

Effects of Deep Brain Stimulation on Cognition, Mood, and Behavior in Parkinson's Disease

a report by

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Disappointed by the limitations of pharmacotherapy, emboldened by technological advances in surgery and radiology, and armed with a better understanding of pathophysiology, physicians and scientists in the 1980s charted a renaissance of surgery for movement disorders such as Parkinson's disease (PD). The desire for a safer alternative to lesional or ablative neurosurgery, coupled with observations that intraoperative electrical stimulation used for target identification could alleviate abnormal movements,^{1,2} prompted the exploration of fully implantable deep brain stimulation (DBS) systems in movement disorders in the late 1980s.³ Use of similar systems was applied to investigations in epilepsy, psychiatry, and a variety of other neurological conditions in the late 1990s and early 2000s, probably for similar reasons to those that spurred DBS for movement disorders. In addition, experience with DBS in movement disorders, observations about the cognitive and behavioral effects associated with DBS, and the availability of animal models catalyzed the extension of DBS to new indications.⁴⁻⁷ This article focuses on summarizing the neurobehavioral outcomes of DBS in PD.

Neurobehavioral Effects of Deep Brain Stimulation in Parkinson's Disease

By far the most attention to neurobehavioral outcomes of DBS has been devoted to PD, and the majority of these studies have examined the outcome of subthalamic (STN) rather than thalamic or pallidal (GPi) DBS. Probably greater controversy attends the neurobehavioral outcomes after STN DBS than after GPi or thalamic DBS, and this probably reflects, at least in part, differences among studies in the sample characteristics, selection and exclusion criteria, length of follow-up, surgical technique, post-operative DBS programming and pharmacotherapy protocols, and the thoroughness and timing of the neuropsychological evaluation protocol. In general, studies employing cognitive screening instruments fail to detect neurobehavioral morbidity. While some may argue that the lack of change on screening instruments suggests that neuropsychological changes detected by more extensive evaluations are not of clinical significance, a recent meta-analysis of the empirical data suggests that screening instruments may be insensitive even to clinically meaningful changes after DBS.⁸ Consequently, cognitive screening measures are probably useful in helping to decide which surgical candidates can be excluded from further evaluation (including full neuropsychological evaluation), but insufficient to adequately document neurobehavioral outcomes of DBS.

Thalamic Deep Brain Stimulation

Four studies⁹⁻¹² have observed no widespread or significant changes in cognition, mood, or behavior after unilateral thalamic DBS, although one study suggested that statistically (but not necessarily clinically) significant declines in verbal memory are associated with left thalamic DBS. Few studies

have examined mood after thalamic DBS, but one study⁹ found an improvement in depressive symptoms four to 10 days after surgery.

Pallidal Deep Brain Stimulation

Unilateral GPi DBS appears cognitively safe, although this conclusion is tempered by the limited number of small-sample studies published.¹³⁻¹⁵ Although patients in one study showed statistically significant declines in visuoconstructional ability and verbal fluency, the changes were rarely of clinical significance. Even when using a liberal criterion of impairment (a test score falling one standard deviation below the mean of normative samples), another study¹³ observed that only six of the 20 patients showed any increase, no matter how small, in the percentage of tests in the impaired range. These patients tended to be older and were taking higher medication dosages prior to surgery. The safety of bilateral GPi DBS has been addressed in a handful of studies, and most found that the procedure is relatively safe from a cognitive standpoint.¹⁶⁻¹⁸ Nonetheless, a small minority of patients may develop cognitive morbidity. One case with magnetic resonance imaging (MRI)-confirmed electrode location had significant executive dysfunction ensuing from bilateral GPi DBS; importantly, when the stimulators were turned off, the impairment was partially reversed, thereby suggesting a direct role of stimulation in the neuropsychological deficit.¹⁹ Relatively isolated cognitive impairments were reported by the Toronto group in four patients.²⁰

Generally, studies using self-report measures of mood state have not observed improvements in depressive symptomatology, but two studies^{21,22} observed improvements in anxiety symptoms after GPi DBS. The clinical significance of these mean changes on symptom inventories is unclear. A case study reported hypomania and manic episodes after unilateral or bilateral GPi DBS,²³ but this morbidity may relate to an interaction between stimulation and medication. Similarly, it is unclear whether hypersexuality reported in isolated cases^{24,25} reflects a possible



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dopamine dysregulation syndrome, medication–stimulation interactions, or a phenomenon that is part of hypomania.

Subthalamic Deep Brain Stimulation

Controversy exists concerning the frequency, nature, and extent of cognitive changes after STN DBS and the factors underlying such changes. The reported frequencies under which neurobehavioral changes occur after STN DBS are quite variable. A recent review²⁶ estimated that cognitive problems (unelaborated upon) are observed in 41% of patients after STN DBS. However, examination of clinical studies suggests that profound changes in cognition are fairly rare. Rodriguez-Oroz and colleagues,²⁷ who carefully defined severity of impairment, found that severe impairments (incapacitating ones) occurred in 1–2% of cases. Moderate impairments (requiring treatment or exerting mild functional impact) and mild deficits (without functional impact) occurred in about 20% of patients. This latter figure is quite similar to that reported in another series,²⁸ but considerably higher than the approximate 4% incidence of cognitive impairment observed in a recent controlled multicenter trial (although it is not clear how this impairment was defined).²⁹ Most studies employing formal neuropsychological evaluations have been uncontrolled and used fairly small samples, and methodological limitations of these studies have been reviewed.^{30–34} These studies, with few exceptions,^{20,35–39} have observed small and circumscribed cognitive changes, most often in verbal fluency (timed oral word generation according to different phonemic or semantic constraints).^{16,17,37,39–58} Even among studies reporting more widespread cognitive declines there is disagreement as to the clinical meaningfulness of these changes. Alegret and co-workers³⁵ interpreted the changes not to be of clinical significance, in contrast to Saint-Cyr et al.³⁸ and Smeding et al.³⁹

As many of the neuropsychological studies of STN DBS have small sample sizes, greater weight should be given to the five controlled neuropsychological studies (excluding studies limited to language or cognitive screening evaluations), even though each has significant methodological and/or conceptual limitations. The first controlled neuropsychological study of STN DBS⁴⁵ compared outcomes in eight patients with bilateral STN DBS, eight patients undergoing unilateral pallidotomy, and eight unoperated PD patients. In that study, a selective decline in semantic verbal fluency was observed in the STN DBS group. Similar findings were observed in three other controlled studies^{48,50,59} and one study was helpful in defining the roles of surgery and stimulation in the changes.⁵⁰ While the procedure as a whole (surgery plus stimulation) was associated with subtle declines in delayed verbal recall and language, the effect of stimulation *per se* (comparing test performance with stimulators turned on and off relative to change observed in a control group) revealed no significant changes.

Another controlled study has found more widespread and serious cognitive changes³⁹ among 99 STN DBS patients evaluated within three months before surgery and six months after surgery compared with 36 medically treated PD patients tested six months apart. The STN DBS group had more marked decline in overall level of cognitive function (approaching statistical significance), verbal fluency, delayed recall, and visual attention, and showed diminished positive effect and increased emotional lability after surgery. However, as noted by the authors of the study, some effects may have been medication-related. For example, the decline in memory was no longer significant from the change in the control group once anticholinergic medication intake was accounted for. A quantitative meta-analysis⁹ of peer-reviewed English-language studies from 1990 to April 2006 that reported interval or ratio data provided pre- and post-

operative data on at least one standardized neuro-psychological test, and provided sufficient information to allow calculation of effect sizes, identified 28 studies that met inclusion criteria. These studies yielded a maximum combined sample size of 612 for calculation of the effect size of changes in various domains of cognition. Given the large number of techniques used in the literature, the tests were assigned to the functional domains they are commonly accepted to measure (e.g. verbal memory, language, attention). Analyses revealed that STN DBS (considered in its entirety as a treatment procedure) was associated with moderate declines in verbal fluency and mild declines in verbal memory and executive function. Mild improvements were observed in psychomotor/information processing speed.

Overall, the uncontrolled, controlled, and meta-analytic findings agree that STN DBS is relatively safe from a cognitive perspective. However, it should be borne in mind that meta-analysis does not, despite attaching greater weight to studies with larger samples, redress the methodological shortcomings of the studies included in the analyses. In addition, research has been unable to reliably identify factors underlying cognitive declines after STN DBS, but potential factors include advanced patient age, pre-existing cognitive impairment, misplacement of electrodes and/or current spread to limbic and associative territories, stimulation parameters, depression, apathy, and changes in medication after surgery. Mood changes and psychiatric complications after STN DBS have received increasing attention. A meta-analysis of 22 studies published between 1993 and 2004⁶⁰ estimated that about 7% of patients develop depression after STN DBS, that hypomania or a manic episode occurs in about 2%, and that other psychiatric disorders such as hypersexuality, lability, psychosis, and hallucinations occur in 4% of patients. Similar figures were reported in a review by Temel and colleagues:²⁶ depression 8%, hypomania or mania 4%, anxiety disorders <2%, and personality changes, hypersexuality, apathy, and aggressiveness <0.5%. These figures coincide with the overall rate of psychiatric matters requiring treatment (9%) in a controlled study of 99 patients.³⁹

Despite the similarity of average estimates, the range of the reported rates of behavioral alterations is quite broad:³² depression 1.5–25%, attempted and completed suicide 0.5–2.9%, and (hypo)mania 4–15%. One retrospective analysis reported transient mood disturbance in as many as 64% of patients.⁶¹ Factors possibly related to this variability in outcomes include patient selection/exclusion criteria, especially with regard to psychiatric illness, ascertainment and definition methods, surgical and post-operative management differences, rigor of study methodology, and surgical experience of a center (in that morbidity typically decreases as center experience increases).⁶² An informal review of studies raises the hypothesis that earlier published studies, studies with small samples (both of these factors may be associated with the experience of treatment centers), and studies with longer follow-up are apt to report a higher incidence of post-operative psychiatric morbidity. For example, one study of 11 patients over five years reported mania/hypersexuality in almost 20% and apathy in almost 10%.⁴¹ Another study of 37 cases collected between 1996 and 1999, using five-year follow-up, reported attempted suicide or suicide in 13.5%, apathy in 22%, disinhibition in 35%, psychosis and/or hallucinations in 27%, aggression in 8%, and dopamine dysregulation syndrome (levodopa addiction) in 8%. In contrast, a recent controlled study of 78 patients using a six-month follow-up reported depression in 5%, suicide in 1% and psychosis in 5%.³⁹ Potential mechanisms underlying psychiatric phenomena after DBS include pre-operative vulnerability,⁶³ stimulation, effects of surgery, psychosocial stressors, and

adaptation and alterations in medication after surgery. Stimulation in or around the STN has been observed to acutely lead to visual hallucinations,⁶⁴ pseudobulbar crying,⁶⁵ laughter and euphoria,^{4,66} and depression.^{67,68} Acute mood changes are typically provoked by stimulation, dorsal or ventral, to the target for motor symptom control,⁶⁹ whereas apathy is associated with ventral and medial STN DBS,⁵⁵ hypomania with anteromedial STN DBS,⁷⁰ and delusions with medial stimulation.⁷¹ Aggression occurs with stimulation in the region of the triangle of Sano,⁷² although aggression has also been observed after stimulation via accurately placed STN electrodes.⁷³

There seems to be a disparity between studies reporting post-operative depression and those using symptom rating scales and self-report inventories showing improvements in mood symptoms. Several studies using patient-report inventories have reported improvement in depressive symptomatology.^{16,38,74,75} Similarly, studies disagree as to whether apathy does or does not increase after STN DBS.^{55,76} On the one hand, studies reporting post-operative incidence of behavioral changes typically do not report a change from the pre-operative state, leaving it possible that the incidence of psychiatric conditions actually improves from pre-operative levels. Indeed, a study has shown that the incidence of psychiatric illness may be greater among PD surgical candidates (before surgery) than among the PD population in general.⁷⁷ Alternatively, patients completing inventories or responding to questions on rating scales may underestimate or be relatively unaware of behavioral changes, as may be indicated by discrepancies in the report of patients and their care partners.³⁸

A topic of increasing interest has been the phenomenon of pathological gambling, and isolated cases of this condition have been reported after DBS.^{39,78} A large retrospective study⁷⁹ identified seven persons who had displayed pathological gambling prior to surgery among 598 patients who underwent STN DBS. The deleterious urge to gamble lessened after surgery, resolving on average 18 months after surgery, but the condition of two patients worsened transiently. An abatement in gambling and other symptoms of dopamine dysregulation syndrome (e.g. off-period dysphoria, non-motor fluctuations) paralleled the course of dopaminergic medication reduction after electrode implantation. Another study of two cases also reported improvement in pathological gambling after STN DBS and concurrent reduction in opaminergic medication.⁸⁰

Comparisons of Unilateral versus Bilateral and Pallidal versus Subthalamic Deep Brain Stimulation

To determine whether second surgery (i.e. a staged bilateral procedure) carries cognitive risks relative to the first surgery, Fields et al.²¹ examined neuropsychological functioning in six patients before surgery, two months after the first GPi DBS operation, and again three months after the second operation. No patient experienced significant declines in cognition and delayed recall was improved relative to baseline following the second operation.

Rothlind and co-workers⁵⁷ recently reported on a randomized comparison of staged, bilateral GPi, and STN DBS in 42 patients and also found that minimal cognitive changes ensued from the second relative to the first operation. Semantic verbal fluency (the ability to quickly name items belonging to a category such as fruits) declined after left DBS regardless of whether the left side was operated on first or second. Although phonemic verbal fluency also declined after left DBS only, a significant effect of the second surgery was not demonstrated.

It is unclear whether GPi DBS is safer than alternative procedures such as pallidotomy or STN DBS. Studies by Merello et al.¹⁵ and Fields et al.⁸¹ found the cognitive safety of GPi DBS and pallidotomy to be comparable. Although some suggest that bilateral GPi DBS may entail less cognitive morbidity than bilateral STN DBS,^{27,74,82} the only randomized comparison of the cognitive effects of GPi and STN DBS has failed to reveal substantial differences between the two treatments.⁵⁷ A larger randomized trial comparing the effects (including the neurobehavioral consequences) of simultaneous bilateral GPi with STN surgery is nearing completion.⁸³

Social Function after Subthalamic Deep Brain Stimulation

Few studies have attended to social adaptation after surgery, a complex matter that has been more adequately addressed in the epilepsy surgery literature. Recent studies consistently provide evidence that gains in motor function and quality of life (QOL) do not necessarily translate into improved social integration and adaptation.^{84,85} Familial relationships can be compromised after DBS,^{85,86} especially when expectations of outcomes and perceived levels of functioning diverge between patient and care partner. In addition, despite improvements in motor function and QOL, patients may not return to work. In one study, only nine of 16 with work before surgery had returned to work 18–24 months after surgery.⁸⁵ Predictors of, and barriers to, social adjustment remain to be identified.

Summary and Conclusions

A review of the literature and meta-analyses indicates DBS for movement disorders to be quite safe from a neurobehavioral standpoint (while improving motor symptoms and both the patient's and care partner's QOL). However, it is also clear that a small proportion of patients have moderate or severe neurobehavioral morbidity. If one combines the various cognitive and psychiatric morbidities reported across studies, it is reasonable to estimate that about 10% of patients with PD undergoing DBS will experience one or more transient or permanent neurobehavioral adverse events. Deserving detailed empirical investigation is the observation in a few small uncontrolled studies that improvements in motor symptoms and QOL may not necessarily translate into social (re)adjustment. Research will need to identify the patient, medico-surgical, and psychosocial factors that are associated with neurobehavioral morbidity and preclude some patients from demonstrating gains in occupational, interpersonal, familial, and marital functioning. ■

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