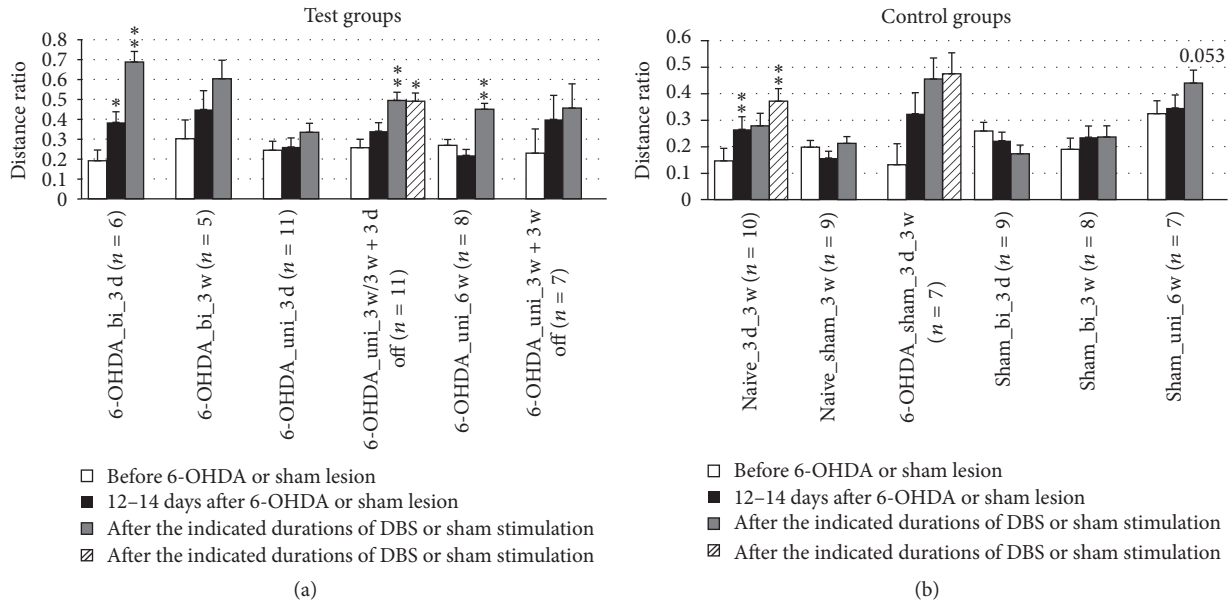


Figure 12: Short-term and long-term effects of DBS with uni- and bipolar electrodes on the anxiety-like behavior (b) of hemiparkinsonian rats as measured by the ratio: migration distance in the center/total migration in the open field. (a) and (b) refer to test groups and controls, respectively. Different column patterns indicate different times of behavioral testing; white: before 6-OHDA or sham lesion; black: 12–14 days after 6-OHDA or sham lesion; gray and hatched: after the durations of DBS or sham stimulation indicated in the group labels. For experimental details see Table 1. Significance levels are indicated with asterisks as follows: $^{**}p \leq 0.01$, $^{*}p \leq 0.05$, b (borderline): $0.05 < p \leq 0.08$ according to one-way ANOVA. Asterisks above black columns refer to white columns; all others refer to black columns.

Table 2: Summary of test results. The improvement and worsening of lesion-induced parkinsonian symptoms by DBS are marked by (+) and (−), respectively. Borderline changes ($0.05 < p \leq 0.08$) are marked by (b); parameters with no detectable DBS effects are marked (0); n.d. stands for "not determined." The results marked with an asterisk could not be interpreted in terms of the therapeutic DBS effects.

Group name	Rotation test	Stepping test initiation time	Stepping test contralateral bias		Corridor test	Open-field test	
		Contralateral paw	Forehand	Backhand		Total distance	Distance ratio*
6-OHDA_bi_3 d	b+	+	0	0	0	—	Up
6-OHDA_bi_3 w	b+	b+	0	0	0	—	0
6-OHDA_uni_ 3 d	+	b−	0	0	0	—	0
6-OHDA_uni_ 3 w	+	0	0	0	+	0	Up
6-OHDA_uni_ 3 w + 3 d off	0	0	0	0	n.d.	+	Up
6-OHDA_uni_ 6 w	0	b+	—	0	0	b−	Up
6-OHDA_uni_ 3 w + 3 w off	0	+	0	0	b+	0	0

4. Discussion

4.1. The Hemiparkinsonian Rat Model. The 6-OHDA-induced hemiparkinsonian rat model has been established for the study of therapeutic approaches for treating PD [11, 35, 49–51]. Although this model is known to reflect the major behavioral impairments that are characteristic of PD patients, animal studies are hampered by restrictions on free movement and/or invasive surgery and by short observation periods lasting from a few minutes [35, 49, 51–54] to a number of days [12, 24, 55–57]. To our knowledge, removable and reusable devices have been previously used by only Forni et al. [28].

Frequencies from 90 to 130 Hz are generally accepted as optimal to elicit the therapeutic effects of DBS in patients [52]. In this frequency range, the clinically observed benefits are maximal and a more normal activity pattern in the nuclei downstream is restored [22]. Recent findings in patients with advanced PD who became refractory to the common high-frequency stimulation have shown a restoration in the improvement of segmental and axial symptoms, gait disturbance, and levodopa-induced dyskinesia after the stimulation frequency was reduced to 60 Hz [58]. Here, we used a pulse frequency of 130 Hz in all experiments, even though this frequency was established for DBS in the much larger human brain.

In PD patients, unipolar stimulation is the preferred mode of DBS. So et al. [51] have also suggested using unipolar stimulation in the hemiparkinsonian rat model, although they did not find differences between the effects of uni- and bipolar stimulations in a drug-induced locomotor test. Our first experiments (up to 3 weeks) revealed greater beneficial effects with unipolar DBS than with bipolar DBS. For these reasons, only the unipolar experiments were extended out to 6 weeks (Figure 4).

4.2. The Outcome of the Different Behavioral Tests. To test the success of lesioning and test initial locomotor function, the classical drug-induced rotation assay was used. Pathological rotation is measured in response to the administration of either the dopamine (DA) receptor agonist apomorphine or the DA-releasing drug amphetamine [43, 44, 59, 60].

In partially lesioned animals, Hefti et al. [59] did not find apomorphine-induced rotation, whereas amphetamine induced a dose-dependent ipsilateral rotation. These authors observed a contralateral apomorphine-induced rotation only in severely lesioned animals, which is comparable to our results. These findings are in line with the results of Da Cunha et al. [60], who investigated the directions of rotation that were induced by either apomorphine or amphetamine in partially and severely lesioned animals. In severely 6-OHDA-lesioned mice, apomorphine-induced rotation was shown to be more informative than amphetamine-induced rotation in discriminating between the different degrees of lesions [61].

Interestingly, we found a reduction in apomorphine-induced rotation if DBS was applied for 3 days or 3 weeks in either the bipolar or unipolar modes, with the latter being more effective (Figure 5; Table 2). Apomorphine-induced rotation returned to pre-DBS levels after 6 weeks of continuous DBS or after 3 weeks of continuous DBS followed by 3 weeks without DBS. As discussed below, STN-DBS-induced therapeutic effects are not predicted to be reflected in the rate of apomorphine-induced rotation. Therefore, the reason for the reduction in apomorphine-induced rotation after 3 weeks of DBS was unclear. This effect was not surgery-induced because it did not occur in the 6-OHDA-lesioned sham-stimulated rats. Assuming that STN-DBS temporarily increases striatal DA turnover, as described by Meissner et al. [50], the hypersensitivity of DA receptors could be transiently reduced at a time scale of weeks. We assume that this effect was not permanent in our model because it is known that the dopaminergic neurons in the substantia nigra pars compacta (SNc) eventually degenerate leading to an almost complete lack of DA release in the striatum.

We believe that apomorphine-induced rotation is not an appropriate parameter for testing the beneficial effects of STN-DBS. Limitations of the apomorphine-induced rotation test have been previously demonstrated. Metz and Whishaw [62] have shown that the apomorphine-induced rotation rate did not correlate with spontaneous and skilled reaching or ladder rung walking tasks. In a study on apomorphine-induced rotation, Chang et al. [63] failed to demonstrate any effect of STN-DBS in 6-OHDA-induced hemiparkinsonian rats. They concluded that the apomorphine-induced imbalance of dopaminergic activation may not necessarily be improved by DBS. In contrast, STN-DBS has been shown to reduce or even reverse the direction of amphetamine-induced rotation in 6-OHDA-lesioned rats [11, 35, 49, 51]. Nevertheless, the amphetamine-induced rotation test has its limitations. Kirik et al. [64] showed that the test for the initiation time in stepping was a more sensitive metric than the amphetamine-induced rotation test. Because of these limitations, some authors have introduced new methods to evaluate the effect of DBS, such as an automated rotarod method for the drug-free quantitative evaluation of overall motor deficits [65].

Additionally, our results showing that a reduction of the initiation time of the contralateral forepaw was induced by DBS were not consistent with the results of the rotation test with unipolar stimulation. The shortest initiation times of the contralateral paw were observed 3 weeks after the cessation of DBS subsequent to 3 weeks of continuous DBS (Figure 6; Table 2). Our histological investigations showed that dopaminergic neurons were not regenerated in the substantia nigra (results not published). This suggests that the persistent DBS effects might be related to the neuronal plasticity in young rats. The increase of the initiation time of the ipsilateral paw after 6-OHDA lesion was much less than the increase on the contralateral side. However, this result did show that both hemispheres are affected by unilateral 6-OHDA lesion, as we have previously shown for the activation of astrocytes in the contralateral striatum after 6-OHDA lesion [66].

Locomotor activity changes detected in the open field test should be interpreted with caution as they may be influenced by various modifying factors, including habituation, the need for exploration, and anxiety effects. Indeed, we observed a habituation to the open field in naïve rats in both the total migration distance and in the anxiety parameter distance ratio. Lesions induced a reduction in locomotor activity, as measured by total migration distance. DBS induced a further decrease, even in sham-lesioned rats (Figure 11; Table 2). This additional decrease was reversed after the cessation of DBS and did not occur in sham-stimulated rats. We interpret the DBS-induced decrease in locomotor activity as a reduction in the health of the animals caused by the electrical stimulation. These results indicate that stimulation parameters have to be reconsidered in future experiments.

In PD patients, anxiety may result from not only the impairment of motor function but also dysfunction of the STN. Experiments with bilaterally STN-lesioned rats in the elevated plus maze test also suggest such a connection [67]. Here, we assessed anxiety-like behavior using the open field parameter "ratio of migration distance in the center to total migration." This parameter quantifies the balance between the need of the animal to explore their environment with the need to be cautious, which prevents them from exploring the unprotected center of a brightly lit open field box. In our setting, naïve rats became more curious and less anxious over time due to habituation. Likewise, the decrease in anxiety-like behavior by 6-OHDA-lesioned rats can be explained by habituation to the open field (Figure 12). Based on these results, the

increasing distance ratio observed after DBS may not be an effect of DBS but rather an effect of habituation. In contrast, the distance ratio of sham-lesioned rats and sham-stimulated naïve rats (i.e., healthy rats with disconnected electrodes) remained at their initial levels. The reduced activity of the rats after electrode implantation suggests adverse effects of the surgery itself and a treatment-related reduction in the rats' health.

The corridor test was originally established to detect lateralized sensorimotor integration [61]. It has been successfully applied to demonstrate the feasibility of the thalamic center-median parafascicular nucleus as a target for DBS in 6-OHDA-lesioned rats [55, 68]. In our study, 3 weeks of STN-DBS with unipolar electrodes reduced sensorimotor neglect. After the cessation of DBS, this effect persisted with borderline significance for at least 3 more weeks (Figure 10). Six weeks of continuous DBS did not have the same beneficial effect.

These findings raise questions about whether different mechanisms are responsible for the observed effects of acute and chronic DBS, as well as about the persistent effects on locomotor and sensorimotor functions. One possible reason for these differences may be the development of an insensitivity toward DBS, reflecting changes in the basal ganglia network [22]. In addition, readjustment of the stimulation parameters may be necessary in chronic DBS, as is common in clinical practice, to compensate for the increasing impedance caused by the development of adventitia tissue at the electrode-tissue interface [69].

Here, we propose that tests of spontaneous locomotion, such as the stepping test, are more relevant for detecting the beneficial effects of DBS and provide different information than the apomorphine-induced rotation test. However, this conclusion does not necessarily apply to the amphetamine-induced rotation test because of the different mechanisms of these two rotation tests (see Appendix).

Our results suggest that persistent DBS effects in 6-OHDA-lesioned neuronal networks may be the result of the protection or regeneration of part of the physiological function of these networks in relation to locomotor activity in the absence of dopaminergic neurons. Alternatively, persistent effects of DBS could arise from DBS-induced effects that mimic a permanent lesion of the STN, for example, by space-consuming effects of the developing adventitia. Such mechanisms may explain our findings of persistent DBS effects on the initiation time of the contralateral forepaw in the stepping test (Figure 6) and, though with borderline significance, on sensorimotor neglect in the corridor test (Figure 10). A DBS-induced "mimicked" STN lesion would be in agreement with the lack of beneficial effects demonstrated in the open field behavior.

The different brain states and resulting behavioral effects are considered in Appendix. Figure 13 illustrates four different brain states in a single scheme of the lesioned hemisphere in the hemiparkinsonian rat: the healthy brain, the effects of a lesion, DBS after lesioning, and apomorphine administration after lesioning.

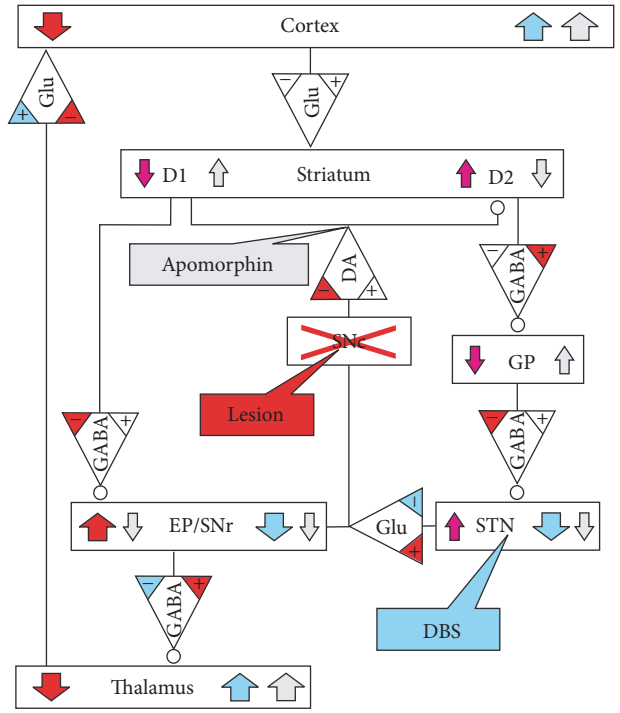


Figure 13: Simplified scheme of the lesioned hemisphere describing the effects of the lesion (red), DBS (blue), and apomorphine administration (light gray) on neurotransmitter release and on the activity (colored arrows) of different brain areas. Induced alterations in receptor numbers or sensitivities are not depicted; for explanation see Appendix. The brain areas are given in the boxes designated by SNc, GP, STN, and EP/SNr. The neurotransmitters glutamate (Glu), DA, and GABA are designated by triangular boxes pointing toward the affected brain areas that may be either excited (direct line input) or downregulated (input with circle). D1 and D2 stand for the dopaminergic receptors in the striatum, which are excited or inhibited by DA or apomorphine, respectively. Rectangular text balloons mark the input sites of lesioning, DBS, and apomorphine. The colored "+" and "−" signs in the neurotransmitter triangles designate the effects of lesioning (red) and DBS (blue) on transmitter release. Color-coding was not attempted for the effects of apomorphine on transmitter release.

4.3. Effects at the Molecular and Receptor Levels. Based on previous studies, apparently contradictory results have been obtained at both the molecular and receptor levels. The DBS-related decreases in the levels of extracellular DA and its metabolites in the dorsal part of the striatum described by Walker et al. [70] are in line with a decreased concentration of the DA metabolite DOPAC (3-4-dihydroxyphenylacetic acid) in the extracellular fluid of the striatum found by Yamamoto et al. [71]. In contrast, He et al. [72] described a DBS-induced increase in the extracellular striatal DA concentration. Recently, GABAergic activation by chronic DBS has been shown to be responsible for the compensation of motor asymmetries in hemiparkinsonian rats [73].

At the level of the receptors, missing neurotransmitter inputs are believed to induce a compensatory upregulation of receptor numbers or sensitivity. According to this view,

a lesion-induced reduction in glutamate release to the cortex and the striatum resulting from alterations in activity along the striatum-D1 receptor-EP/SNr-thalamus pathway will result in an upregulation in glutamate receptors in the cortex and striatum. However, DBS after lesioning was found to reverse the increased striatal glutamate receptor numbers [57] and to increase the number of D1 receptors, which probably improves motor symptoms in PD patients [74]. At the same time, DBS decreases the number of D2/D3 receptors in the nucleus accumbens of rats, which may contribute to adverse DBS-induced neuropsychiatric side effects, such as apathy [74].

Most biochemical studies have been conducted under acute or subchronic (up to 7 days) STN-DBS. However, a deeper insight into the DBS-mechanisms and its long-term or persistent effects (≥6 weeks) require animal models that are suitable for combining biochemical, electrophysiological, optical microscopy, and other imaging methods, along with behavioral testing.

5. Conclusion and Outlook

To our knowledge, we present the first behavioral investigation in freely moving rats with chronic instrumentation for up to 6 weeks, which allowed the animals to adapt to the instrumentation and allowed us to conduct comparative behavioral tests at different times under acute DBS conditions and after the cessation of DBS. In our setup, we found unipolar stimulation to be more efficient for achieving several beneficial long-term DBS effects. In our tests of behavioral changes, the stepping and corridor tests were the most appropriate for the evaluation of DBS-induced locomotor and sensorimotor improvements. When DBS was stopped after 3 weeks, some effects persisted for at least 3 more weeks, such as the reduction of initiation time of the contralateral paw in the stepping test and the slight reduction of the contralateral bias in the corridor test. In contrast, performance in the apomorphine-induced rotation test showed no improvement after 6 weeks. Our findings may indicate a regeneration of neuronal circuits in the absence of dopaminergic neurons. This would make apomorphine-induced rotation a suitable test to determine the long-term success of 6-OHDA lesioning but not a very informative test for determining the beneficial effects of DBS. In interpreting anxiety-like behaviors, researchers must consider habituation effects in relation to the durations between test repetitions in both sham and experimental animals.

The determination of very fast reaction times was difficult. To improve the statistical power of these tests, a larger sample size should be combined with video detection of reaction times. Our model can be considered a versatile platform that allows for the independent testing of separate elements, such as electrodes and counter-electrodes. Relatively simple modifications to our model will allow for the testing of unexplored target regions in other neurodegenerative disorders.

In addition, various electrical parameters can be tested, such as stimulation frequency and signal shape. To our knowledge, no systematic investigations have been conducted on whether the frequencies applied to humans are suitable for use with much smaller animals. We believe that this topic needs further investigation, taking into account allometric effects for organisms with various brain sizes. Our results may help in developing a reduced set of test parameters to facilitate this research.

Major problem remains to be elucidated about the mechanism by which DBS acts. Although 6-OHDA lesioning induces PD-like symptoms, the long-term DBS effects in our model may be a result of the emergence of new or a strengthening of existing neuronal circuits that compensate for the absence of dopamine in the brains of young rats. This outcome may suggest that the DBS-related locomotor and sensorimotor improvements, with no detectable improvements in the results of the rotation test, indicate DBS effects in the activation of neuronal substitute circuits. If this hypothesis is supported by future research, investigations of the effects of stimulation may be helpful in other areas, such as stroke research.

Appendix

A Simplified Scheme of the Lesioned Hemisphere in the Hemiparkinsonian Rat

Figure 13 presents a simplified scheme of the lesioned hemisphere, illustrating different brain states, which are immediately induced by alterations in neurotransmitter release and in the activity of different brain areas. Long-term alterations in receptor numbers or sensitivities are not depicted. It should be noted that the scheme can attempt only a qualitative description of the separate effects. The interplay of the lesioned hemisphere with its nonlesioned counterpart must be considered to explain the overall effect, for example, the effect of amphetamine administration. The rotation effects may be explained by the assumption that the induced hyperactivation of the cortex of one hemisphere leads to a general pattern of muscle activation contralateral to the hyperactive side, which would result in a bending of the body toward this side and, subsequently, to rotation contralateral to the hyperactive hemisphere.

The depicted effects will, in principle, also apply when one of the successive treatments is omitted. Thus, the scheme allows for predicting multiple scenarios, such as the effects of DBS without a lesion or apomorphine administration without DBS. Nevertheless, the actual magnitudes of the combined effects on the activity of the various brain areas may vary significantly, leading to different individual responses. Short summaries of the different states illustrated by Figure 13 are given below.

Healthy Brain. No colors or arrows, which designate deviations from the normal brain activity, apply.

Lesion Effect. Obliteration of the SNc (red cross) stops DA input for D1 and D2 receptors in the striatum. Along the D1 pathway, the reduced GABAergic inhibition results in an increased activity of the entopeduncular nucleus/substantia nigra pars reticulata (EP/SNr). Along the D2 pathway, the

effect on the globus pallidus (GP) is inverse. The increased GABAergic inhibition of the GP leads to a reduced inhibition of the STN, resulting in an increased activity of the EP/SNr in line with the effect on the D1 pathway (note that reduced arrow widths symbolize the parallel D1 and D2 signaling pathways to the EP/SNr). The simultaneous effects of the D1- and D2-signaling pathways result in an increase in EP/SNr activity, which leads to an increased inhibition of the thalamus and a subsequent reduction in the activity of the cortex of the lesioned hemisphere.

Apomorphine Effect (Induced Rotation) after Lesion. The missing DA input to the striatum after SNc obliteration leads to an oversensitization of the D1 and D2 receptors to apomorphine, a DA agonist, in the striatum of the lesioned side. After systemic administration of apomorphine, both the D1- and D2-mediated effects (gray arrows) lead to a downregulation of the EP/SNr and, consequently, a stronger output from the thalamus to the cortex of the ipsilateral hemisphere compared to the contralateral hemisphere, where D1 and D2 receptors retain normal sensitivity. Overactivity of the ipsilateral cortex increases muscle tension on the contralateral side of the body, resulting in a bending that leads to contralateral rotation.

DBS Effect. DBS reduces the hyperactivity of the STN, which results in a reduced activity of the EP/SNr. In an ideal case (as indicated by the width of the blue arrow in the STN box), this reduced activity may normalize the inhibition of the thalamus and consequently the cortex activity. This outcome requires that STN-DBS can overcompensate the effect of the lesion along the EP/SNr pathway. If so, unilateral DBS in nonlesioned animals should overactivate the thalamus and the cortex in the stimulated hemisphere. Indeed, like apomorphine in lesioned animals, DBS in nonlesioned rats has been shown to induce contralateral rotation [75]. In lesioned animals, DBS is unable to reverse the hypersensitivity of the D1 and D2 receptors and thus has no effect on apomorphine-induced rotation. The concordant DBS and apomorphine effects prevent the detection of therapeutic DBS effects in apomorphine-induced rotation tests.

Amphetamine Effect (Induced Rotation) after Lesion. Amphetamine induces an increased DA release and inhibits its reuptake. In 6-OHDA-lesioned rats, amphetamine effects can occur in only the contralateral hemisphere because the dopaminergic neurons are degenerated in the ipsilateral SNc. Systemic amphetamine administration hyperactivates the contralateral cortex, resulting in ipsilateral rotation. DBS should reduce the asymmetry in the cortex activities of the hemispheres by activating the cortex of the lesioned (ipsilateral) hemisphere. Indeed, a reduction or even reversion of the amphetamine-induced rotation by STN-DBS was found in 6-OHDA-lesioned rats [11].

These considerations suggest a higher relevance of amphetamine-induced rotation tests for assessing therapeutic DBS effects, although apomorphine-induced rotation tests are useful for determining the success and degree of lesion induction.

Disclosure

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Comparison of Globus Pallidus Interna and Subthalamic Nucleus in Deep Brain Stimulation for Parkinson Disease: An Institutional Experience and Review

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Deep Brain Stimulation (DBS) has revolutionized the lives of patients of Parkinson disease, offering therapeutic options to those not benefiting entirely from medications alone. With its proven track record of outperforming the best medical management, the goal is to unlock the full potential of this therapy. Currently, the Globus Pallidus Interna (GPi) and Subthalamic Nucleus (STN) are both viable targets for DBS, and the choice of site should focus on the constellation of symptoms, both motor and nonmotor, which are key determinants to quality of life. Our article sheds light on the specific advantages and drawbacks of the two sites, highlighting the need for matching the inherent properties of a target with specific desired effects in patients. UT Southwestern Medical Center has a robust and constantly evolving DBS program and the narrative from our center provides invaluable insight into the practical realities of DBS. The ultimate decision in selecting a DBS target is complex, ideally made by a multidisciplinary team, tailored towards each patient's profile and their expectations, by drawing upon scientific evidence coupled with experience. Ongoing research is expanding our knowledge base, which should be dynamically incorporated into an institute's DBS paradigm to ensure that patients receive the optimal therapy.

1. Historical Perspective

Therapeutic targets for ameliorating the disabling symptoms of Parkinson disease, namely, tremor, were discovered early in the 20th century by neurosurgical observations, leading to an era of ablative procedures targeting the basal ganglia, refined further by advancements such as stereotactic surgery. The advent of levodopa therapy in the 1960s resulted in a decline in surgical management; however, the eventual emergence of side effects and suboptimal control of medication related phenomena such as dyskinesias and motor fluctuations have renewed the interest in surgical interventions [1]. While the use of electrical stimulation of the nervous system for pain control and seizures has been in play from the early part of the 20th century, the role of DBS in Parkinson disease can be traced to the outpatient stimulation of the thalamus and globus pallidus for motor disorders in 1972 by Bechtereva, to the first implanted stimulator for tremor in a Multiple Sclerosis patient in 1980 by Brice and McLellan, and last but not least to the first reported case of DBS in Parkinson disease at the ventral intermediate nucleus of the thalamus in 1987, by Dr. Benabid's group in France [2, 3]. This was followed by a rapid exploration into the potential of DBS, resulting in a field continuously evolving and improving in its technique, technology, knowledge, and mandate [4]. The evolution of therapies for Parkinson disease involves an incredible journey of collaboration between clinical and basic sciences. A fortuitous observation linking Parkinsonian

symptoms in young drug users resulted in the identification of MPTP [5], with the subsequent development of animal models [6] which allowed robust experimentation and proof of therapeutic targets for Parkinson disease [7–9].

2. Introduction and Evolution of the Program

The Deep Brain Stimulation program at UT Southwestern Medical Center in Dallas began in 1998 following FDA approval of DBS (in 1997 for essential tremor and 2002 for Parkinson disease), with steady growth in the number of procedures performed, up to 45 per year in 2016. The rapid evolution of the program mirrors the data available through various large studies, on the benefits of DBS versus medical therapy alone. Two landmark clinical trials [10, 11] demonstrated the efficacy of DBS over best medical management in improving motor functions, on-time without dyskinesias, and quality of life at 6 months, which have to be weighed against an increased risk of serious adverse events. While DBS does cause a significant improvement in motor scores as compared to medical management, this does not always translate into an improved quality of life, since complications associated with DBS surgery such as seizures and negative effects of DBS on cognition and mood may not allow the motor gains to be perceived and may in fact decrease quality of life. At UTSW, as part of a continuous quality improvement process [12], the DBS program collects data on both motor improvement and quality of life for analysis of patient outcomes, which will allow us as an institution to track our performance and ensure the best possible results.

Medical decision-making represents the art and science of weighing evidence based information with practice preferences, both comfort and experience, and target selection for DBS in Parkinson disease patients is no different. The availability of several studies and analyses on this topic, including some randomized controlled and blinded trials which allow a higher level of confidence in their results, provides objective and up-to-date information, which equips physicians to exercise greater scientific rigor into their decision-making process and importantly enables patients to consent with relevant prognostic data.

3. Target Sites

The main targets for DBS in Parkinson disease are GPi (Globus Pallidus Interna) and STN (Subthalamic Nucleus), with the balance between the two tilting back and forth in light of new evidence. This decades-long duel has its origins in the pallidal preference for ablative procedures which was swiftly replaced by an overwhelming preference for STN when several prominent studies backed its superiority [13, 14]. The first study with a side by side comparison of the two sites in 2001 showed significant motor benefits of DBS therapy at either site and led to its FDA approval for Parkinson disease. While this study was not designed to compare the two sites in theory, the authors set the precedent for STN preference [15]. This penchant towards STN in DBS has been reexamined in several rigorous trials [16–18] which did not uphold its dominance, allowing a "rematch" as aptly termed [19, 20]. These reports have culminated in a consensus in the field to move away from a 'one size fits all' use of STN for the disease, to a target choice which is tailor-made to a patient's specific symptoms and profile.

4. Site Selection

At UTSW, the target for DBS surgeries for patients of Parkinson disease is selected during the neuromodulation committee meeting, a multidisciplinary board comprising neurologists (movement disorders specialists), neurosurgeons, a dedicated DBS coordinator, speech language pathologists, physical therapists, and neuropsychologists. This process requires a comprehensive list of preselection tests, scales, and procedures in addition to motor scoring such as preoperative neuropsychological testing, brain MRI, physical therapy assessment, speech, and swallow assessment, to determine eligibility and site and maintain a baseline record of parameters to compare outcomes [12]. In terms of symptom alleviation, patients are selected to undergo DBS based on their response to levodopa. A levodopa challenge test, with an improvement of 30% on the UPDRS III (Unified Parkinson Disease Rating Scale, motor score), is accepted as the best predictive factor for successful DBS outcomes [21]. At UTSW, this motor scale is performed and videotaped both off medications and after an effective dose of levodopa. It is important for patients to be counseled on the expected results of DBS on each of their symptoms (both positive and negative) in order to align patient expectations with outcomes. It is at this monthly meeting that patients' history and test results are reviewed to ensure suitability for the DBS procedure, and if so, what the optimal target would be, based on the symptom profile and operative constraints if any. This inclusive, multispecialty, on-the-spot input is invaluable for a comprehensive assessment, with a thorough evaluation of the risk-benefit ratio for each unique case. This meeting incorporates relevant and recent studies in its decision-making to ensure scientific due diligence, reflected by the due process followed at UTSW to evaluate patients on a case by case basis, moving away from the global trend of STN as the site for DBS. We have performed 30 surgeries with GPi as the target and 28 with STN target through our DBS program, with an overlap occurring due to switching or addition of the other target site for enhanced symptom control. Over the last 2 years, these numbers are 22 with GPi as the target and 18 with the STN target.

5. Comparison of the Target Sites

A comparison of the two targets encompasses various parameters, such as therapeutic benefits, mechanisms of action, and adverse effects.

5.1. Anatomy. The anatomical differences between the two sites, namely, their size and location, are the basis for some of the observed differences. The GPi is roughly 3 times the size of STN and thus requires a higher charge density. Studies show that the DBS stimulation settings in patients with pallidal stimulation are significantly higher in amplitude and pulse

width as compared to STN stimulation (with no difference in frequency) which results in more frequent battery changes and higher opportunity for surgical complications [16, 22, 23]. However, the disadvantages of stimulation applied to a compact target such as the STN include a spread of current to neighboring circuits, resulting in increased number of stimulation related adverse effects. The smaller size of the STN makes it harder to place the leads exactly in the designated sensorimotor areas, possibly overlapping with the limbic or associative areas of the STN and could be responsible for the various cognitive and psychiatric side effects by activation of nonmotor circuitry [20].

5.2. Symptoms

5.2.1. Motor Symptoms and On-Off Period. Motor control is the primary treatment goal of Parkinson disease management and both GPi and STN-DBS equally improve motor function [24, 25]. The UPDRS III is used universally as a scale to measure the motor improvement after DBS and is assessed in varying combinations, with medication off and on and stimulation off and on. In a randomized trial conducted to compare DBS at the 2 sites at Veterans' Affairs and university hospitals (the Veterans Affairs Cooperative Studies Program), the motor improvements with medications off and stimulation on showed no statistical difference between the effects of DBS at either target at time periods extending out to 24 months [16] and 36 months [17]. Both time periods showed a slightly higher improvement with the pallidal target and a slight worsening with STN-DBS when both medications and stimulation were on. However, this effect was exaggerated (pallidal improvement and STN deterioration) when both medications and stimulation were off. Different studies show conflicting results: a randomized trial with a 1-year follow-up period (NSTAPS) showed a greater change in motor scores in the medication off phase with STN-DBS versus GPi [23], with the 3-year follow-up showing the same result [22], but no differences between the 2 sites in the medication on group. The major advantage with DBS is the amount of time spent in the "on" versus "off" period, a significant disability faced by patients managed medically. While most studies confirm this advantage and peg it at 4–6 hours of time saved from the "off" phase, with no difference between the STN or GPi sites, this is a measure usually tracked by the patients themselves through a diary and/or part IV of the UPDRS which does not always allow a rigorous analysis [20].

At UTSW, the DBS coordinator utilizes several scales to assess the motor performance both prior to the procedure and at follow-up visits. This includes parts 1–4 of the Unified Parkinson Disease Rating Scale, with part 3 performed on and off medications in the following combinations: stimulation off, medications off; stimulation on, medications off; and stimulation on, medications on. Specific tests are used for DBS performed for nonparkinsonian conditions such as essential tremor or dystonias.

5.2.2. Tremor. With respect to individual symptoms, resting tremor responds successfully to both GPi and STN-DBS [20, 26]. It is postulated that tremor may be more effectively controlled with STN-DBS in part due to the size of the nucleus allowing a more complete stimulation-coverage of the area, which may be insufficient for the larger GPi [19]. The exact location of the leads within these nuclei is being studied for optimal tremor control. While the resting tremor is often suppressed, a coexisting essential tremor may progressively worsen with time, which could be addressed by using the posterior subthalamic area (PSA) as a target site [27] or the ventralis intermedius (VIM) nucleus, often used as an additional site for suppression.

At UTSW, an interesting case report of a patient who did not experience optimal tremor control with bilateral STN-DBS was presented at the ANA (American Neurological Association) in 2015 and is possibly the first case of unilateral GPi lead rescue for tremor due to STN failure and stimulation related side effects [28]. The patient was a 59-year-old right handed man with a diagnosis of Parkinson disease made at UTSW 6 years ago, who presented for DBS evaluation with severe right sided tremors (the initial symptoms) and milder left sided tremors affecting both upper and lower extremities along with other typical Parkinsonian symptoms such as rigidity and bradykinesia (predominantly right sided), hypophonia, stuttering speech, and slow gait. Due to disabling tremors refractory to optimal medical management, the patient opted for bilateral STN-DBS within 2 years and initially experienced nearly complete resolution of his right sided tremors. However, he could not tolerate the long-term side effects of stimulation such as tingling, numbness, and incoordination along with an eventual loss of left sided tremor control; in addition, the patient stopped taking his medications due to meager benefit and adverse effects. Neuroimaging demonstrated a misplaced lead on the right side which could be responsible for the stimulation related adverse effects (SAEs). The patient, limited by his medication intolerance and symptom resistance, consented to undergo another DBS procedure, a right sided unilateral GPi rescue lead with the expectation of better tremor control with the alternative target. Postoperative programming resulting in optimal tremor control especially on the left could be achieved with dual right sided (both STN and GPi) along with left-STN stimulation. While there are a few recent case reports of GPi-DBS serving as a "rescue" lead for symptoms such as dystonia, behavioral features, and dyskinesias in patients with STN-DBS [29, 30], this particular case serves as an example for the use of GPi rescue leads for a STN-DBS refractory tremor. The addition of rescue GPi leads reflects possible mechanistic differences, such as complementary activation of the GPi, aside from its indirect stimulation via STN-DBS. The supplementary GPi lead could allow the activation of additional motor pathways which may not be accessed via the STN, without concurrent stimulation of limbic and associative fibers, thus eliminating unnecessary side effects, along with an element of its inherent efficacy for the alleviation of a symptom such as dystonia [28, 30].

5.2.3. Rigidity and Bradykinesia. Rigidity and Bradykinesia are motor symptoms that respond well to DBS at both targets. A study (COMPARE trial) showed greater improvement in rigidity with a unilateral STN-DBS lead versus GPi lead at

a 7-month follow-up time point [26] but no such significant advantage between the two sites could be found in bilateral DBS studies at 6 months [17] or 12 months [18]. While most studies do not show a difference between the target sites for improvement in bradykinesia [17, 26], some studies have shown an advantage of STN stimulation [18, 31].

5.2.4. Dyskinesia. Dyskinesia suppression is achieved at either target through fundamentally different mechanisms, direct stimulation effects of GPi-DBS and medication reduction in STN-DBS. This difference is responsible for the dyskinesia suppression in STN-DBS in the absence of active stimulation contrasted to GPi-DBS, which requires active stimulation for dyskinesia control at 3 months. However, dyskinesia control in GPi-DBS can be seen at 12 months even with stimulation off and can be attributed to long-term effects on dopaminergic pathways [18]. While a study reported a difference between bilateral GPi versus STN-DBS (89% versus 62% improvement in dyskinesia, resp.), it was not significant [18], but it went on to set the precedence of accepting GPi as superior in dyskinesia reduction [19]. STN-DBS has been associated with an exacerbation of dyskinesias [25] and "brittle dyskinesias" unamenable to control by optimizing programming and medication, requiring rescue surgery with GPi [32]. The superior suppression of dyskinesias, independent from medication, allowing flexibility in dose adjustment (to prevent dose-reduction side effects) and the absence of extraneous dyskinesias put GPi in the lead for patients with predominantly dyskinetic symptoms.

While motor manifestations of Parkinson disease are often well managed medically and with DBS, there is a shift in the patient experiences towards other often disabling abnormalities of gait, posture, speech, cognition, mood, and autonomic disturbances, all of which are important determinants of quality of life.

5.3. Cognition. A decline in cognition significantly affects quality of life and is seen both in the natural progression of the disease and after DBS. The effects of DBS on cognition, mood, and behavior are extensively studied, with most studies revealing lower abnormalities after GPi-DBS as compared to STN-DBS, largely responsible for the "rematch," a shifting away from the STN only approach.

The issues concerning cognition and DBS are multifold. Cognitive risk factors in patients do not serve as blanket exclusion criteria for surgery; rather they influence patient counseling for postoperative expectation setting and possibly target selection. Patients with preexisting dementias are usually disqualified from DBS surgery due to risk of worsened cognitive outcomes [33, 34]. However, in patients with mild cognitive changes, the decision to undergo DBS is a risk-benefit analysis between improved motor symptoms and likely cognitive worsening, which may in turn impact the overall ability to function and quality of life. Issues of competency to consent for this invasive procedure as well as the ability to participate during the surgery itself and keep up with the extensive follow-up testing are brought to the forefront in patients with diminished cognitive reserve.

At the 24-month follow-up of the Veterans Affairs Cooperative Studies Program, to compare bilateral DBS at both targets, results showed a slight decrease in neurocognitive function in both groups with a significantly greater decline in processing speed in the STN group, especially in the visuospatial domain [16]. At 36 months, this effect was maintained, albeit the Parkinson Disease Questionnaire-39 (PDQ-39) cognition subscale scores did not reach a significant difference between GPi and STN. However, testing such as the Mattis Dementia Scale and measures of verbal fluency (the Hopkins Verbal Learning Test) did show a significant difference between the two sites (favoring GPi) [17]. A long-term (10-year follow-up) study of STN-DBS demonstrated a 46% prevalence of dementia in patients, with no relationship to mortality, occurring about five and a half years after the surgery. It must be kept in mind that dementia is a known nonmotor complication of Parkinson disease with an overall prevalence of about 40% and this reaches as high as 83% in patients who have the disease for over 20 years [35]. The presence of dementia is heavily linked to the age of patients, thus making age of onset of Parkinson disease a compounding factor while comparing dementia prevalence after certain duration of disease. This could explain why the latter long-term study (where patients had early-onset disease) did not show as high as previously observed dementia due to skewing of the data [36]. Another randomized trial that compared the two sites with unilateral stimulation, with a specific emphasis on mood and cognition (COMPARE), demonstrated no changes between the two sites in semantic fluency but a greater decline in letter fluency in the STN group, which did not reach their predetermined level of significance [26]. This study also demonstrated that the decline in letter fluency in the STN group was irrespective of stimulation setting (location) as compared to GPi. A meta-analysis of the effects of DBS on cognition showed small decreases in overall cognition as well as in domains such as memory, attention, executive function, psychomotor speed following STN-DBS, and moderate decreases in verbal fluency both semantic and phonemic. GPi-DBS on the other hand showed only a small deficit in attention and verbal fluency [37]. This superior effect of GPi on cognition has to be balanced by the conflicting data from the 24- and 36-month follow-up of a trial (NSTAPS) which shows no statistical difference between the 2 sites on a composite score encompassing adverse effects of behavior, cognition, and mood [22, 23].

A randomized trial using bilateral STN stimulation with a constant current device had an interesting and seminal finding that the decline in verbal fluency noticed after STN-DBS occurred in both the activated (stimulation turned on) and inactive leads (implanted but never activated) allowing one to infer that these effects are likely due to surgery itself and possibly the surgical trajectory rather than specifically STN-DBS [38].

Relying solely on cognitive screens is not always adequately sensitive to detect the often subtle postoperative

cognitive changes, which require an in-depth neuropsychological assessment consisting of a wide array of tests spanning all domains [39]. UTSW has taken the approach of gathering extensive data through a battery of tests administered by a qualified neuropsychologist prior to surgery. The preoperative tests include cognitive tests, tests of executive function, tests for attention and processing speed, language testing, memory test, visuospatial tests, and testing mood and behavior. Scores from each test are converted to a global score as well as individual domain scores, which along with qualitative analysis are used to prepare a graph enabling an easy visual interpretation of data at the monthly committee meeting. Postoperatively, cognitive function is tracked through the Montreal Cognitive Assessment (MoCA) and this along with surgical complications, motor, and quality of life data are discussed at the outcomes review meeting. This ensures that patients with suboptimal outcomes are immediately identified and corrective action, if any, can be undertaken [12].

However, despite preoperative cognitive screening, several patients go on to develop cognitive dysfunction including dementia, often within 6 months of surgery [34, 39, 40]. While dementia is part of the natural progression of the disease, surgery likely plays a precipitating role. Cases have been reported of immediate postoperative cognitive decline following STN-DBS, often associated with suboptimally placed leads [41, 42]. At UTSW, we have identified two such patients who presented with disabling cognitive symptoms soon after DBS [43].

A 67-year-old male patient living with Parkinson disease for 7 years with normal preoperative cognition underwent bilateral STN-DBS. Apart from mild global atrophy, minor word-finding difficulties, and slowed thinking, he could independently manage his finances and medications. After an uneventful surgery, he experienced relief of motor symptoms and had his medications reduced; however, cognitive changes were noticed by his family within a matter of days. He experienced prominent memory and executive function declines, including impulsiveness, disinhibition, poor judgment, and inappropriate behavior. His REM behavior disorder symptoms worsened and he was frequently angry. Neuropsychological testing after 2 months revealed frontal lobe dysfunction with significantly reduced problem solving, attention, memory, and phonemic fluency, compared to preoperative levels, unchanged by increasing his levodopa dose. Similar testing 14 months after surgery revealed global cerebral dysfunction, with major involvement of the frontal lobes, consistent with dementia. He was evaluated for undetermined spells for which EEG did not reveal abnormalities and was subsequently treated for orthostatic hypotension. The second patient was a 57-year-old man with Parkinson disease for 9 years, who underwent bilateral STN-DBS. He was preoperatively found to have mild global atrophy, past history of medication induced hallucinations, practically minor problems with memory, and mild frontal-subcortical cognitive deficits on testing, which were stable over a year. He experienced confusion after an uneventful surgery, which worsened after the battery placement. Despite motor benefits, he became inattentive and disoriented, with worsening anxiety. Neuropsychological testing 3 months after surgery revealed global decline, with prominent frontal-subcortical involvement, consistent with mild to moderate dementia. In both cases, a medical work-up was unrevealing and MRIs taken 1 month postoperatively did not show any signs of infection, hemorrhage, or infarct. A study of the lead trajectory revealed they all passed through the frontal lobe, lateral ventricle, and posterior-medial border of the STN, with the lead in Patient 1 travelling further caudal towards the midbrain-pontine junction after a year. The lead positions in the first patient were noted to be posterior-medial in the STN, rather than in the dorsal STN for optimal motor benefit, and at a much greater than intended depth. Turning the stimulation off for a few weeks did not halt the cognitive decline in the patients, which the authors suggest to be attributed to the lead positions, its trajectories, and the surgery itself hastening the process [43]. This highlights the necessity of stringent preoperative screening and counseling in patients with mild cognitive impairment undergoing DBS as both hallucinations albeit medication related and prior cognitive impairment (as seen in the second patient) are risk factors for this adverse outcome [40]. The quality improvement project has identified this as an area that would benefit from cycles of plan-do-study-act. With adequate postoperative MRI scans, it is possible to correlate clinical outcomes with lead locations and trajectories. This along with neurosurgical input would allow a plan to ensure more accurate lead placement and localization [12].

5.4. Mood and Behavior. Several patients experience stimulation related changes in mood and behavior such as depression, hallucinations, impulse control disorder, apathy, and dopamine dysregulation syndrome. These adverse effects may be related to preexisting psychiatric illnesses, stress, medication reductions, surgery-related factors, changes in social situations following surgery, and mismatched patients' expectations versus outcomes [34]. While these occur in patients of both STN and GPi-DBS, several studies have shown a preponderance of negative effects on these parameters with STN-DBS. A study of 24 patients with bilateral STN-DBS revealed that careful selection of patients was required to enjoy the motor benefits of DBS. A preponderance of anxiety and emotional hyperreactivity after surgery along with other undesirable behavioral side effects and maladjustment to the family or social environment resulted in unsatisfied patients, despite motor improvements [44].

A trial to compare the effects of unilateral DBS at the STN and GPi, specifically on mood and cognition (COMPARE trial), gathered data on the impact of DBS using Visual Analogue Mood Scales (VAMS) with several subscales. Seven months after surgery, there were an overall reduction of tiredness in both groups and improved scores in "feeling happy" and "less tense"; however, feelings of anger, confusion, and irritability increased. There was no significant difference between the two sites in these subscales of mood, except for an increased anger in the STN group [26]. Based on the position of the leads in this study, the most undesirable outcome (less happy and energetic, more confused, and sad)

occurred in a ventral stimulation setting at both sites, which could be a possible explanation for patients who suffer severe mood changes due to incorrect lead placement.

The Beck Depression Inventory II, used as a measurement tool, showed an improvement in the GPi group contrasted to a decline in the STN group [17], with similar findings by a meta-analysis showing greater improvements in this scale in the GPi group [25]. However, the former study (Veterans Affairs Cooperative Studies Program) showed that the differences between the two sites disappear by 36 months [18]. While most studies concur on the greater negative outcomes of STN-DBS on mood and behavior, a randomized and blinded trial (NSTAPS), on the contrary, demonstrated no differences between the GPi and STN in a composite score, designed to measure various aspects of mood, cognition, and behavior, and the findings remained constant at the 12-month and 36-month follow-up [23, 24].

Changes such as delirium, hallucinations, anxiety, hypomania, and apathetic mood have been noted in the perioperative period, in patients who underwent STN-DBS with no similar changes noted in patients who underwent GPi stimulation [18]. While perioperative changes usually resolve, the existence of hallucinations prior to surgery must be evaluated while determining eligibility for the procedure. Drug-induced hallucinations are expected to improve due to dosage reductions made possible after STN-DBS, but those due to the disease itself are worsened and usually serve to exclude patients from the procedure. In a long-term (10 years) follow-up of STN-DBS patients, hallucinations were present in nearly 60% of the group. These hallucinations occurred approximately 4 years after the surgery, were associated with a higher mortality and the use of antipsychotics, and, importantly, showed no significant difference in the dopaminergic medication doses in those suffering from psychotic symptoms versus those who had no such symptoms [36].

There is a wide range of effects of DBS on impulse control disorders (ICD), ranging from complete resolution of preexisting disorders partial resolution and generation of new ICDs after DBS. A study following a group of patients with bilateral STN stimulation patterned the above, with 23% of the cohort having preexisting ICDs, of which 84% of them benefited from their resolution after DBS, and the rest had an appearance of new eating disorder symptoms. There is a strong association between dopaminergic medication dose and ICD occurrence, strengthened by the observation that reducing medications after STN-DBS correspondingly reduces the incidence of ICDs; however, this cannot explain the occurrence of new ICDs in patients with already reduced doses of medication following DBS. Of the cohort that did not have preexisting ICDs, 14% developed them transiently, a year after surgery, lasting for about 15 months, all of which disappeared at the 3-year follow-up. Compulsive eating disorders were the most frequently seen behavior after STN-DBS and could account for the weight gain seen after STN-DBS [34, 45]. The physiology of impulsiveness due to dopaminergic drugs is different from stimulation effects of STN-DBS and could be responsible for the new symptoms. Attempts to stabilize ICDs should be undertaken prior to the procedure, as DBS while providing relief in certain cases cannot be used as an indication for surgery [20].

A large concern with the neuropsychological changes seen after DBS is the increased possibility of suicide following STN-DBS. While suicide (attempts and completed) have been observed [34], a large study examining this did not show a statistically significant difference in the onset of suicidal ideation between the group treated with DBS as compared to the group treated with best medical therapy (1.9% for DBS versus 0.9% for BMT) [46]. This held true while comparing the suicidal ideation between patients randomized to STN or GPi-DBS at 6 months (1.5% versus 0.7%, resp.), albeit several of the proxy symptoms were worse in the STN group. The reasons for this are multifold: medical and neurological conditions and complications related to the disease and surgery, the often drastic reduction of dopaminergic medication (possibly accounting for the decreased risk in GPi-DBS), the preexistence of psychiatric comorbidities such as depression, and the change in impulsivity, all of which play a role in increasing the risk of suicidal ideation. This reiterates the need for careful preoperative neuropsychological assessment, continuous monitoring of depression, and careful observation for the emergence of impulsive behaviors and warning symptoms by family members.

A study analyzing the subjective or patient-perceived benefits following STN-DBS revealed negative outcomes in spite of almost universal motor benefits in patients who underwent bilateral STN-DBS. Older age and longer duration of disease were not associated with perceived negatives outcomes; rather, the main predictors were axial symptoms and apathy [47]. This study highlights apathy as the single most important contributing factor towards subjective negative outcomes after DBS, significantly higher in these patients at baseline (prior to DBS surgery) as well as at the 12-month follow-up, with similar findings for depression. The aggravation of apathy in patients receiving stimulation is independent of any changes in depression or cognition and could be related to stimulation adverse effects or medication reduction. While patients are usually counseled that their axial symptoms would not be controlled by DBS, they are often perceived to have worsened, which may be in part due to their progression after surgery or that patients focus on them upon resolution of other motor symptoms. This in turn affects the quality of life scores and their own perception of benefit after surgery, highlighting the absolute need for setting expectations with the patient and their caregivers clearly and repetitively.

Possible explanations for the greater deterioration of cognitive and psychological parameters in STN-DBS patients include the effects of anatomical size and medication reduction. Leads placed in the STN may spread the current into the associative and limbic regions of the nucleus as well as areas such as lateral hypothalamus, zona incerta, and medial forebrain bundle, all of which have extensive limbic connections. The role of dopaminergic medications which are dramatically reduced in STN-DBS patients but relatively maintained in GPi patients may play a part in the latter's cognitive advantage. This framework can be applied to understand impulse control disorders as an imbalance

between excess of dopamine with stimulation of limbic circuits leading to their hyperactivity [21]. This necessitates a balance between reducing the dosage of medication and increasing the intensity of stimulation. A study of bilateral STN-DBS patients observed that it is possible that certain depressive disorders may be unmasked after the surgery itself. Patients with previously undiagnosed or unnoticed behavioral disorders experienced a decompensation after STN-DBS. This again highlights the need for extensive preoperative neuropsychological counseling, delving into relevant topics, such as present or remote addictive behaviors, personality disorders, and depressive disorders, and, importantly, an in-depth examination of the sociofamilial environment of the patient [44].

At UTSW, mood and behavior are evaluated with cognition prior to the procedure and at follow-up visits, as explained above. The battery of tests includes the Beck Depression Inventory II, the Questionnaire for Impulsive-Compulsive Control Disorders in Parkinson disease-Rating Scale (QUIP-RS), and the Quick Inventory of Depressive Symptoms (QUIDS). Mood and behavior changes are also captured in the quality of life data which is reviewed at follow-up meetings, albeit there is lack of formalized testing in these domains in the absence of patient complaints or adverse events. Armed with this knowledge, it is imperative that patients' caregivers play an active and ever-vigilant role in the assessment for subtle changes in the patient's mood, behavior, and affect, after the DBS procedure. At UTSW, we have incorporated realistic expectation setting in our preoperative consent forms [12] clearly explaining which symptoms are likely to improve, which ones are not expected to improve, and possible side effects. However, it is in our interest to ensure and recheck that the patients and their caregivers have a complete understanding of these points and are not overwhelmed by the extent of testing or holding on to unrealistic expectations.

5.5. Quality of Life. The aim of all therapy is to ultimately improve quality of life for patients; this especially holds true for interventions such as DBS which are invasive and expensive and potentially have serious adverse effects. While controlling the motor symptoms of Parkinson disease is the primary goal of medical and surgical therapy, nonmotor symptoms such as mood, cognition, sleep, autonomic dysfunction, speech, and swallowing deficits form a large part of the disease burden and are important determinants of quality of life. These symptoms are more often than not resistant to medical and DBS therapy and often negatively impact patients' perception of therapy, despite the control of the cardinal motor symptoms.

Parkinson Disease Questionnaire, PDQ-39, is almost universally used as a measure of quality of life across 8 domains or subscales: mobility, activities of daily living, emotional well-being, social support, stigma, cognition, communication, and bodily discomfort.

A trial comparing bilateral DBS at the 2 sites (NSTAPS) did not find a significant difference in the quality of life measured through the Parkinson disease quality of life questionnaire-PDQL, not only at the 12-month follow-up but also at the 36-month follow-up [22, 23]. The Veterans Affairs Cooperative Studies Program after 24 months found the quality of life as measured by the PDQ-39 improved in most domains in both groups, with no significant differences between them. Although there was a minor deterioration in communication in both groups and worsened social support after pallidal stimulation versus improved support after subthalamic stimulation, these were not statistically significant, with an overall positive impact on quality of life [16]. However, by 3 years, these quality of life gains were diminished, with scores returning to baseline in certain domains such as emotional well-being, social support, and cognition, with no differences between the 2 sites [17]. Activities of daily living followed a very similar trend, which did not show sustained gains at 3 years after DBS, despite motor improvements. This loss of benefit is important to note while counseling patients on DBS. A randomized trial studying the effects of unilateral DBS GPi versus STN on mood and cognition allowed an in-depth analysis on the impact across various subscales of quality of life, 6 months after surgery [48]. With similar improvements in motor and mood symptoms, patients who underwent GPi-DBS reported a significantly higher quality of life as compared to those who underwent STN-DBS, with both groups showing improvement in 6 subscales (mobility, activities of daily living, emotional well-being, stigma, cognition, and bodily discomfort) but not on social support or communication. The level of depression measured by the Beck Depression Inventory II was predictive of overall quality of life improvements as well as the performance on the subscales of emotional well-being and support. The decline in category fluency was also correlated with a decline in the communication scale in the STN-DBS group. The overall impact found by this study, albeit with unilateral DBS, is an improvement in the quality of life at both target sites, markedly higher in the GPi-DBS group, affecting the various domains differently.

Nursing home placement is another component, intimately linked to ability to carry out activities of daily living and quality of life. A study which followed the long-term performance of STN-DBS across a span of 10 years found 42% of their patients were admitted into a nursing home, and this had a correlation with higher age at the time of surgery [36]. Parkinson disease patients have a higher risk than the general population to be admitted into a nursing home, linked to their duration of disease, age, and dementia, but studies have also shown that nursing home placement is less in DBS treated patients as compared to medically managed patients alone (6% versus 15%) [49].

Recently, studies have reviewed the PDQ-39 as the standard questionnaire used to assess quality of life across the various disease specific domains. Despite almost universal usage including our institution, it has its drawbacks. It does not capture various side effects seen with STN-DSB, such as apathy, speech difficulties, and impulsive behaviors and underreports axial symptoms. The PDQ-39 was designed prior to this data being available and cannot comprehensively outline the extent or magnitude of benefit or impairment experienced by the patients. Since apathy plays a major role

in the patients' perceptions of benefit, the quality of life scale ought to include apathy in its computation [47]. It is essential to have a scale that reflects all the known parameters which are affected by DBS and to that effect a group has worked to develop and validate a new deep brain stimulation impairment scale (DBS-IS). The scale consists of 22 questions for 6 subscales, with a high reliability and validity. The subscales include postural instability and gait difficulties, cognitive impairment, speaking problems, impulsivity summed score, and difficulties related to the DBS device. This DBS-IS is not designed to replace the PDQ-39, rather it is complementary to it and can assist in DBS candidate selection; for instance, high preoperative apathy or postural and gait imbalance scores may caution against the procedure.

At UTSW, the PDQ-39 is measured by the DBS coordinator both prior to surgery and during follow-up visits. We have not incorporated this new scale in our practice at UTSW and will probably wait for a refined version which addresses some of the drawbacks. These limitations include being designed exclusively with STN-DBS patients, possible missing other target specific symptoms, as well as being constructed with patient and care-giver experiences over a period of 1 year after surgery, which may not accurately represent or capture the long-term experiences with the DBS procedure [50]. It is important to note however that this group addresses a clinically relevant gap and the extensive preoperative testing and follow-up performed at our institute can incorporate these parameters.

5.6. Gait and Balance. Improvements in gait and balance mirror the effects of levodopa in the "on" period, which is increased by DBS. However, this gain is often lost due to progression of the disease, possibly hastened by surgery [40] and lesional effects of the procedure itself. It is vital to counsel patients on the ineffectiveness of DBS on medication unresponsive gait and balance issues. At UTSW, automated gait and balance assessments (in the medication "on" and "off" phase) using the APDM Mobility Lab (consisting of up to 6 wireless sensors on the patient, to measure the various kinetic parameters during predefined tasks such as walking and turning, which are analyzed using various plug-ins such as iTUG and iSWAY) provide objective measures of gait and sway [12]. This testing is carried out both pre- and postoperatively. A randomized trial at the veteran's affairs and university hospitals showed the superiority of GPi over STN-DBS for gait issues when both medications and stimulation were off, which lasted for an extended period (24 months) [16] with conflicting findings in another trial (NSTAPS) which showed STN-DBS superiority for gait in the off phase in a post hoc analysis [23]. Experimentation using DBS at the pedunculopontine nucleus (PPN) as an alternate management site for gait and balance instability is underway [51], yet to be performed at UTSW pending stronger safety and efficacy data.

5.7. Speech and Swallowing. Axial functions such as speech and swallowing are complex functions and have a direct relation to mortality (by aspiration) and need to be addressed for optimal quality of life. A review of the effects of DBS on swallowing highlights the fact that while most studies suggest an impairment of swallowing with STN-DBS, there was no clinically significant impairment or improvement measured, and studies notably did not compare STN to GPi or unilateral versus bilateral stimulation [52]. STN-DBS has been reported to help reduce the vocal tremor in patients with a trade-off of reduced volume, and DBS induced dysarthria, possibly due to the spread of stimulation to the corticospinal tract, ultimately reducing speech intelligibility [20, 53]. At UTSW, the effects of DBS on these functions are recognized and their comprehensive assessment is part of the preoperative work-up for patients. This involves a swallow evaluation and laryngeal video stroboscopy and performing the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) and the Voice Handicap Index (VHI-10). This potential deterioration of speech and swallow functions after DBS is addressed while counseling patients for the procedure and specific treatments if possible are instituted before the surgery. Ideally we would make speech and swallow testing part of the postoperative work-up to track progress and enable early detection of deterioration if any, but since we are limited within the framework of insurance, this testing is performed postoperatively only in cases with reported adverse events.

5.8. Autonomic Symptoms. Patients with Parkinson disease often suffer from autonomic symptoms; their response to DBS remains variable and understudied and mainly in STN targets. While STN-DBS was thought to impact blood pressure and heart rate, studies have not demonstrated statistical changes. The positive effect of STN-DBS on constipation is noted but this is likely to be related to increased patient mobility. A direct effect of STN-DBS on bladder dysfunction has been theorized but is not clear [21].

5.9. Sleep. STN-DBS has demonstrated an improvement in the quality of sleep for patients, with an increase in total sleep time, time spent in REM, and slow wave sleep as measured by polysomnography and the PDSS: Parkinson disease subjective sleep scale. The improvement in scores was noticed when stimulation was off and can be attributed in part to the surgical lesioning of the STN nucleus itself. These effects were related to the extent of motor gains and the reduction of day time sleepiness due to reduced medications, thus improving night time sleep quality. The few studies tracking this data have not shown a difference between the two sites in sleep benefits [23]. Similarly, there is limited and conflicting evidence on the effects of STN-DBS on apathy and fatigue, from mild improvement to worsening, possibly related to the effects of decreased medication, with a possible emergence of fatigue as a long-term complication of STN-DBS [21, 54]. At UTSW, we have not incorporated the PDSS or polysomnography into the DBS program design for outcome tracking but are open to its utilization pending clinical need.

5.10. Pain. Patients of Parkinson disease experience different types of pain: musculoskeletal, dystonic, central, radicular, and somatic, exacerbated during the off period. The relief

afforded by DBS to motor symptoms such as rigidity and dystonias is largely responsible for ameliorating the first 2 categories and possibly acting on central pain as well. A paradoxical effect of body discomfort is observed infrequently in patients particularly of STN-DBS as the reduced blood levels of levodopa result in a decreased pain threshold [21]. At UTSW, patients' pain and discomfort are tracked in the Parkinson Disease Questionnaire-39 (PDQ-39), a self-assessment of various quality of life parameters including bodily discomfort.

5.11. Mortality. It is worthwhile to investigate whether the improvement in quality of life and motor function in patients with Parkinson disease has an overall impact on mortality: is there a change in the natural progression of the disease with DBS?

Patients with Parkinson's disease have a higher mortality than the general population, with an odds ratio of 2.56 and a 5-fold higher chance of being placed in a care facility. So far, while drug therapies in some studies have shown a positive influence on the disease when started early on, they have not yet shown any change in mortality or the ability to prevent the onset of dementia or falls [55]. On the other hand, a trial exploring this question demonstrated that patients who underwent bilateral STN-DBS had significantly longer survival and were also significantly less likely to be admitted in a residential care facility (6%) as compared to matched patients (15%) who, while eligible for DBS, opted to be managed medically [49]. Another outcome observed in this study was a large cohort of patients in the medically managed group who died of respiratory causes as compared to the DBS group (20% versus 2%), likely related to aspiration due to swallowing impairments. This suggests that improved deglutition is a benefit of STN-DBS, with a favorable mortality advantage (albeit this study focuses on a STN target). Another long-term STN-DBS study (10-year follow-up) demonstrated that mortality had a 2-fold increase with an older age at the time of surgery (above 60 years) as well as a 9-fold increase in men. Surprisingly, the duration of disease or its severity or response to medications was not correlated with mortality. A higher age at surgery was also shown to be associated with increased nursing home placement [36].

A survival gain with DBS is usually not discussed with patients while considering them for DBS, information which should be incorporated into decision-making. At UTSW, while there is no fixed age cut-off for surgery, it is a factor discussed while weighing the risk to benefits of DBS in a particular patient. We have not formally tracked mortality data on patients who have undergone DBS at our center. So far two patients with DBS (one STN and one VIM (ventralis intermedius)) have passed away, but circumstances around their death involved multiple compounding factors and cannot be solely attributed to DBS. It is important for our quality improvement endeavors to have this data to allow outcomes tracking, and steps to ensure completeness of our database will be put in place soon.

Armed with the data showing that increased age at surgery is a risk factor for suboptimal outcomes and evidence that opting for DBS at an earlier stage of the disease rather than after exhausting all options is associated with superior motor and quality of life outcomes [56], a trend is emerging towards changing the age consideration for DBS surgery. At UTSW, the average age at surgery is 73 years for STN and 66 years for GPi. It also revises the treatment paradigm and presents the opportunity to begin consideration for DBS at an earlier time period. The ability to have a unified transition to surgical therapeutic options if required is a draw for several patients with Parkinson disease at UTSW, with in-house multidisciplinary teams available for seamless coordination of care.

5.12. Medication Reduction. There is a unanimous finding that medication (measured as levodopa equivalent dose (LED) or LEDD (levodopa equivalent daily dose)) is markedly reduced after STN-DBS as compared to a slight reduction after GPi-DBS. Studies have shown varying reductions such as 38% for STN-DSB versus 3% for GPi-DBS [18] or absolute dose reductions of 408 mg in the STN-DBS group versus 243 mg in the GPi-DBS group [16] at 2 years after surgery, which, despite slowly increasing by 36 months [17], remains significantly reduced as compared to baseline. While this is not the primary goal of surgery, this reduction in medication allows respite for patients suffering from disabling side effects which affect quality of life such as orthostatic hypotension, drug-induced dyskinesia, and fluctuations in "on" and "off" time. The reduction in medication should be managed cautiously, as a rapid reduction in certain medications such as dopamine agonists could lead to dopamine agonist withdrawal syndromes (DAWS).

The assumption that the reduction in medications is a pure positive effect must be examined, with evidence highlighting the complex interplay between symptoms, side effects, target stimulation, and medications. The possible increased suicidal ideation observed after STN-DBS has been linked to a reduction in dopaminergic medication [1]. Observations demonstrate the loss of prior positive effects of STN stimulation in the medication "on" phase especially for gait and balance, with worsened motor scores at extended time points (3 years after surgery) as compared to baseline [17]. This, coupled with the deterioration of motor scores in STN-DBS patients in the "off-off" (both medications and stimulation) phase, not seen in GPi-DBS patients which retain stable scores [57], bolsters the theory of dopaminergic medication advantage, and not merely disease progression as a possible explanation for these phenomena. This leads to various lines of thoughts such as the desirability of medication reduction in the absence of side effects, the nature of the relationship between medications and stimulation, whether STN stimulation interferes with dopaminergic stimulation, and whether there is an inherent disease modulating effect of GPi-DBS outside the role played by medications [58].

6. Unilateral Leads

Asymmetrical symptoms are a hallmark of Parkinson disease, and although uncommon, patients with predominantly unilateral symptoms have the option to undergo a single lead

placement. A trial to compare the effects of unilateral DBS at the GPi and STN on mood and cognition (COMPARE) found no significant difference in motor and cognitive outcomes between the 2 sites, with differences in verbal fluency noted in STN-DBS when not in optimal settings [26]. A follow-up of these patients after 6 months reveals that more than half (52%) opted for implantation of a second lead for better management of their motor symptoms. Of the half that chose to remain with a single lead, two-thirds of them had GPi implantation. Thus, factors such as STN site lead and a lower asymmetric score were associated with a higher risk to convert to a bilateral implantation, in addition to worsened motor function (high UPDRS III scores), gait dysfunction, and dyskinesias. A possible explanation for this could be the different mechanisms of action of the two nuclei. Since GPi directly suppresses dyskinesias, it may serve to affect the contralateral side as well and continue to exert effects even without medication reductions, which makes unilateral GPi an attractive option for patients with severe one-sided dyskinesias. Bilateral STN leads are associated with greater medication reduction than unilateral leads; hence, adequate control of dyskinesias often requires both leads. Patients with predominantly unilateral symptoms could achieve motor control with a single lead, reducing the perioperative morbidity and side effects associated with bilateral implantation, and retain the ability to convert to bilateral leads when required [59].

7. Programming Paradigms at UTSW

Through a systematic process of testing each electrode, threshold settings are determined which elicit clinical benefit and adverse effects which are used in future programming. The stimulation settings are determined by varying voltage and pulse width along with contact points and occasionally frequency, all of which require a high level of skill to optimize thousands of combinations to attain symptom relief, with minimal DBS side effects. Programming offers the ability to manipulate advanced stimulation settings to achieve best possible outcomes even in cases with suboptimal lead placement. DBS programming and medication titration are delicately intertwined and require close monitoring until the patient experiences a stable and optimal state, a process that usually takes around 6 months. Following an optimization of settings, it is usually safe to expect that other Parkinson disease related effects cannot be managed by tweaking the DBS settings. It is also possible to anticipate DBS failures, early in the course of programming, in the case of low thresholds for adverse effects or unsustained benefits associated with a lead [1].

8. Surgical Complications and Adverse Events

Most studies and DBS programs track adverse events often with additional classification into mild, moderate, or severe to assist in analysis and comparative studies. The source of these events can be related to surgery, the device, stimulation, and medications or due to the progression of the disease itself and are not often distinguishable. It is observed that patients treated by medication alone have a higher frequency of adverse events overall; however, the patients with DBS experience a higher frequency of serious adverse events [10].

Surgical complications include infection (4%), intracranial hemorrhage (4.4%, leading to 1% rate of permanent neurological deficits), device related problems such as migration of leads (2.4%) and lead fracture (3%), and seizures (3.2%) and are considered major or serious events [21]. While the incidence of surgical complications may be considered equal between GPi and STN, it is theoretically possible that GPi, with a shorter battery life which may require more frequent battery changes, predisposes to higher infection rates. Adverse events were more common in the initial year after the surgery as compared to the following years, suggesting a favorable long-term safety profile aside from initial perioperative risks [60]. The Veterans Affairs Cooperative Studies Program showed no difference between the types (severity) or frequencies of adverse events at the two target sites, with most severe events resolving by the 24-month mark [16]. A study of bilateral STN-DBS with a constant current device demonstrated that while certain side effects such as fatigue and dysarthria were related to stimulation, others such as gait dysfunction and dyskinesias were present in the absence of the leads being activated, indicating a possible correlation to the surgery and/or tract itself [38]. Another surgical factor is the tract followed by the DBS lead during implantation; while it is inherently different for each target, it plays a role in the development of side effects independent of the effects of stimulation. A study showed a direct relation between the overlapping of electrode trajectories with the caudate nucleus in STN-DBS patients and the decline in cognition and memory [61]. Optimizing this trajectory and ensuring accurate lead placement are vital to achieve minimal side effects.

Certain side effects such as dysarthria were notably seen in the first 12 months after surgery, implying a relationship with DBS rather than progression of the disease. Other such symptoms linked to the DBS include dysphagia, excessive salivation, blepharospasms, and weight gain [36]. A randomized and blinded trial between the 2 sites noted the presence of perioperative complications in mood and cognition predominantly in the STN-DBS group such as delirium, hallucinations, and anxiety which resolved with time, but cognitive changes remained persistent [18]. The impact of DBS on various motor and nonmotor effects, such as impulse control disorders, depression, and worsening cognition, has been described in the relevant sections.

As part of the quality improvement initiative at UTSW, adverse events and complications, either minor or transient, are recorded to allow for an analysis of trends if any and devise improvements by the neuromodulation network meeting. This analysis is possibly the next quality improvement study (cycles of plan-do-study-act) which will be undertaken at UTSW by the movement disorders section in an effort to continually optimize our outcomes. There were a total of 9 surgical or device related complications in 28 patients studied, occurring in DBS performed at the STN as well as

the VIM (ventralis intermedius) nucleus of the thalamus over the last 2 years [12].

9. DBS Failure

Suboptimal results from the DBS procedure are often labeled as DBS failures. Factors common to these "failures" include inadequate presurgical screening, improper patient selection, incorrectly placed leads, suboptimal programming, battery failure, and hardware related issues [1]. Patients are likely to switch their provider and DBS center in the hope of improved outcomes. Treatment options include optimizing the programming and medications to manage side effects or enhance benefits, as well as second surgeries, for correcting lead location in case of lead migration or incorrect placement or placing rescue leads at the other target site, which could be unilateral or bilateral.

A randomized trial comparing DBS at the 2 sites (NSTAPS) had 8 patients of GPi-DBS (from a total of 65) who had to undergo STN-DBS resurgery due to lack of benefits. Of these 8 patients, 5 had leads placed correctly. Similarly, 1 patient of STN-DBS (from a total of 63) had a unilateral GPi lead implanted, and one was reoperated to correctly position the leads [22]. A waning of prior positive response to GPi-DBS after a few months to years has been noted in several cases from the 1990s, which may be indicative of a surgical technique, patient selection, or postoperative management issue and often lead to surgical implantation of STN leads [62]. However, for the most part, studies showed long-term stability of GPi-DBS and STN-DBS [17]. The case report from UTSW on suboptimal tremor control with bilateral STN-DBS [27] discussed above is an example of DBS failure, due to improper lead placement.

10. Cost-Effectiveness

Since DBS is an expensive and long-term undertaking, it is important to discuss the cost-effectiveness of the procedure and accurately identify patients who will benefit from it given the risks and benefits. A study using the University HealthSystem Consortium (UHC) Clinical database found the average DBS procedure cost to be \$39,152 ± \$5340 [63], with the median cost of implantation in 2013 being \$34,052 at UHC-affiliated hospitals.

A study of the cost-effectiveness of DBS with medical therapy as compared to the best medical therapy (BMT) using various analytical models from the Medicare payer perspective, considering a 10-year horizon, found total costs of DBS to be \$130,510 versus \$91,026 for BMT, with a gain of 1.69 QALYs more than BMT, and a total of \$23,404 per QALY, with greater benefit seen in younger age and longer follow-up [64]. A similar study in the UK pegged this at £20,678 per QALY gained [65]. The cost of the surgery is partially offset by the reduction in medication costs, for which STN-DBS with its drastic reduction shows a higher benefit. Expensive medication delivery routes such as continuous intestinal infusions of levodopa show a maximum cost benefit after surgery. In a randomized, single-blinded clinical trial to compare the differences between DBS with medical therapy versus medical management (ODT) in early stage Parkinson disease, an analysis of the cost savings showed that while drug costs increased 72% in the ODT group, they declined by 16% in the DBS + ODT group from baseline to 2 years. This difference resulted in a saving of \$7150 per patient with DBS over the 2 years, which when extrapolated for the long-term (10 years) resulted in savings of \$64,590 [66]. With a longer battery life likely related to programming characteristics STN-DBS shows a possible economic advantage with fewer surgical procedures required for battery changes.

We at UTSW have not undertaken a cost-benefit analysis, as costs depend on and vary with differing patients' insurances which skew the relevant data; however, it is a topic that will be researched to understand the financial implication of DBS, for both the patient and the institute.

11. Unanswered Questions

While DBS is widely used in the management of Parkinson disease, there are several questions that remain open, and the quest to solve them will hopefully strengthen the success of DBS in improving the quality of life in patients.

Questions regarding unilateral versus simultaneous bilateral lead implantation and the utility of the staged operations require further studies to determine benefit one way or another. The safety of unilateral implantation with concomitant decreased operative adverse effects especially in the elderly has to be weighed against the possibility of a second procedure for inadequate benefit and is usually considered in patients with extreme asymmetry of symptoms.

Issues faced by patients such as gait-freezing and other axial symptoms not addressed by DBS require studies to provide potential solutions. Research into stimulating multiple leads at different locations to address specific DBS and Parkinson's related symptoms is underway.

With increasing evidence for DBS at an earlier stage in the disease for superior outcomes [56], there is a need to define optimal age range and disease duration to experience the maximum benefit from this procedure. A recent prospective, randomized, single-blind clinical trial in early Parkinson disease (on medications for 1–4 years only) compared the motor and quality of life outcomes of the groups on optimal drug therapy (ODT) versus DBS with ODT. The study revealed that patients managed medically are 2–5 times more likely to experience clinically important worsening than the patients treated with DBS + ODT [67]. These results increase the options available to patients in the early stages of Parkinson disease and highlight the need to reexamine the therapeutic guidelines in place today.

Cases of DBS failures corrected by dual stimulation of alternate targets, the "rescue leads" as discussed above [28–30], point to the need for larger trials on the safety and efficacy of using dual stimulation as a therapeutic option in patients of single target DBS with inadequate symptom control due to SAEs or disease progression. This dual stimulation of both the target sites could also be considered as a potential DBS treatment strategy from the get-go, based on the symptom and patient profile, and needs further exploration.

While a majority of studies have an end point of 24 or 36 months, there are scarce long-term studies that have tracked patient outcomes over a span of 10 years [36]. With a possible trend emerging to perform DBS early in the course of the disease, it is imperative to have multiple studies addressing the long-term sequelae of DBS, both positive and negative, and to assess the impact on disease progression. This in turn may refine the patient and target selection and provide information for enhanced decision-making, for both patients and providers while analyzing the risk-benefit ratio.

12. Future Directions

DBS has become standard of care for treating patients living with Parkinson disease as well as a wide range of other movement disorders. The aim of research in the field is to have a clear understanding of the mechanisms of action of DBS and the physiological and anatomical basis of various side effects seen, so as to design a DBS process which will allow patients to achieve maximum control of all their symptoms (including ones traditionally resistant to DBS) with minimal side effects to enhance the quality of life. Research in this field has resulted in several potentially and therapeutically beneficial outcomes such as expanded scope, new targets, enhanced surgical techniques allowing precise target localization and trajectory such as frameless, and nonmicroelectrode recording techniques, advances in imaging such as functional and microstructural imaging, refined hardware design such as constant current devices, optimized programming sequences, and other cutting-edge techniques.

Continued research to elucidate the mechanisms of action of DBS at different targets and charting the anatomical zones and fiber bundles to explain corresponding side effects observed are important aspects of DBS research to understand and avoid the neuropsychiatric effects that accompany this procedure. Refining technical aspects such as contact selection may provide a solution to avoid these unintended effects [68]. Advances in stereotactic localization and imaging have made it possible to obtain accurately placed electrodes without patient participation, precluding the need for "awake" surgeries and allowing patients who are not ideal candidates for such "awake" procedures to benefit from DBS performed under general anesthesia, termed "asleep DBS." "Asleep DBS" has been studied and shown to be both safe and effective, affording the patient significant motor benefit at 6 months after surgery [69], with no significant differences in the complications, hospital stay, or 30-day readmission rates as compared to the traditional awake surgery [70]. The availability of data from a meta-analysis on this question, showing similar efficacy and lower complications overall between awake and asleep DBS [71], makes this a viable option to include in the monthly neuromodulation committee meetings.

Research into new targets is underway and can potentially address the gaps in therapy with DBS at the STN and GPi. Studies on the pedunculopontine nucleus (PPN), chosen for its anatomic connections with the basal ganglia and its functional role in motor modulation and locomotion, demonstrate improvements in gait and balance including gait-freezing, the results of which are variable and need to be confirmed through rigorous trials. The PPN poses surgical access complications and has zones with varying functions; hence, studies need to address technique as well as costimulation of other targets [72]. Attempts to address gait and balance impairments using dual STN and Substantia nigra pars reticulata stimulation show promising effects on gait-freezing, with no additional effects on balance, mood, or cognition, and are being investigated in clinical trials [73]. Stimulation of the intralaminar thalamic complex comprising the parafascicular and centromedian nucleus is being evaluated for possible therapeutic benefit owing to its location in the basal ganglia circuit and projections to the striatum. DBS at this location modulates thalamocortical circuits with a positive effect on tremor [74].

Studies incorporating stimulation of novel targets in addition to the standard STN or GPi provide a theoretical means of addressing adverse effects or levodopa unresponsive symptoms. Experiments on the reward circuitry could address issues such as apathy, depression, and possibly other ICDs [75]. Through discovery of neural networks and rigorous trials, a possibility of multiple electrodes at different targets to address the various motor and nonmotor symptoms may be a distinct possibility, which along with real-time closed-loop programming may provide a dynamic control of a majority of symptoms, optimizing the patient's quality of life [20].

13. Conclusion

Deep Brain Stimulation has revolutionized the lives of patients living with Parkinson disease. The very decision to undergo the procedure and the choice of the target site are in essence a series of risk-benefit analyses. This entails balancing the probability of improved quality of life, relief of tremor, rigidity and other motor symptoms, reduced medications and their side effects with the possibility of potentially fatal or disabling surgical complications and other procedure related adverse effects, such as worsened cognition or other negative psychiatric outcomes, and changing the extent of impact of declined verbal fluency. Computing the best outcomes in these complex scenarios should be done on a case by case basis, using each patient's symptom, disease, medical, risk, and demographic profile along with patient expectations to reach the optimal management plan. This tailored approach to selecting the target site for patients undergoing DBS is the result of years of data from various studies, trials, and case reports, which allows a DBS team, including the neuromodulation network at UTSW to anticipate potential adverse outcomes and plan ahead to circumvent them, for the best possible results. If a patient has a history of hallucinations or has diminished cognitive reserve, GPi-DBS may provide motor benefit without the possibility of cognitive decline, if patients suffer significant medication related dyskinesias; STN-DBS can offer relief. In a similar vein, studies have also helped in planning the lead location and trajectory, with leads in the ventral zone of the STN, associated with a greater incidence of adverse effects. This planning and refining of patient and target selection, surgical trajectory and

lead localization by imaging or microelectrode recording, DBS programming, and other hardware parameters have resulted in optimizing patient outcomes and unlocking the full potential that DBS has to offer. Research endeavors aim to continually enhance the DBS process by addressing the unmet needs and unanswered questions, through expansion of our knowledge based on the process mechanisms itself, technological improvements, trials to test or observe the safety and efficacy of various therapeutic options in DBS, and other novel ideas.

An indicator of the commitment of a DBS program towards its patients is the standard it holds itself up to and the accountability it has towards all its stakeholders. At UTSW, the quality improvement effort spearheaded by the movement disorders group in the department of neurology fulfills these obligations by subjecting various aspects of the program to a rigorous examination, cycles of plan-do-study-act, with the intention of ensuring these high standards. This endeavor has resulted in the design of the current processes, namely, the neuromodulation network and the formal structure in place for preoperative assessment and follow-up. An important element of this program is capturing data to allow tracking of outcomes and feedback [12]. The ultimate goal of these data-driven initiatives is to ensure that the DBS program dynamically processes and incorporates information to optimize outcomes in an agile environment. The commitment of the institutional leadership itself towards the success of the DBS program should be highlighted, as their financial support for the newly implemented processes is vital. The combined dedication of all the stakeholders to ensure the best possible patient outcomes is a testament of resolving of UTSW towards improving the lives of those living with Parkinson disease by developing safer and better DBS paradigms.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Clinical Study

Subthalamic Nucleus Deep Brain Stimulation in Early Stage Parkinson's Disease Is Not Associated with Increased Body Mass Index

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Previous studies suggest that deep brain stimulation of the subthalamic nucleus (STN-DBS) for Parkinson's disease (PD) leads to weight gain. This study analyzes changes in body mass index (BMI) in 29 subjects from a prospective, single-blind trial of DBS in early stage PD (age 50–75, Hoehn & Yahr stage II off medication, treated with antiparkinsonian medications for ≥6 months but <4 years, and without a history of motor fluctuations, dyskinesias, or dementia). Subjects were randomized to DBS plus optimal drug therapy (DBS+ODT; $n = 15$) or ODT ($n = 14$) and followed for 24 months. Weight and height were recorded at baseline and each follow-up visit and used to calculate BMI. BMIs were compared within and between groups using nonparametric t-tests. Mean BMI at baseline was 29.7 in the ODT group and 32.3 in the DBS+ODT group ($p > 0.05$). BMI change over two years was not different between the groups ($p = 0.62$, ODT = −0.89; DBS+ODT = −0.17). This study suggests that STN-DBS is not associated with weight gain in subjects with early stage PD. This finding will be tested in an upcoming FDA-approved phase III multicenter, randomized, double-blind, placebo-controlled, pivotal clinical trial evaluating DBS in early stage PD (ClinicalTrials.gov identifier NCT00282152).

1. Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is an FDA-approved adjunctive treatment for Parkinson's disease (PD) when symptoms are no longer adequately controlled by medications. DBS therapy is demonstrated to significantly improve motor symptoms and quality of life for PD patients. Despite its clinical success, isolated studies suggest that STN-DBS is associated with postoperative weight gain and increased body mass index (BMI) [1]. While average weight gain after STN-DBS is reported as a 12.8% increase from preoperative body weight [2], the most significant weight gain typically occurs within the first few months after surgery (8.4% BMI increase [3]), with gradual increases thereafter [1]. These reports of weight gain following STN-DBS are concerning because of the implications for this effective PD therapy leading to additional health complications such as obesity and/or diabetes [4].

STN-DBS is a potent therapy that treats many features of PD that cause weight loss as PD progresses (e.g., dyskinesias and other motor fluctuations and side effects of medical therapy, such as nausea and loss of appetite [5]). For nearly 20 years, DBS has been indicated for advanced stage PD (average disease duration of 10.8 years [6]); this PD patient population has prolonged exposure to the negative effects of the disease progression as well as medication-associated complications leading to considerable weight loss [7]. Therefore, it is not currently clear whether the postoperative weight gain previously reported is due to active STN stimulation or is a consequence of the typical postoperative reduction in medication need and/or the general benefits for PD secondary to DBS therapy.

Vanderbilt University completed a pilot safety and tolerability clinical trial testing STN-DBS in early stage PD (NCT#00282152) [8]. This study offers a unique cohort to evaluate potential postsurgical changes in BMI in early stage

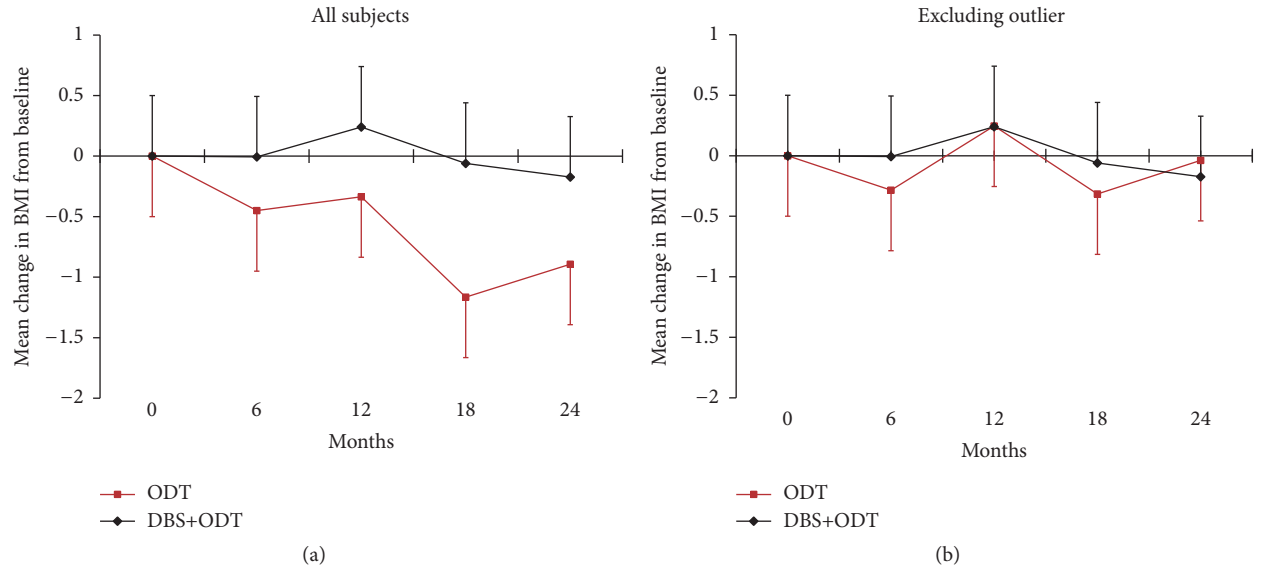

FIGURE 1: Body mass index change from baseline. (a) Average change in BMI from baseline at 6, 12, 18, and 24 months (± SEM). ODT $n = 14$, DBS+ODT $n = 15$. (b) One subject experienced significant weight loss (BMI decreased by 12 points from baseline to 24 months) and was excluded from this secondary analysis. ODT, $n = 13$; DBS+ODT, $n = 15$.

PD patients not yet experiencing many of the negative effects related to PD progression. Here, we investigated changes in BMI in the only prospective, randomized clinical trial of STN-DBS in very early stage PD.

2. Materials and Methods

Thirty subjects with early stage PD enrolled in the pilot clinical trial. The study was approved by the Vanderbilt University Institutional Review Board (IRB#040797) and the FDA (IDE#G050016). Subjects age 50 to 75 were eligible for enrollment into the study if they were diagnosed with idiopathic PD, treated with medications for more than six months and less than four years, Hoehn & Yahr stage II off medication, and without any history of motor fluctuations or dyskinesias [8–10]. Subjects were excluded if they had any major psychiatric illness, previous brain injury or operative intervention, or contraindications to surgery. A multiphased informed consent process ensured subjects' understanding of the study [11].

Subjects were randomized to receive DBS plus optimal drug therapy (DBS+ODT ($n = 15$) or ODT alone ($n = 14$; one subject dropped out after baseline due to family and career-related circumstances)). Subjects' heights and weights were recorded every six months at each week-long Clinical Research Center (CRC) study visit.

BMI was calculated at each visit using the height and weight collected on day one of the week-long antiparkinsonian medication and stimulation washout. Mean BMI for each group at baseline, 6, 12, 18, and 24 months was calculated (Figure 1). All within- and between-group comparisons were carried out with nonparametric t-tests, Wilcoxon Signed Rank test, and Mann-Whitney U test, respectively. Data are reported as mean ± standard deviation (SD) unless otherwise indicated.

3. Results

There was no significant difference in average BMI at baseline between the ODT (29.6 ± 4.2) and DBS+ODT groups (32.3 ± 5.7; Table 1; $p = 0.25$). All but one of the subjects in the pilot trial were overweight or obese at baseline (97%, 28/29 with BMI ≥ 25; Table 1).

Over the two-year study period, BMI change for the DBS+ODT group was not significant ($p = 0.63$; Figure 1). Although there was a reduction in average BMI in the ODT group over the two-year period, it was not a significant change from baseline to 24 months ($p = 0.75$). Additionally, the between-group difference in change in BMI score at 24 months was not significant ($p = 0.62$).

There was no BMI change in patients treated with STN-DBS from baseline to the first follow-up visit at 6 months ($p = 0.65$; Figure 1(a)) (prior studies reported the most rapid weight change after the first few months following surgery [4]). One subject in the ODT group experienced a gastrointestinal disorder unrelated to the study, which led to dramatic weight loss over the course of the trial (BMI was reduced by 32.6% from baseline to 24 months). A secondary analysis, conducted with this subject excluded, demonstrated that the slightly lower change in BMI for the ODT group compared to the DBS+ODT group was driven by this subject's extreme weight loss (Figure 1(b)).

4. Discussion

These results suggest that STN-DBS is not associated with weight gain in early stage Parkinson's disease. There was minimal change in BMI for the DBS+ODT group over two years (average BMI reduction = −0.17 ± 2.3). Although the BMI for the ODT group decreased slightly over two years (average BMI reduction = −0.89 ± 3.6), this change did not reach

Table 1: Characteristics at baseline[a].

Characteristic	ODT ($n = 14$)	DBS + ODT ($n = 15$)
Gender		
Male	12	14
Female	2	1
Age (years)		
Mean	60 ± 7.0	60 ± 6.8
Range	51–69	52–74
Baseline medicine use		
Mean duration (years)	2.1 ± 1.1	2.2 ± 1.4
Mean L-dopa equivalents (mg/day)	569 ± 389	451 ± 304
BMI category		
Healthy ($18.5 < \text{BMI} \leq 24.9$)	1	0
Overweight ($24.9 < \text{BMI} < 30$)	7	7
Obese ($\text{BMI} \geq 30$)	6	8
BMI (kg/m^2)	29.7 ± 4.3	32.3 ± 5.7

[a]Modified Table 1 from [10]. Mean ± SD.

significance ($p = 0.75$) and was largely driven by one patient who experienced dramatic weight loss from a gastrointestinal disorder unrelated to the study (Figure 1(b)). These findings suggest that weight gain previously observed in advanced PD patients [1] may not be due to STN stimulation but instead may result from the magnitude of symptom improvement that DBS provides in patients with a more advanced stage of PD.

It is well known that many PD patients experience weight loss with disease progression, and reduced BMI is correlated with increased disease severity [12]. There are many features of advanced PD that likely contribute to weight loss, including increased muscle rigidity, levodopa-induced dyskinesia with increased energy expenditure, and/or depression [5, 7]. Therefore, the great degree of improvement that advanced PD patients experience after STN-DBS therapy more likely explains the weight gain observed in previous isolated studies.

Here, we analyzed an early stage cohort not yet suffering from disabling features of PD that can lead to weight loss, and there was no significant change in BMI after STN-DBS for early stage PD patients. Because this study was open-label, it is possible that BMI changes were influenced by the subjects' awareness of their treatment allocation. Limitations for this study also include the study's small sample size and gender imbalance. It is also important to note that a majority of subjects were overweight or obese at baseline (28/29, Table 1).

Despite its superior clinical benefit over medications alone, one of the *perceived drawbacks* of STN-DBS therapy in advanced PD is its stimulation-associated weight gain [1]. This weight gain is likely due to a variety of factors including postoperative decreased energy expenditure [1] and dosage reduction in PD medications [2]. Since symptoms are typically mild in early stage PD, difference in pre- and postoperative energy expenditure is not expected to change as much as with advanced stage PD.

5. Conclusion

These results suggest that STN-DBS does not cause increased BMI in early stage PD. More study is needed to confirm these findings and the FDA has approved a phase III multicenter, randomized, double-blind, placebo-controlled, pivotal clinical trial evaluating DBS in early stage PD.

Disclosure

Medtronic representatives did not take part in data collection, management, analysis, or interpretation of the data or in preparation, review, or approval of the manuscript.

Conflicts of Interest

Vanderbilt University receives income from grants or contracts with Allergan, Intec, Ipsen, Lundbeck, Merz, Medtronic, and US WorldMeds for research or educational programs led by Dr. Charles. Dr. Charles receives income from Allergan, Alliance for Patient Access, Ipsen, and Medtronic for consulting or education programs. There are no conflicts of interest for Sarah H. Millan, Mallory L. Hacker, Maxim Turchan, Anna L. Molinari, and Amanda D. Currie.

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Research Article

Are Patients Ready for "EARLYSTIM"? Attitudes towards Deep Brain Stimulation among Female and Male Patients with Moderately Advanced Parkinson's Disease

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Objective. To explore, in female and male patients with medically treated, moderately advanced Parkinson's disease (PD), their knowledge and reasoning about Deep Brain Stimulation (DBS). *Methods*. 23 patients with PD (10 women), aged 46–70, were interviewed at a mean of 8 years after diagnosis, with open-ended questions concerning their reflections and considerations about DBS. The interviews were transcribed verbatim and analysed according to the difference and similarity technique in Grounded Theory. *Results*. From the patients' narratives, the core category "Processing DBS: balancing symptoms, fears and hopes" was established. The patients were knowledgeable about DBS and expressed cautious and well considered attitudes towards its outcome but did not consider themselves ill enough to undergo DBS. They were aware of its potential side-effects. They considered DBS as the last option when oral medication is no longer sufficient. There was no difference between men and women in their reasoning and attitudes towards DBS. *Conclusion*. This study suggests that knowledge about the pros and cons of DBS exists among PD patients and that they have a cautious attitude towards DBS. Our patients did not seem to endorse an earlier implementation of DBS, and they considered that it should be the last resort when really needed.

1. Introduction

Deep Brain Stimulation (DBS) of mainly the subthalamic nucleus (STN) has become an established surgical procedure for patients with advanced Parkinson's disease (PD) [1–3].

Nevertheless, it is not unusual that the beneficial effect of DBS is mitigated by various side-effects such as dysarthria, decrease in verbal fluency, and changes in behaviour, fatigue, and depression [4–6]. Careful selection criteria of patients considered for DBS have been established, including Levodopa response, age, normal brain MRI, good cognition, and realistic expectations [3, 7]. Following adequate information about the pros and cons of the procedure [8], the final decision to undergo surgery will be taken by the patient.

Research on the decision-making process of patients having already undergone DBS for PD had shown in retrospect that the individual patient's knowledge about (and attitude towards) DBS had been crucial for their final decision to undergo DBS [9]. However, non-operated upon patients' own thoughts, considerations, and apprehensions concerning advanced therapy for PD have received scarce attention in the literature [10, 11]. This issue is all the more interesting in light of existing gender differences, with more men than women undergoing DBS for PD [12–15] and given the current trend of suggesting DBS earlier in the disease progress [16–18].

The aim of this qualitative study was to explore, in female and male patients with medically treated, moderately advanced PD, their knowledge, feelings, and reasoning about DBS.

2. Material and Methods

2.1. Participants. In order to enroll in this study patients who may have had reason to consider DBS as a treatment alternative, a strategic selection was used: a nurse specialized in PD at Umeå University Hospital helped us to identify patients with

Table 1: Sociodemographic and clinical characteristics of 23 participants (10 women) with Parkinson's disease.

	Whole group	Men (%)	Women (%)	*P*
Number of Participants	23	13/(56.5)	10 (43.5)	
Age	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	
Age at diagnosis	52.4 ± 7.15 (40–63)	53.7 ± 7.5 (41–63)	50.7 ± 6.7 (40–61)	ns
Years since diagnosis	7.8 ± 4.7 (1–19)	8.0 ± 4.3 (3–17)	7.6 ± 5.5 (1–19)	ns
Age at interview	60.2 ± 6.8 (46–70)	61.6 ± 7.2 (46–70)	58.3 ± 6.1 (47–67)	ns
LEDD (mg)[€]	1185.5 ± 555.4 (525–2322)[€]	1356.7 ± 618.9 (525–2322)[€]	889.6 ± 250.4 (600–1310)[€]	ns
Number of daily doses[¥]	5.3 ± 1.8 (3–9)	5.9 ± 1.9 (3–9)	4.3 ± 1.2 (3–6)	0.045
Number (%) of patients who needed assistance in some daily activities	13 (56.5)	9 (69.2)	4 (40)	
Civil status	*N* (%)	*N* (%)	*N* (%)	
Cohabitant/single	19 (83)/4 (17)	11 (85)/2 (14)	8 (80)/2 (20)	
Level of education	*N* (%)	*N* (%)	*N* (%)	
Primary school	5 (21.7)	3 (23.1)	2 (20.0)	
High school	7 (30.4)	4 (30.8)	3 (30.0)	
University	11 (47.8)	6 (46.2)	5 (50.0)	
Employment status at time of interview	*N* (%)	*N* (%)	*N* (%)	
Working full time	1 (4.3)	1 (7.7)	0	
Working part time & sick-leave part time	7 (30.4)	2 (15.4)	5 (50.0)	
Sick-leave full time	8 (34.8)	4 (30.8)	4 (40.0)	
Retired	7 (30.4)	6 (46.2)	1 (10.0)	
Perceived general health at time of interview[#]	*N* (%)[#]	*N* (%)[#]	*N* (%)	
Excellent	1 (4.5)	0 (0.0)	1 (10.0)	
Very good	5 (22.7)	3 (25.0)	2 (20.0)	
Good	5 (22.7)	2 (16.7)	3 (30.0)	
Fair	10 (45.5)	7 (58.3)	3 (30.0)	
Bad	1 (4.5)	0 (0.0)	1 (10.0)	
Overall impact of PD on life at time of interview	*N* (%)	*N* (%)	*N* (%)	
Mild	1 (4.3)	1 (7.7)	0	
Moderate	22 (95.7)	12 (92.3)	10 (100.0)	
Severe	0	0	0	
Number of members of PD society (%)	19 (82.6)	11 (84.6)	8 (80.0)	

L-dopa = Levodopa.
LEDD = Levodopa equivalent daily doses.
[€]Missing data in 4 (1 male) patients.
[¥]Missing data in 2 female patients.
[#]Missing data in 1 male patient.

PD who despite high and/or frequent doses of dopaminergic medication experienced difficult symptoms and problems in daily life. There were 36 patients (23 males, 13 females) who fulfilled these criteria. Information about the study was sent to them and they were asked if they agreed to participate in an interview. One reminder was sent to those who did not answer. Twenty-one patients (14 men) accepted to be interviewed. One 80-year-old patient was excluded since he would not have been eligible for DBS due to high age. Three additional women were recruited along the same criteria after contact with Parkinson's Disease Society. Table 1 shows the description of the 23 enrolled patients.

The local ethical board at Umeå University approved the study, and all patients gave written informed consent before the interview (D.No: 2012-36-32M).

2.2. Data Collection. Data were collected through qualitative interviews [19, 20]. The majority of the interviews were conducted face to face by one interviewer (MS, GMH, or KH) in a setting chosen by the patient, usually in the patient's home. Due to practical difficulties (e.g., long distances) four patients were interviewed by telephone. The interviews were semistructured, with open-ended questions concerning broad areas, such as how the patients felt and reacted when

they received the diagnosis, their experiences of PD and its treatments over time, how it has been and how it is now to live with PD, their knowledge about treatments other than oral medication, especially DBS, and how they felt and thought about future treatment. In this paper, we focus on the patients' knowledge, feelings, and reasoning about DBS. Sample questions related to this focus included the following: *"Can you tell about the treatment that you currently have for Parkinson's disease?"; "Do you know of other treatments than oral medications?"; "How did you learn about these other treatments?";* and *"What do you think and feel about DBS as a treatment for PD?"* The interviewer tried to facilitate the narrative by follow-up questions such as, *"Please, can you explain further"; "What do you mean?"; "Please, could you give me an example?"*

Each interview lasted 60–140 minutes and was digitally recorded and transcribed verbatim.

In addition to the interview, each participant completed a short questionnaire about sociodemographic information. The patients were also asked to assess the overall impact of PD on their health by answering the questions *"In general, how do you perceive your overall health on a five-point scale (excellent, very good, good, fair, bad)?"* and *"How do you experience the overall impact of your Parkinson's disease (mild, moderate, severe)?"*

The patients' Levodopa equivalent daily doses (LEDD) at time of the interview were obtained from the patients' medical record.

2.3. Data Analysis

2.3.1. Qualitative Analysis of the Interviews. According to qualitative research design [19], preliminary analyses of the transcriptions were conducted in parallel with the interview process. The authors could thereby learn and reflect during the interview process, refine interview questions, and be alert when new aspects were described.

The main analysis of the interviews was made according to the constant comparison technique in Grounded Theory [19, 20]. The analysis contained the following phases:

(1) In a first phase all researchers separately read and coded three interviews and then met to compare codes and discuss content and meaning of the participants' experiences. Case narratives summarizing the essentials of each interview were written down. Another three interviews were then coded, compared, and summarized, and this process of sorting the data continued until all interviews were worked through and summarized in case narratives.

(2) In a second phase all interviews were reread by the first author and passages that concerned the participants' thoughts, reflections, and utterances about future treatment and DBS were identified, cut out, and organized in separate *"considerations-about-treatment"* files, one for each participant. These files were read and systematically coded and compared for similarities and differences by all researchers separately. In joint sessions the codes were compared and discussed, and categories and subcategories were elaborated. A core category embracing the content and meaning in the participants' narratives was also established.

(3) Thereafter the "*considerations-about-treatment*" files were analysed specifically for similarities and differences between men and women.

(4) Finally the whole interviews were reread to ensure that the categories and interpretations could be recontextualized into the interviews, that is, that the results were grounded in the data.

2.4. Statistical Analysis. Descriptive continuous variables were presented as average ± standard deviation and range by use of the SPSS for Mac 21.0. A p value < 0.05 was considered significant.

3. Results

3.1. Demographic Data and Clinical Outcome. Table 1 shows the sociodemographic and clinical characteristics of the participants, their self-assessed general health, and the overall impact of PD on life as a whole, as well as the Levodopa equivalent daily dose (LEDD). The mean disease duration was 7.8 years and the mean LEDD was 1186 mg. One patient was treated with Duodopa pump. Thirteen patients (4 women and 9 men) reported that they needed help in some of the daily activities. All but one patient considered that PD had a moderate overall impact on their life (Table 1).

3.2. Interviews. The participants displayed interest and engagement in the interview. They described in detail their symptoms and how these impacted on their everyday life. The most common symptoms reported by the patients were in various combinations: shaking, stiffness, wear-off and fluctuations, involuntary movements, cramps, fatigue, gait problems, low mood, and sensitivity to stress. There were no differences in symptom profile between men and women.

With respect to DBS, all participants were knowledgeable about it, and shared their views and reflections about DBS as a potential additional treatment. The sources of their knowledge were information from (and discussions with) medical staff, as well as information from the Internet, from watching TV-programs and by reading newsletters published by the patients' society. Several participants had also met other people who had undergone DBS for PD.

The analysis of the interviews resulted in the core category "Processing DBS: balancing symptoms, fears and hopes." This core category was underpinned by two main categories: "*Neurosurgical treatment requires careful consideration*" and "*Timing of concurrent issues of importance for DBS.*" Each of these two categories was supported by three and four subcategories, respectively (see Table 2). In the following, the categories and subcategories are presented and illustrated with quotes from the participants. The participants are given fictitious numbers from Mr. 1 to Ms. 23.

3.2.1. Processing DBS: Balancing Symptoms, Fears and Hopes. The participants' main opinion about DBS as a treatment

Table 2: A core category underpinned by two main categories. Each main category is supported by three and four subcategories, respectively.

Core category	Processing DBS: balancing symptoms, fears and hopes	
Main categories	Neurosurgical treatment requires careful consideration	Timing of concurrent issues of importance for DBS
Subcategories	(1) *Worries related to the neurosurgical procedure* (2) *Cautious attitudes towards outcome after DBS* (3) *Concerns about suitability of DBS for one's own symptoms*	(1) *Bringing up the issue of DBS* (2) *Utilizing the treatment alternatives gradually, step by step* (3) *Considering disease progression and life situation* (4) *Hoping for future breakthrough in PD research*

alternative was that DBS was not on their agenda for the time being. However, most of our interviewees considered that DBS might become an alternative later due to progress of the disease or to drawbacks and inefficacy of medication. Their current situation and the degree of difficulties that they experienced in daily life, as well as their hopes for research and discoveries of new and better treatment options for PD, also impacted on the way women and men reasoned about eventual DBS treatment.

Neurosurgical Treatment Requires Careful Consideration

(1) Worries Related to the Neurosurgical Procedure. Both men and women expressed worries about undergoing a neurosurgical intervention and the potential risk of damaging a very important and sensitive organ. Mr. 1 described his fascination about the capacity of the brain and at the same time his fear of being damaged during surgery: *"I remember a fishing tour, it is twenty-five years ago, I can spot it in a split second…"* and he continued "*they* (the electrodes) *are very close to the memory centre."*

Some of the participants' considerations consisted of more general expressions about surgery being something that always could pose a risk, whereas other concerns were more specifically related to the surgical procedure per se, such as being attached to the surgical equipment. Such thoughts implied feelings of uneasiness, as phrased by Mr. 10, "*would you like to be strapped up?*" The participants expressed both positive and negative concerns about the new routine of having DBS under general anaesthesia: on one hand, they felt relief at being asleep during drilling of the skull, and on the other hand they expressed fear of being totally without control during the course of surgery.

(2) Cautious Attitudes towards Outcome after DBS. Both men and women were concerned about what they perceived to be an inconsistent outcome after DBS. They had noticed that some friends and acquaintances who had DBS felt very well while others seemed to have deteriorated to a state worse than before surgery. Mr. 1 referred to the following observation of a friend: *"I know a person who was convinced DBS would turn out well and that was also the case initially, but then he encountered complications and now he is not that well anymore."* The participants' thoughts and considerations were mainly related to a potential negative outcome after DBS rather than to possible positive effects, and the risk of impaired balance after DBS was frequently mentioned as a concern.

Another common perception among the interviewed patients was that after DBS some patients seemed to need higher and more frequent doses of medication. The participants regarded this as a negative outcome of DBS. Ms. 14 said, *"I think that they* (fellow people with PD after DBS) *are in need of lots of medications."* Further, some of the participants had met people who after DBS did not seem to be their "*usual self*" any more. They were more low-spirited and nearly depressed, as told by Ms. 16, who stated, *"I must say that they became low, I would say depressed and their reasoning was in a different way, as well"*; and Mr. 3 stated, "*I think they have become more quiet, one might say a bit less positive.*" These participants implied thus that there is a possible risk that DBS may induce personality changes.

(3) Concerns about Suitability of DBS for One's Own Symptoms. The participants expressed concerns about whether they themselves would be suitable candidates for DBS surgery. The interviewees whose tremor was their main symptom considered that the shaking was difficult to treat only with oral medication, and they also knew that DBS might be efficient for alleviating tremor, "*I would probably be a good candidate for DBS because I am shaking…*" (Ms. 18). On the other hand, participants with impaired balance explained that they were less likely to be ideal candidates for DBS and Mr. 7 said that his neurologist considered that *"to offer me surgery would not be a good idea because it can lead to worsening of gait and some patients may get poorer balance."*

Timing of Concurrent Issues of Importance for DBS

(1) Bringing Up the Issue of DBS. The participants considered that they had enough knowledge about DBS as a treatment alternative, and the majority of them expressed no wish or need for more discussion about DBS for the time being.

Three women reported that they had found it difficult to consider DBS surgery when their clinician suggested it early in the course of the disease, and when one of them was referred to the DBS team, she declined to undergo the presurgical evaluation. Six of the men had been offered DBS and two of them declined to undergo presurgical screening. Among the four men who were assessed in view of DBS, two were not found to be ill enough, while the two others

eventually understood that they were not considered suitable due to early signs of cognitive decline. Both of them expressed that it would have been easier to accept the denial of DBS had they received a careful explanation of the reasons, as exemplified by Mr. 1: "*yes, my understanding perhaps would have been better if I had had a proper explanation as to why they instead recommended pump to me.*"

Still, bringing up the issues about DBS was considered highly relevant for two of the male participants and they were awaiting the right moment to bring it up themselves, as Mr. 12 put it: "*well, absolutely, I can bring up DBS myself, but today I do not feel it is the right time.*"

(2) Utilizing the Treatment Alternatives Gradually, Step by Step. The participants considered oral medication as the basic treatment, and they were hoping to be able to keep their current treatment stable for as long as possible. They considered advanced treatment alternatives, such as infusions and injections and DBS as a limited treatment resource. These different treatment alternatives were described as something linear, to be taken step by step. The typical description was that medication was followed by an increase of oral medication, thereafter apomorphine injection pens, and then pumps and finally ending with DBS. This can be illustrated by Mr. 8 in the following: "*I have to put up with certain things because I know that the more medications I 'waste' the more I tear on future resources*" and Ms. 19 stated that "*DBS is the last* (treatment alternative)." To utilize the last step, that is, DBS, was something unwanted, and, for the participants, it implied having nothing left to turn to if needed after surgery. Mr. 13 explained, "*So I'm still acting cowardly. You also need to have some treatment alternative left.*" Thus, the majority described DBS as a step they rather would postpone as long as possible. For a few patients though, DBS was more of a natural treatment step when medication no longer efficiently could control the symptoms of the disease, as described by Ms. 20, "*if the impact of medication ceases, then there is more* (DBS), *like a continuum.*"

(3) Considering Disease Progression and Life Situation. Even if most participants did not consider DBS in their current situation, they envisaged it as an alternative later on, if, or when, the symptoms became even worse. Both women and men expressed that when the disease had progressed to a level when they would have great difficulties managing their lives, DBS might be an additional treatment option. At a certain point of disease progression, any treatment that may provide a better life could be considered. This reasoning was put forward by Ms. 23 in the following: "*When I no longer am able to brush my teeth, then I might consider DBS*" and by Mr. 6: "*I would keep away from it* (DBS) *as long as possible. But it is hard to say, if you are struck by these difficulties you might feel that you would do anything . . ..*"

(4) Hoping for Future Breakthrough in PD Research. The participants were aware of the importance of research for improved life conditions for persons with PD, and they expressed hope that research would open up for totally new treatments. Some conveyed a hope for a real cure of the disease, rather than only better or newer pills to keep the symptoms at a manageable level, as uttered by Ms. 20, "*and then some researcher will find something marvelous.*" The patients' wishes for research-driven new and better treatments were particularly focused on nonsurgical options rather than new surgical procedures. They hoped for more efficacious oral medication, for reducing the numbers of daily doses to only one intake a day and for an easier handling of equipment when using pumps. Expectations and hope related to DBS were expressed in more general terms, such as wishes for even better surgical skills and techniques. There was awareness about stem cells research and also about alternative nonmedical treatment such as dietary advice, for example, eating blueberries.

However, even if most participants hoped for breakthroughs in research they underlined that research takes time and Mr. 4 confessed that he nowadays had low expectations: "*I've been interested but I have sort of given up on that now. It takes so long before it becomes available, stem cells and so on.*"

4. Discussion

The aim of this interview study was to explore attitudes towards (and perceptions of) DBS, among women and men with medically treated, moderately advanced Parkinson's disease, who could have had reasons to consider DBS as a treatment option. The most interesting findings were that both women and men were quite knowledgeable about DBS but they did not feel that DBS was an option for them for the time being. They had respect for DBS as being a serious surgical procedure done on the brain, and they considered that it should be kept as a last resort. They were also aware of its side-effects such as impaired balance and personality changes. In contrast to what has been reported in the literature [21–26] and what is commonly depicted in the lay press [27], our patients kept low expectations from DBS. However, the patients were also aware of the symptom profiles that are commonly considered to benefit from DBS (such as tremor) as well as the contraindications, such as balance problems and cognitive decline. There were no differences in those respects between male and female participants. On the whole, despite having had the disease for several years and despite the myriad of symptoms that they described, there was an agreement among patients that DBS should be utilized as a last treatment, when all other options were exhausted. This approach, conveyed by the patients themselves, is at odds with the recent "EARLYSTIM" trend in the literature in favor of proposing DBS for patients earlier in the disease progression [16–18].

4.1. Patients' Considerations about DBS. How come that our patients showed more reserved and less enthusiastic attitudes towards DBS than what one can commonly find in the literature? [16–18]. There may be several explanations to this: our patients had in general a high level of education with 78% of them having a high school or university degrees (Table 1), which could imply that they were able to better judge information conveyed by the lay media and health care professionals. Additionally, 83% of our patients were members of a Parkinson's disease organization (Table 1) and hence may be

well knowledgeable about the disease and its various treatments modalities, including their side-effects, as shown in other studies [8, 28]. Another factor to consider is that several of our patients had friends and acquaintances who had had DBS and they could thus see that the reality of DBS was sometimes different from the glamour, in particular concerning the side-effects. Patients who were on DBS may have conveyed to our participants a sense of disappointment despite the motor improvement [29]. The fact that our patients rated the impact of PD on their life as moderate (Table 1) and did not have a very long disease duration did not motivate them to consider a surgical procedure that may harbor complications and side-effects: they felt that for the time being they may have more to lose than to gain from DBS. In this respect, it is important to underline that it may be difficult for patients to admit that a chronic progressive illness is "severe" such that it may lead to seeking a treatment that they consider as a "last resort." Hence, our patients would most probably not have submitted themselves to an "EARLYSTIM" procedure [16, 30]. Three of the 13 men and five of the 10 women who were interviewed were still professionally active and this could also be a factor that influenced their attitude to DBS especially in relation to the possible side-effects from surgery that all patients were aware of. Finally, our patients expressed hope that research would bring about other non-surgical treatments that they would benefit from, enabling them thus to avoid a surgical procedure on their brains.

4.2. Gender Differences in Perceptions of DBS? Earlier studies have shown that, in relation to the gender prevalence of PD, women are underrepresented among those treated with DBS [12, 14, 15, 31]. The reason for this is unknown but it has been suggested that women might be more "afraid" of (and hesitant towards) neurosurgery compared to men [32]. Our results here showed that the narratives and ways of reasoning about DBS were similar in men and women. Both men and women contributed to all subcategories and categories. Both expressed some worries for surgery and its risks and had modest expectations on the positive effects of DBS. Likewise, both men and women considered DBS to be a treatment modality to postpone until the symptoms were too difficult to cope with and to consider when no other treatment option was left. Consequently, our results do not give evidence for any differences in perceptions and attitudes towards DBS among men and women that could explain the male predominance among patients treated with DBS for Parkinson's disease [12, 15, 16]. Additionally, it seems that our patients may not endorse an "EARLYSTIM strategy" for treatment of their PD, such as has been advocated recently in the literature [16, 17].

5. Limitations of This Study

For this study, near half of the patients who were invited to participate either declined the invitation or did not reply. This may have introduced a selection bias in favor of patients who are more outgoing and willing to discuss their disease and attitudes to DBS. Additionally, our participants are all living in Sweden and the results may not be applicable elsewhere.

6. Conclusions

In conclusion, our study showed that patients with moderately advanced PD who would be potential candidates for DBS had indeed good knowledge about the pros and cons of this treatment modality and expressed a realistic view about its potential limitations. They were not ready yet to submit to "early" DBS; they perceived DBS as a last resort that should be carefully considered only if absolutely needed. There were no differences between men and women concerning their reasoning and attitude towards DBS.

Conflicts of Interest

All authors declare no conflicts of interest.

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