Movement Disorders
Vol. 21, Suppl. 14, 2006, pp. S305–S326

Deep Brain Stimulation: Neuropsychological and Neuropsychiatric Issues

Valerie Voon, MD,[1,2]* Cynthia Kubu, PhD,[3] Paul Krack, MD,[4] Jean-Luc Houeto, MD,[5] and Alexander I. Tröster, PhD[6]

[1]*Department of Psychiatry, Toronto Western Hospital, Toronto, Canada*
[2]*Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA*
[3]*Department of Psychiatry and Psychology, Cleveland Clinic Foundation, Cleveland, Ohio, USA*
[4]*Department of Neurology and INSERM U 318, University of Grenoble, Grenoble, France*
[5]*Department of Neurology, Poitiers University Hospital, Poitiers, France*
[6]*Department of Neurology, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA*

Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor, cognitive, neuropsychiatric, autonomic, and other nonmotor symptoms. The efficacy of deep brain stimulation (DBS) for the motor symptoms of advanced PD is well established. However, the effects of DBS on the cognitive and neuropsychiatric symptoms are less clear. The neuropsychiatric aspects of DBS for PD have recently been of considerable clinical and pathophysiological interest. As a companion to the preoperative and postoperative sections of the DBS consensus articles, this article reviews the published literature on the cognitive and neuropsychiatric aspects of DBS for PD. The majority of the observed neuropsychiatric symptoms are transient, treatable, and potentially preventable. Outcome studies, methodological issues, pathophysiology, and preoperative and postoperative management of the cognitive and neuropsychiatric aspects and complications of DBS for PD are discussed. © 2006 Movement Disorder Society

Key words: Parkinson's disease; deep brain stimulation; depression; cognition; subthalamic

A range of neuropsychiatric symptoms have been increasingly recognized in Parkinson's disease (PD) and are presumed to be due to the underlying neurodegenerative process, dopaminergic medications, underlying vulnerabilities, and/or psychosocial factors. These symptoms range from disorders of cognition, mood (depression, mania), anxiety, hallucinations, to apathy.[1,2] More recently, a group of behaviors resulting from the chronic and pulsatile administration of dopamine (the dopamine dysregulation syndrome) has been identified.[3] These behaviors include "hedonistic homeostatic dysregulation" or a form of excessive and pathological use of dopaminergic medications for nonmotor purposes and medication-induced hypersexuality and pathological gambling. While the efficacy of bilateral deep brain stimulation (DBS) for the motor symptoms of advanced PD has been well established,[4] the effects of DBS on these nonmotor cognitive and psychiatric symptoms are less clear.

Thisarticle expands on the cognitive and neurobehavioral aspects of DBS for PD and is intended as a companion to the preoperative and postoperative sections of the consensus articles. The concept of neuropsychological or cognitive issues and neuropsychiatric or neurobehavioral issues will be separated for the sake of clarity, although overlaps will occur. It is recognized that on a clinical level, the assessment, management, and pathophysiology of these symptoms do not exist independently. It should be noted that in the vast majority of well-selected patients, DBS has demonstrated efficacy and safety. Furthermore, despite the range of postoperative psychiatric symptoms reported, the majority of

*Correspondence to: Dr. Valerie Voon, Human Motor Control Section, NINDS/NIH, Building 10, Room 5S213, 10 Center Drive MSC 1428, Bethesda, MD 20892. E-mail: voonv@ninds.nih.gov
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.20963

symptoms are transient, treatable, and potentially preventable.

As very few data on stimulation of the ventrointermedial nucleus (Vim) of the thalamus exist, this article will focus primarily on the published literature on stimulation of the subthalamic nucleus (STN) and globus pallidus internus (GPi) for PD. Outcome studies, methodological issues, pathophysiology, and the preoperative and postoperative management of the cognitive and psychiatric aspects of DBS for PD are discussed. The outcomes are covered in more detail in the preoperative and postoperative sections of the consensus articles and will only be briefly discussed here. The focus of the article is on methodological and pathophysiological issues. Issues regarding preoperative and postoperative management of psychiatric aspects of DBS are found primarily in the tables.

OUTCOME STUDIES

A range of postoperative cognitive and neurobehavioral symptoms have been reported following STN DBS and GPi DBS. While cognitive and neurobehavioral symptoms were found to be less frequent following GPi compared to STN DBS in several small studies,[5–7] the literature is far from conclusive as detailed comparative data have not been published. The discrepancies in neurobehavioral outcome have been postulated to be related to changes in dopaminergic medications, anatomical differences between the STN and GPi, and methodological issues. For instance, STN DBS is associated with a greater reduction in dopaminergic medications than GPi DBS and symptoms such as depression and apathy have been have been linked to postoperative dopaminergic withdrawal states.[8,9] Consequently, some of the post-STN stimulation neurobehavioral symptoms might reflect differences in management of dopaminergic medication following surgery rather than surgical site per se. Alternatively, the STN is much smaller and more variable in orientation than the GPi. Thus, current spread to adjacent nonmotor circuits and possible electrode misplacement are more likely to occur with STN than GPi DBS, thereby resulting in greater stimulation-related neurobehavioral symptoms. Finally, it is likely that methodological issues and biases in the literature contribute to the perception that STN DBS is associated with greater neurobehavioral morbidity. For example, the literature on GPi DBS has small cohort sizes, limited long-term follow-up data, and does not focus on neuropsychiatric issues. The apparently greater rate of cognitive and psychiatric adverse events after STN compared to GPi DBS may also reflect report bias. The early studies examining outcome following GPi DBS focused on motor symptoms with relatively little attention paid to nonmotor symptoms. In contrast, the more recent STN DBS studies have made a more concerted attempt to evaluate nonmotor as well as motor outcome following surgery. Similarly, while there have been no reports of psychiatric symptoms and very few cognitive studies following Vim DBS, this literature has the same methodological limitations and further selection bias issues as the GPi literature.

As there is a more comprehensive literature including several reviews on neuropsychological outcomes following DBS surgery for PD, we refer readers to recent comprehensive reviews pertaining to the neuropsychological literature.[10,11] The outcome studies on cognition and stimulation for advanced PD are summarized in Table 1.

Subthalamic Stimulation

Cognitive Outcomes

The vast majority of the neuropsychological outcome literature following DBS for PD has been published with patients who underwent DBS in the STN. The findings from these studies must be viewed with significant caution as most studies suffer from small sample sizes and only three of the published studies included a PD control group.[12–14]

The majority of the outcome literature suggests that STN DBS results in relatively little cognitive morbidity in well-selected patients.[13,15–20] Isolated studies note mild improvements in mental flexibility,[15,21,22] working memory,[22] visuomotor sequencing,[16,20,22,23] conceptual reasoning,[22,23] and overall cognitive function.[23]

The most robust finding across studies appears to be a decline in word fluency,[12–16,20,23–27] although other studies have also reported declines in verbal memory,[13,15,23,24,28,29] conditional associative learning,[22] visuospatial memory,[15,24,29] processing speed,[24] and selected measures of executive function.[29] Specific patient subgroups (e.g., older patients, patients with moderate cognitive impairment prior to surgery) may be at greater risk of sustaining cognitive and neurobehavioral deficits.[15,24,28–30] However, this has not been unequivocally demonstrated. For example, the available data do not make it clear if older age per se or other medical comorbidities associated with older age are responsible for the increased neurobehavioral changes found in some older patients following surgery.

Most studies include dementia as an exclusionary criterion; thus, there are no large-scale prospective data

TABLE 1. *Cognitive outcome studies following deep brain stimulation for advanced Parkinson's disease*

Reference	Sample size	Exclusion criteria	Medications/stimulation status	Postoperative test interval (mo)	Improvements	Declines
Alegret and colleagues[15]	STN = 15	>75 years, MMSE ≤ 25, major depression, marked atrophy	*Off* medications, ON stimulation	3	Trails B	Phonemic and Semantic Word fluency, visuospatial (JOLO), verbal memory (Rey AVLT), Stroop Color and Word,
Ardouin and colleagues[16]	STN = 49, GPi = 13	Significant cognitive or mood impairment	ON stimulation, *off* medications variable	3-6	Trails A and B	Phonemic and Total Word fluency
Daniele and colleagues[23]	STN = 20	History neurosurgery, dementia, severe psychiatric diagnosis, MMSE <20	*On* medications, ON/OFF stimulation	3, 6, 12, 18	MMSE (ON and OFF stimulation at 3, 6, 12 months); WCST-modified (ON stimulation at 3, 6, 12 months)	Phonemic Word fluency (ON and OFF stimulation, 3, 6, 12 months), verbal learning (Rey AVLT; OFF stimulation, 3 months)
Dujardin and colleagues[28]	STN = 9	Not specified	*On* medications, ON stimulation	3, 12	3 months: reaction time test (trend)	3 months: verbal memory (Grober and Bushke Word List Test); 3 months: 30% (n = 3) overall cognitive decline defined as a decline more than 1 SD below preoperative scores on 20% or more of tests; 12 months: Stroop Interference
Funkiewiez and colleagues[96]	STN = 50	Not specified	*On*/*off* medications, ON/OFF stimulation	3-48	None noted	None noted
Funkiewiez and colleagues[26]	STN = 70	Not specified	ON stimulation, mostly *off* medications	12, 36	None noted	Word fluency
Gironell and colleagues[14]	STN = 8, unilateral GPi (L = 5, R = 3), PD controls = 8	> 70 years, MMSE < 25, major depression, marked atrophy	*On* medications, ON stimulation	6	None noted	STN: Semantic Word fluency
Hariz and colleagues[31]	n = 1	Not specified	*On* medications, ON stimulation	1, 12	None noted	Overall cognitive function (assessed via Kokmen Short Tests of Mental Status)
Hershey and colleagues[32]	STN = 24	Dementia on clinical examination, history of neurological events, non-PD diagnosis	*Off* medications, ON/OFF stimulation	2	None noted	Stimulation reduced working memory/ response inhibition under high-cognitive-demand conditions (Spatial Delayed Response Task, Go–No Go Task)
Jahanshahi and colleagues[22]	STN = 7, bilateral GPi = 6	Not specified	*Off* medications, OFF/ON/OFF stimulation	Not specified	STN stimulation: trails B, WCST, random number generation; STN or GPi stimulation: trails A, Stroop Control, PVSAT, Missing Digit Test, modified	GPi stimulation: random number generation, WCST; GPi or STN stimulation: conditional associative learning (Visual–Visual Conditional Learning Test)
Krack and colleagues[18]	STN = 49	Dementia, major ongoing psychiatric illness, > 70 years	*On* medications, ON stimulation	1, 3, 5 years	None noted	Three patients developed dementia (per DSM-IV criteria) over 5-year interval
Limousin and colleagues[126]	STN = 20	> 70 years, MMSE < 24, MRI abnormality	*Off* medications, ON stimulation	12	None noted	None noted
Lopiano and colleagues[127]	STN = 16	Dementia, depression psychosis, MRI abnormality	Not specified	3	None noted	None noted
Moretti and colleagues[12]	STN = 9, PD controls = 9	Not specified	Not specified	1, 6, 12	None noted	Stroop, Phonemic, Semantic, Syllabic Word fluency

TABLE 1. *(Continued)*

Morrison and colleagues[13]	STN = 17, PD controls = 11	Dementia	ON/OFF stimulation, medications variable	~ 3	None noted	Surgery (without stimulation): attention and language composite scores comprised of several measures (Digit Span forward and backward, Brief Test of Attention, Boston Naming Test, Phonemic and Semantic word fluency); mild declines in verbal memory (Hopkins VLT-R, Randt Memory Test) as a function of the procedure (electrode placement and stimulation)
Moro and colleagues[27]	STN = 7	Dementia, ongoing psychiatric problems, prior brain surgery, poor general condition, mild parkinsonism or unstable drug regimen	Not specified	9	None noted	None noted
Perozzo and colleagues[19]	STN = 20	"Important cognitive decline," severe depression, psychotic symptoms, MRI abnormality	*On*/*off* medications, ON stimulation	6	None noted	None noted
Pillon and colleagues[20]	STN = 48, GPi = 8	Significant cognitive or mood impairment	Most patients *off* medications, ON/OFF stimulation	3, 12	STN stimulation: Stroop Word and Color, Trails; Graphic Series; reaction time; Spatial Working Memory	STN stimulation: Semantic Word fluency;
Saint-Cyr and colleagues[24]	STN = 11	Dementia, prior neurosurgery, unstable medical status, MRI abnormality, current psychiatric complications	*On* medications, ON stimulation	3-69-12	None noted	Working memory (PASAT, Digit Span, Backward), Trails B, manual speed and coordination (Purdue pegboard, coin sorting while finger tapping), Phonemic and Semantic Word fluency, verbal memory (CVLT Long Delay Free and Cued Recall), visuospatial memory (Battery of Memory Efficiency), declines more apparent in patients > 69 years
Trepanier and colleagues[29]	Unilateral pallidotomy = 42, bilateral STN = 9, bilateral GPi = 4	Dementia, other neurological or unstable medical disorders, prior neurosurgery, MRI abnormality, current psychiatric complications	*On* medications, ON stimulation	3, 6, ± 12	None noted	STN: Trails B, verbal memory (CVLT Long Delay Free and Cued Recall), Phonemic Word fluency, visual learning and memory (Battery of Memory Efficiency); GPi: Phonemic Word fluency, verbal memory (CVLT Long Delay Free and Cued Recall)
Volkman and colleagues[5]	STN = 16, GPi = 11	Not specified	*On* medications, ON stimulation	6, 12	None noted	None noted
Witt and colleagues[21]	STN = 23	Dementia (<130 DRS)	*On* medications, ON/OFF stimulation	6-12	ON stimulation: Random Number Generation Test	OFF stimulation: Stroop Interference errors

TABLE 1. *(Continued)*

Fields and colleagues[54]	Staged bilateral GPi = 6	Dementia, psychiatric disturbance (except for mild depression)	*On* medications, ON stimulation	2 months after first DBS; 3 months after second DBS	Delayed verbal recall (CVLT Long Delay Free Recall, Logical Memory II), WCST, Perseverative Errors	None noted
Fukuda and colleagues[128]	L GPi = 2, bilateral GPi = 5	Not specified	ON stimulation	Not noted	DLPFC activation during motor sequence learning	None noted
Miyawaki and colleagues[62]	Bilateral GPi = 1	Not specified	*On* medications, ON stimulation	One month after left DBS; 3 weeks right DBS	Left GPi: Stroop Color/Word; WMS-R Figural Memory Right GPi: CVLT Total Trials and Long Delay Free Recall	Right GPi: CVLT perseverations, Free and Cued Recall intrusions
Tröster and colleagues[56]	GPi = 9		*On* medications, ON stimulation	3	None noted	DRS Construction subtest, Semantic Word fluency
Vingerhoets and colleagues[55]	L GPi = 13, R GPi = 7	Dementia, MMSE < 24, nonidiopathic PD, MRI abnormalities, any illness that would compromise neuropsychological evaluation	*On* medications, ON stimulation	3	None noted	None noted on group analyses, individual patient analyses showed decline in ~ 30% of patients based on study defined cognitive impairment index
Hugdahl and Wester[65]	Mixed thalamotomy and Vim DBS	Not specified	*Off* medications? ON stimulation	Not noted	Verbal memory	None noted
Schuurman and colleagues[68]	Mixed thalamotomy and Vim DBS with PD (thalamotomy = 21,DBS = 19), ET = 13, MS = 9	MMSE < 24	*On* medications, ON stimulation	6	None noted	Left stimulation: Semantic Word fluency
Tröster and colleagues[67]	Vim = 9, L = 5, R = 4	Non-PD diagnosis	ON stimulation, *on* medications	4	Verbal memory (CVLT, Delayed Recognition, Logical Memory II)	None noted
Tröster and colleagues[129]	Vim = 1	Not specified	3, 6 months: *on* medications and ON stimulation; 18 months: *on*/*off* medications and ON/OFF stimulation	3, 6, 18	3 months: DRS Construction; 6 months: semantic word fluency, verbal learning (CVLT); 18 months (ON vs. OFF stimulation): semantic fluency	3 months: Semantic Word fluency, verbal learning; 18 months (ON vs. OFF stimulation): episodic memory
Woods and colleagues[66]	Unilateral Vim = 6	No longer responsive to DA medications or intolerable DA SE	*On* medications, ON stimulation	12	DRS Conceptualization; Verbal Memory (CVLT Long Delay Free Recall, WMS-I, Logical Memory I)	None noted

AVLT, Auditory Verbal Learning Test; CVLT, California Verbal Learning test; DA, dopamine; DLPFC, dorsolateral prefrontal cortex; DRS, Mattis Dementia Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorder, 4th edition; GPi, globus pallidus interna; JOLO, Judgment of Line Orientation Test; L, left; MMSE, Mini Mental Status Exam; PVSAT, Paced Visual Serial Addition Test; R, right; SD, standard deviation; STN, subthalamic nucleus; Trails A and B, Trail Making Test, Part A and B; Vim, ventrointeromedial nucleus of the thalamus; VLT, Verbal Learning Test; WCST, Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale–Revised; SE, side effects.

available documenting the potential effect of STN DBS on cognitive function in patients who met diagnostic criteria for dementia prior to surgery. Krack and colleagues[18] reported the gradual development of dementia in 3 of 49 patients who were followed for 5 years following placement of DBS electrodes in the STN. No patient met diagnostic criteria for dementia prior to surgery. The authors attributed the development of dementia to ongoing Parkinson's disease progression as no acute cognitive changes were evident immediately following

surgery in the three patients and the bulk of the literature indicates that stimulation does not result in marked cognitive declines.

Although most of the literature suggests that STN DBS is relatively benign from a cognitive perspective, there are reports of patients who sustained significant cognitive decline following surgery. Morrison and colleagues[13] stated that 1 of their 20 subjects demonstrated significant cognitive decline following surgery with later improvement in function following STN stimulation. Despite the improvement noted with stimulation, his overall cognitive function was worse after surgery and he had to move from an independent to an assisted living setting due to cognitive changes. He was an older man, but another case report by Hariz and colleagues[31] documented a similar negative outcome in a 53-year-old following placement of DBS electrodes in the STN. Thus, it does not appear that age per se is the only predictor of a potentially deleterious cognitive outcome. To date, little has been done to assess potential cognitive risk factors systematically.

Only a handful of studies have systematically examined the role of stimulation and/or medications on neuropsychological performance. Systematic assessment ON and OFF STN stimulation demonstrated either no significant cognitive effects[13] or improvements in processing speed,[20,22] working memory,[20,22] random number generation,[21,22] and problem-solving[22] with stimulation. One study demonstrated a decline in performance on a conditional associative learning task[22] following stimulation, and impairments in response inhibition measures (self-detected errors on Stroop interference task) have also been documented.[21] Performances on working memory and response inhibition measures under high-cognitive-demand conditions were shown to decline with STN stimulation.[32] Systematic assessment *on* and *off* medications during STN stimulation was not associated with cognitive changes[19] on a variety of neuropsychological measure, including tests sensitive to frontostriatal dysfunction [the Raven Color Matrices, Corsi Block Tapping Test, Bisyllabic Words Repetition Test, Paired Associates Learning Test, Spatial Learning Test, Rivermead Behavioural Memory Test, Visual Search Test, Reaction Times Tests, Modified Wisconsin Card Sorting Test, Trial Making B Test, and word fluency measures (category, phonemic)]. These findings are at odds with previous reports in the literature that demonstrated cognitive changes associated with dopaminergic medications in unoperated PD patients. The discrepant findings might reflect methodological issues such as limited power or measurement factors and clearly, more data are needed to evaluate the role of medication status in cognitive function ON and OFF STN DBS.

Neuropsychiatric Outcomes

Like cognitive outcomes, the outcome data on neuropsychiatric symptoms should be approached with caution due to similar methodological issues. The following frequencies of postoperative psychiatric symptoms have been reported following STN stimulation. Transient confusion in the immediate postoperative period has been reported in 1% to 36% of patients.[4,8,18,33–40] Postoperative hypomania has been reported in 4% to 15% of patients, usually occurring within the first 3 postoperative months.[18,38,41,42] Emotional reactivity, or excessive mood-congruent emotional responses to minor triggers, was identified in 75% of STN stimulation patients.[30] Suicide attempts and/or suicides have been documented in uncontrolled series ranging from 0.5% to 2.9%.[18,30,43,44] A multicenter study of 450 STN DBS patients reported a postoperative suicide rate of 0.5%.[45] In contrast, a study of 120 patients who underwent DBS (including PD, dystonia, and essential tremor patients) documented a postoperative suicide rate of 2.9% in PD patients who had undergone STN DBS.[44]

Individual episodes of postoperative depression have been reported in 1.5% to 25% of patients.[8,18,30,33,38,46–48] Although overall group depression scores have been reported to improve at 3, 12, and 36 months,[8,26,42,49,50] the clinical relevance of these findings is not clear. Studies designed to examine mood symptoms utilizing standardized diagnostic criteria reported frequencies of 21% and 25% with the onset of depression within the first 2 postoperative months.[25,30] Another study distinguishing between depression requiring antidepressants and depression secondary to dopaminergic withdrawal symptoms reported rates of 18% and 38%, respectively.[8] In a large 3-year study using patient-rated depression scale cutoff scores, moderate to severe depression was documented at baseline in 33%, in 20% in the first postoperative year and in 15% in the third postoperative year.[26] Without a control group, the implications of these reported frequencies are not clear. Potential misinterpretations of findings in uncontrolled studies are illustrated in the literature on pallidotomy. Early uncontrolled studies suggested an elevated risk of postoperative depression following bilateral posteroventral pallidotomy.[51,52] However, a subsequent prospective randomized wait list control group study did not demonstrate any differences in depression outcomes in the surgical or wait list control group.[53] Furthermore, the only risk associated with de-

pression was a past history of depression, irrespective of surgical procedure.[53]

Within the first 3 postoperative months, transient apathy occurs as part of the dopaminergic withdrawal syndrome, although the incidence is not known. The proportion of patients with apathy as measured on the UPDRS part I was documented at baseline to be 8.7% and at the third postoperative year to be 24.6%.[26] Permanent apathy was reported in the long term in 12% of patients, among whom 80% had an associated dementia.[18] In this same longitudinal study, no visual hallucinations were reported within the first 3 postoperative months but in the long term 10% developed visual hallucinations. Sixty percent of the patients with hallucinations also had associated dementia.[18] Overall, 6% of patients in the study developed dementia in the long term.[18] One study reported that 6% developed visual hallucinations or psychotic symptoms, although whether these occurred in the early or late postoperative period is not clear.[8]

The effects of DBS on patients' social reintegration and adjustment have received limited attention. In a retrospective study, late age of onset of PD was associated with poor global social adjustment. Persistent levodopa-induced motor symptoms were associated with poor adjustments in social outcome measures. Despite motor improvements, 25% had a deterioration in marital relations following surgery.[30]

The frequency of reported psychiatric symptoms in the literature varies for a variety of reasons: selection bias (e.g., differences in the inclusion of patients with preoperative psychiatric and cognitive vulnerabilities), measurement bias (e.g., differences in methods of assessment and diagnostic ascertainment), or lack of systematic consideration of confounding variables (e.g., differences in the rate or degree of change of dopaminergic medications).

The most common psychiatric symptoms observed include apathy, emotional reactivity, depression, and hypomania. The reasons for such a range of symptoms observed is due to the multifactorial etiology of the psychiatric symptoms, including preoperative vulnerability, changes in dopaminergic medications, surgical and stimulation effects, underlying PD-related factors, and psychosocial effects. The pathophysiology underlying these different psychiatric symptoms is discussed in more detail below.

GPi Stimulation

Cognitive Outcomes

Neuropsychological changes following GPi DBS have been investigated. Several studies have not documented any significant cognitive decline following GPi DBS.[29,54,55] Mild declines in semantic word fluency[56,57] and visuoconstruction scores[56] have been documented. Pallidal surgery (i.e., pallidotomy or GPi DBS) in PD patients appears to disrupt frontosubcortical circuits underlying efficient shifting between semantic categories and/or access to semantic categories rather than affecting semantic stores.[58]

In one study, a subgroup of older patients demonstrated a higher postoperative rate of mild cognitive deficits, although the clinical and statistical significance of these findings is uncertain.[55] In particular, this study defined cognitive change in a very liberal manner (any magnitude of change in the percentage of tests falling 1 SD below normative means) and did not find any significant changes in average scores.

These observations highlight that some patients might be at increased risk for neurobehavioral deficits following DBS. For example, significant executive dysfunction was described in a case report following chronic bilateral GPi stimulation that was partially reversible with discontinuation of stimulation.[59]

Neuropsychiatric Outcomes

Postoperative psychiatric symptoms in GPi DBS are believed to be less frequent than after STN DBS. In one unblinded comparative study, 3 of 16 STN versus 0 of 11 GPi patients developed depression requiring psychiatric treatment.[8] In a 1-year follow-up of a small blinded parallel randomized study, whereas none of the 11 GPi patients developed neuropsychiatric complications, 2 of 12 STN patients developed transient perioperative anxiety, 1 of 12 transient hallucinations responding to a decrease in levodopa dose, and 1 of 12 persistent apathy in the context of cognitive changes.[6] In an extension of a third unblinded randomized comparative study reporting on the 3- to 4-year outcomes, persistent neuropsychiatric adverse events were more common in the STN compared to GPi group, although few details were reported. For instance, 11 of 49 STN patients developed unspecified mild–moderate memory or psychiatric difficulties compared to 1 of 20 GPi patients. Of these psychiatric events, 3 of 49 STN patients had a mild–moderate depression compared with 1 of 20 GPi patients.[7]

While these preliminary data are intriguing, based on the reasons previously discussed, the literature is far from conclusive; larger controlled studies using systematic validated assessment tools are required. Overall improvement in group depression and anxiety scores have been documented with bilateral GPi, although the clinical relevance is not known.[8,60,61] One study that differ-

entiated between primary and secondary anxiety suggested that GPi stimulation improved primary anxiety symptoms.[61] Case reports of mania have been reported.[62] Case reports of hypersexuality have been reported, although it is unclear if this was part of a manic syndrome or dopamine dysregulation.[63,64]

Thalamic Stimulation

Very few studies have examined the neuropsychological consequences of Vim DBS for the treatment of PD. These studies have been hampered by small cohorts, mixed thalamotomy or Vim stimulation groups, or mixed patient groups with non-PD diagnoses, thus limiting generalization of the findings. On the whole, thalamotomy or Vim DBS appears not to have a significant effect on cognitive abilities.[65,66] Improvements in verbal memory have been documented.[65–67] Left-sided Vim stimulation may be more likely to be associated with verbal fluency decline.[68] Despite the limited evidence, Vim is considered a relatively safe target with fewer cognitive or neurobehavioral sequelae, particularly since postoperative changes in dopaminergic medications are less necessary and the stimulation site is less likely to overlap with regions with limbic activity (see Lang and colleagues in this issue for further details on patient selection).

METHODOLOGICAL ISSUES

Numerous methodological issues confront DBS research on neurobehavioral outcomes.[10,11] The greatest methodological issues in the current literature are the small sample sizes and the general absence of control groups.

Sample Size and Power to Detect Effects

Modest sample sizes limit the power of a study to detect the effects of DBS on cognition and behavior and also limit the reliability and generalizability of findings. For instance, a recent study investigated the issue of sample size by calculating the effect sizes and statistical power associated with verbal fluency changes reported in previously published studies.[69] The parameter of verbal fluency was selected given its relatively common and sizeable neuropsychological change after DBS. The authors found that the power to detect verbal fluency changes was typically very low, ranging in published studies from 0.06 to 0.45 (power is expressed in a range from 0 to 1, with 1 indicating perfect or 100% power, and adequate power is commonly accepted to be 0.80 or above). Furthermore, in reviewing 30 neuropsychological studies of STN DBS, only 2 of 30 studies had adequate power to detect large effect sizes and none had the power to detect small or medium effects. Consequently, the neuropsychological safety of DBS may be overestimated.

Control Groups and Inferences About Change

The absence of control groups makes it difficult to determine whether a change occurring after DBS might also have occurred in a nonoperated control group, thus reflecting non-DBS factors (e.g., disease progression, medication, test–retest practice effects, or some other extraneous variable). Several practical and ethical difficulties exist in selecting and obtaining a control group.[10] Given the now widespread availability of DBS, it is increasingly difficult to recruit the most relevant control for DBS research: a surgical wait list control group. A PD control group not matched to the surgical group in disease and demographic characteristics is a secondary option and is preferable to using a normal control group. However, even use of a wait list control group is not without potential interpretative pitfalls. Since medication dosage is often greatly reduced after STN DBS, neurobehavioral changes, when they occur in the surgical but not the control group, cannot confidently be interpreted as effects of DBS. Medication effects, although expected to be mild, can both positively and negatively impact cognitive functions and have a more profound effect on mood. The interactive effect of surgery or DBS and medication is a further complexity. For example, it has recently been shown that pallidotomy may alter the effect that levodopa has on certain cognitive functions.[70]

Test–Retest Effects

The absence of a control group makes it difficult to determine the extent to which changes in test scores reflect practice effects. When individuals undergo repeated evaluations using the same or similar test instruments, scores may improve simply due to experience with the test rather than improvement of the function being evaluated. Strategies to minimize practice effects include employing multiple versions of the test that differ in specific content but not in difficulty, maximizing the test–retest interval, or utilizing statistical techniques such as Reliable Change Indexes or standardized regression-based norms.[71–73] Notably, a familiarity or "test wise" effect may occur even when alternate forms are used.

The proper PD control group remains necessary even when one has knowledge of test–retest effects in test normative samples because it is generally not known whether similar test–retest effects occur in normative and

clinical populations. For instance, there is suggestion that practice effects may not occur in PD on numerous tests.[13,74] The absence of "assumed practice effects" complicates interpretations of both the presence and the absence of test score changes. For example, if a practice effect does not occur in PD, then postoperative score gains likely represent improvements rather than practice effects, while the lack of gain or decrements likely represent a true lack of change or deterioration, respectively. Conversely, if practice effects occur in PD, then a lack of gain may represent a decline. Furthermore, if practice effects do occur, then small declines in scores may actually represent a sizeable deterioration in function, and a score gain would have to exceed the practice effect before it is considered an improvement. Interpreting individual patient test score changes is rendered even more complex by possible interactions between surgery, medication, stimulation, and practice effects.

Changes in Average Scores vs. Caseness and Frequency of Changes

Most studies focusing on neurobehavioral changes associated with DBS report changes in group mean scores on various tests, symptom self-report inventories, and rating scales. Studies should more consistently report the frequency of individual changes of various magnitudes and also changes in caseness. That is, changes in average scores and caseness (the number of persons having a condition, such as depression, before and after surgery) do not always go hand in hand and may be misleading.[75] The establishment of caseness and frequency of changes of given magnitude are important in determining the incidence of certain conditions before and after surgery and thus more accurately define the risks of morbidity.

Other Methodological Issues

The current lack of accurate estimates of the incidence of various conditions before and after DBS highlights several other methodological needs. Specifically, studies should be prospective and assess neurobehavioral functions systematically. Unfortunately, many studies appear to have relied on the patient's or caregivers' spontaneous report of changes after surgery, subjective impressions of patients and physicians, or on retrospective searches of databases in documenting cognitive or psychiatric changes following DBS. Studies should also use standardized criteria and test instruments and several authors have already commented thoughtfully and extensively on considerations in neuropsychological test selection for movement disorders surgery.[20,24,72]

To identify preoperative predictors of neurobehavioral morbidity, preexisting neurobehavioral conditions should be accurately defined and systematically assessed and diagnosed. The identification of neurobehavioral outcome predictors represents an urgent clinical need. Most studies have excluded, not assessed, or not reported on patients with preoperative neurobehavioral symptoms. In order to determine the role of preoperative neurobehavioral symptoms in postoperative outcomes, prospective studies with such groups of patients are required.

The screening of patients for behavioral conditions, the formation of diagnostic subgroups, and outcome evaluation should be achieved using different test instruments, otherwise circularity may occur. Since a score on a given instrument is usually the best predictor of a score obtained by the same person on that instrument at a later time point (given shared construct and method variance), separate measures would ideally be used to define risk factors and outcomes. Consequently, an ideal evaluation would utilize multiple measures of the same construct that rely on different administration methods to provide convergent evidence of change.

Several other knowledge gaps related to methodological and study design limitations remain to be addressed in future studies. Very few studies have compared STN DBS outcome with stimulators turned ON or OFF.[20,22] Fewer studies have examined the relationship between stimulation parameters and cognition,[76] behavior,[77] or subjective psychotropic effects.[26] No studies have systematically varied stimulation parameters and assessed cognition in a within-subject design. Future studies should clearly indicate stimulation parameters in their patients and how electrode placement was verified. Behavioral studies, in addition, should control for standard markers associated with neurobehavioral outcomes (e.g., family history of depression and depression outcome in PD, the effects of mood on obsessive–compulsive rating scores) and psychosocial factors. The literature is difficult to interpret given the significant heterogeneity in participants, surgical and neurobehavioral evaluation methods, time intervals between assessments, and postoperative medication adjustments. Large multicenter collaborative studies are likely needed to address important questions about neurobehavioral outcomes and their prediction, and in particular, about long-term outcomes.

TABLE 2. *Regions implicated in psychiatric symptoms associated with subthalamic stimulation for Parkinson's disease*

Neuroanatomical regions	Comments
Medial limbic subthalamic nucleus	Connection via indirect CSTC pathway to limbic cortical regions[88,130]; embroyologically and structurally related to LH with efferents to VTA[88,131]; implicated in psychiatric symptoms of STN stimulation[81]
Anterodorsolateral sensorimotor subthalamic nucleus	Most effective site of stimulation for motor symptoms[132,133]; potential regions affected: current diffusion to ZI or H2 fields of Forel[132,134]; retrograde stimulation of afferent dopaminergic or serotonergic neurons from SN or DRN; anterograde stimulation of ascending dopaminergic neurons projecting to basal ganglia[135,136]
Anterior cingulate (AC), orbitofrontal cortex, amygdala	Connection to medial limbic STN via indirect CSTC pathway and connections of basal ganglia circuitry[88,130]; impaired performance on response conflict task associated with decreased activation of right AC in STN DBS patients[137]
Lateral hypothalamus and ventral tegmental area	Medial limbic STN embryologically and structurally related to LH; efferent projection from LH to VTA[88,131]; VTA implicated in reinforcing effects of drugs of abuse[138]; implicated in psychiatric symptoms of STN stimulation[81]
Subgenual cingulate (Cg25)	Cg25 postulated to play a modulatory role in major depression and normal sadness[139]; Cg25 efferents to LH in nonhuman primates[140]; LH and medial limbic STN embryologically and structurally related[88,131]; Cg25 efferents to brainstem, ventral striatal, and thalamic regions[140] with indirect connections to STN
Zona incerta	Structural and functional relationship between hypothalamus and rostral ZI implicated in autonomic symptoms[141]; cingulate cortical efferents to rostral and dorsal ZI in rodents[142]; reciprocal projection of SN pars reticulata and pars compacta to ZI[143]; reciprocal projection of amygdala to rostral ZI in rodents[144]; fiber bundles within or adjacent to ZI: ascending dopaminergic neurons from SN[135,136]; ascending serotonergic fibers; fields of Forel and pallidosubthalamic fibers[119]; stimulation of ZI associated with depressive symptoms[89]
Substantia nigra	Reciprocal projections of STN to SN[88]; ascending projections from SN to striatum via MFB run through ZI and appositioned to anterodorsal border of STN[135,136]; stimulation of SN pars reticulata (± pars compacta) associated with acute depressive symptoms[78]
Medial forebrain bundle	SN and VTA project to striatum and cortex via MFB which ascends near ZI[135,136]
Pedunculopontine nucleus	Reciprocal projections of PPN to STN[88,145]; implicated in STN hyperactivity in PD animal model[145]; observed motivational effects in excitotoxic lesioned PPN in rodent models may be mediated by executive deficits[146,147]
Dorsal raphe nucleus	Serotonergic fiber efferents from DRN to STN[88]; ascending serotonergic fibers to widespread cortical regions run through ZI
Area TE of inferotemporal cortex	CSTC pathway originating in area TE[117]; hypothesized to be involved in visual hallucinations in PD[117]
Fiber bundles	Stimulation more likely to affect large myelinated axons than cell bodies[148]; most effective site of stimulation at anterodorsal border of sensorimotor STN with current diffusion to fiber bundles located at or near ZI[132,133]
Thalamic nuclei	Afferents from parafascicular (PF) thalamic nuclei to STN implicated in STN hyperactivity in PD animal models[145]; PF nuclei project primarily to limbic and cognitive STN regions[88]

Adapted from Voon and colleagues.[45]

CSTC, cortico–striato–thalamo–cortical; DRN, dorsal raphe nucleus; LH, lateral hypothalamus; MFB, medial forebrain bundle; PD, Parkinson's disease; PPN, pedunculopontine nucleus; SN, substantia nigra; STN, subthalamic nucleus; VTA, ventral tegmental area; ZI, zona incerta.

PATHOPHYSIOLOGY OF PSYCHIATRIC AND COGNITIVE SYMPTOMS ASSOCIATED WITH SUBTHALAMIC STIMULATION

The postoperative cognitive and psychiatric symptoms evident following DBS, similar to those observed in PD itself, most likely reflect a multifactorial etiology. For instance, six etiological factors, which are not necessarily mutually exclusive, can be postulated to account for the psychiatric symptoms following STN stimulation: preoperative factors (including premorbid psychiatric vulnerabilities),[30] surgical factors (e.g., the duration of the surgical procedure, electrode trajectories, the number of electrode passes, complications),[24] STN stimulation factors (e.g, placement, parameters),[78] postoperative factors (e.g., antiparkinsonian drug changes),[9] psychosocial adjustment,[79] and underlying PD-related factors (e.g, the neurodegenerative process and involvement of nondopaminergic symptoms).[80] The following section on pathophysiology focuses primarily on STN stimulation rather than GPi or Vim. Given the paucity of data in the literature, the following discussion is by nature speculative. Some aspects of the pathophysiology on neurobehavioral symptoms and its relationship to stimulation for PD have been reviewed in the literature.[45,81]

Table 2 outlines neuroanatomic regions and downstream connections of potential psychiatric relevance, which may be affected by STN stimulation either directly, by current spread, or by misplaced electrodes.

Table 3 summarizes some of the neurobehavioral changes associated with the treatment of PD with specific reference to STN activity. The range of behavioral symptoms associated with presumed increases or de-

TABLE 3. *Neurobehavioral symptoms proposed to be associated with stimulation of the subthalamic motor, cognitive, and limbic regions in Parkinson's disease*

Behavior of Interest	Increased STN activity[88,149-152] (*off* drug or OFF STN stimulation)	Decreased STN activity[152,153] (*on* drug or ON STN stimulation)
Motor (motor circuit)	Bradykinesia,[149-151] rigidity,[149-151] tremor,[153] *off* dystonia[154]	Dyskinesias[152,154]
Cognition (DLPFC)	Bradyphrenia,[155,156] executive function deficits,[157,158] impaired working memory,[157,158] reduced conditional associative learning[22]	Enhanced cognitive flexibility,[21,22] improved executive function,[22] improved working memory,[20] increased psychomotor speed,[22]
Response inhibition (ventromedial orbitofrontal cortex)		Disinhibition/impaired response inhibition[21,22,24]
Mood (anterior cingulate and orbitofrontal cortex)	*Off* period depression[8,9,159-161]	Mania/hypomania, impaired emotional control[9,30,41,43,84,92,96]
Motivation/ goal directed behavior (anterior cingulate)	Apathy[22,23,111,112]	Aspects of dopamine dysregulation syndrome[3]

Adapted from Funkiewiez and colleagues.[96]
STN, subthalamic nucleus; DLPFC, dorsolateral prefrontal cortex.

creases in STN activity was used to organize the data and the presumed relationships to various frontosubcortical circuits are highlighted. Increased STN activity is generally associated with restricted behavior and decreased STN activity typically results in excessive behavior. It is recognized that the symptoms likely have a significantly more complex pathophysiology.

Depression

Individual episodes of postoperative depression have been reported in 1.5% to 25% of patients.[8,18,30,33,38,46–48] The literature on the prevalence of postoperative depression is discussed in the outcomes section.

The prevalence of depression in PD is between 40% to 50%,[82] with the incidence rate reported to be 1.86% per year.[83] The natural course of PD likely plays a greater role in the depression occurring long after surgery as opposed to that observed soon after surgery.

Based on the literature, it is not clear if a history of preoperative depression is a risk factor for early postoperative depression. For instance, in one retrospective review, 33% of patients with a preoperative history of depression developed postoperative depression, suggesting that a history of preoperative depression acts as a risk factor but is not necessarily predictive of this outcome.[30] In contrast, a prospective study found that a personal history of depression, family psychiatric history, and preoperative depression scores did not differentiate between the postoperatively depressed (25%) and nondepressed groups.[25] The factors associated with postoperative depression included postoperative confusion and female gender.[25] Severe depression at baseline appears to be a risk factor for depression in the long term. Ten percent of 77 patients had severe depression at 3 years, of which half had been severely depressed at baseline.[26] A preoperative survey documented that 60% of patients presenting for STN surgery had a past history of depression requiring antidepressants.[84] Whether effective treatment and antidepressant prophylaxis of the preoperative depression change this risk is not known.

Dopaminergic medication withdrawal has been associated with transient depressive symptoms.[8,9] The affective and behavioral effects of levodopa abuse have been compared to those due to psychostimulants (drugs that increase catecholaminergic activity), suggesting similar underlying neural substrates to the withdrawal states.[85] In addition, dopaminergic agonists have also been demonstrated to improve depression rating scores in major depression associated with PD, suggesting a potential dopaminergic role.[86]

Reports of stimulation-locked depressive states are infrequent but help delineate an association with stimulation. However, the significance of these acute changes is not clear; for instance, it is not known if the symptoms persist in the long term or if neuroplastic changes occur. Clinical observations must also carefully differentiate between acute stimulation-induced mood symptoms and autonomic or anxiety effects.[77] The STN is a small nucleus (180 mm^3)[87] surrounded by dense fiber bundles.[88] STN stimulation may be associated with mood changes due to current spread to the small medial limbic tip of the STN, the surrounding fiber bundles, or stimulation may affect afferent or efferent connections to cortical, brainstem, and thalamic regions by anterograde or retrograde stimulation. In addition, current may spread into adjacent structures, such as the posterior hypothalamus or midbrain tegmentum and their connections.

A depressive state fulfilling DSM-IV criteria was reported with stimulation of the left central substantia nigra

primarily within the pars reticulata.[78] The symptoms were suggested to be due to stimulation of nigral or nigrothalamic fibers. An increase in cerebral blood flow was demonstrated in the left orbitofrontal cortex, globus pallidus, amygdala, anterior thalamus, and the right parietal lobe. A similar state was reported with stimulation of the right zona incerta/fields of Forel,[89] suggested to be due to stimulation of fiber bundles within the zona incerta/fields of Forel, or connections of the STN to the substantia nigra or pedunculopontine nucleus. Right-sided BOLD signal increases were demonstrated in the superior prefrontal cortex, anterior cingulate, anterior thalamus, caudate, and brainstem and decreases in medial prefrontal cortex. The symptoms reported in the latter paper could not be reproduced despite a trial of identical stimulation parameters suggesting a role for neuroplastic adaptation.

In contrast, two patients were described with stimulation-linked easy tearfulness, which was qualitatively different from the patients' premorbid experience of major depression.[43] Similar symptoms of acute sadness secondary to an increase in stimulation parameters has also been described.[90] Three of these five cases of acute depressive states had a premorbid history of depression suggesting a potential interaction between an underlying vulnerability and the site of stimulation.[43,89]

These reports suggest that while dysphoric states may occur with stimulation of electrodes located within the STN, depressive symptoms that are associated with the range of vegetative, cognitive, and motivational symptoms of a major depression may be more likely to be associated with electrodes misplaced outside the STN.

Stimulation of optimally placed contacts in either unilateral STN or GPi was found to be associated with greater improvement of mood in comparison to being OFF stimulation in a study of acute mood changes following blinded randomized changes in stimulation.[77] Stimulation dorsal or ventral to the optimal contact was associated with greater worsening of mood for the STN group than for the GPi group. Changes in mood were suggested to be more likely to be associated with STN stimulation as compared to GPi given differences in the sizes of the nuclei and thus greater current spread to the nonmotor STN, adjacent fibers, and nearby structures.

Psychosocial factors including psychological responses to motor and functional changes, unrealistic expectations, poor supports, or changes in identity or relationships are also likely to play a role in postoperative depression. Psychosocial changes have been reported following other major life-altering surgeries[91] and have been noted after STN stimulation.[30] Furthermore, psychosocial factors such as marital status, past and current stressors, support, and underlying personality traits can also be associated with depression in the general population.

Based on the literature[8,9] and on clinical experience, we speculate that the dysphoric or depressive symptoms that occur within the first three postoperative months are most commonly secondary to dopaminergic withdrawal symptoms potentially interacting with premorbid vulnerabilities. That acute mood changes may not be reproducible using the same parameters suggests a role for neuroplastic adaptation. Stimulation-induced acute psychiatric symptoms, while intriguing, are infrequent and likely transient. As yet, there has not been any convincing evidence for long-term effects of STN stimulation resulting in depressive symptoms. Stimulation within the STN may occasionally be associated with dysphoria. However, the limited frequency of occurrence of acute stimulation-induced dysphoric symptoms suggests either a placement effect within the STN (e.g., that the stimulated electrode was located closer to the medial limbic STN or that current had spread to peri-STN regions) or a potential interaction with underlying vulnerabilities such as a mood diathesis, emotional reactivity, or personality traits consistent with an affective release phenomenon.

Depressive symptoms occurring late in the postoperative period may be more likely related to premorbid vulnerabilities, the natural course of depression in PD, and psychosocial factors. Dopaminergic withdrawal may still continue to play a more muted role and the symptoms should be distinguished from apathy.

Hypomanic/Manic Symptoms

Postoperative hypomania has been reported in 4% to 15% of patients following STN stimulation surgery, usually occurring within the first 3 postoperative months.[18,38,41,42]

The observation of stimulation-linked mirthful laughter and more chronic euphoria and hypomania occurring within the same patient who had undergone STN stimulation has led some authors to hypothesize a continuum of symptoms characterized by mood elevation with potentially similar underlying pathophysiology.[92] Mirthful laughter is characterized by excessive and inappropriate laughter in response to trivial stimuli. In contrast to pathological laughter in which the affective state of laughter is dissociated from the mood state, in mirthful laughter, the affective state of laughter is congruent with the mood state of mirth.

However, euphoria is common following transplant surgery,[93] suggesting a commonality in the observed psychological reactive improvements following life-altering surgery. As such, the euphoria observed after STN DBS may also be related to psychological reactive improvements.

In contrast, the hypomania or mania observed after STN DBS may be more likely to have alternate explanations related to underlying biological factors. For instance, hypomania has been observed prior to initiation of STN stimulation, suggesting an etiological effect of localized edema or a microlesion effect.[41] Furthermore, two patients in whom high STN stimulation parameters temporally linked to acute mirthful laughter have been described.[92] The authors proposed that chronic stimulation of the STN–limbic system, particularly involving the lateral hypothalamus and ventral tegmental area projections, could play a role in the observed euphoria, hypomania, and improvements in depression rating scores. A dissociation between the motor and limbic circuits has further been reported in a patient in whom stimulation-linked manic symptoms did not improve with termination of stimulation, whereas immediate changes in parkinsonian symptoms were apparent OFF stimulation.[94]

Stimulation of the limbic system outside of the STN, such as within the midbrain caudal to the substantia nigra, has also been implicated with manic symptoms.[95] Proposed etiologies have included stimulation of ventral tegmental area projections or midbrain projections to the frontal cortex.

STN stimulation and dopaminergic medications have been observed to be synergistic. Postoperative mania improves with either a decrease in stimulation or with a decrease in dopaminergic medications, thus emphasizing the role of appropriate postoperative management of stimulation and medications.[9,41] Mania, hypomania, and euphoria have all been associated with dopaminergic medications. Parallels between the mood-enhancing effects of levodopa and STN stimulation were investigated using systematic questionnaires[96] measuring the perception of euphoria, motivation, fatigue, anxiety, and tension. Patients in the ON stimulation state and those *on* levodopa both perceived a greater improvement of these features as compared to the groups of patients in the OFF stimulation state and those *off* levodopa. Given their similarities, mood-elevating properties of both STN stimulation and levodopa were suggested to be mediated by the STN–limbic system.

Some of the reported patients with postoperative manic symptoms have a history of premorbid depression, emotional lability, or a family history of bipolar disorder, suggesting the potential role of premorbid vulnerability.[41,92,94] A preoperative survey documented 10% of patients presenting for STN stimulation had a history of medication-induced mania.[84] Of four patients described in the literature with a preoperative history of medication-induced hypomania/mania, two have had transient postoperative mania, suggesting an interaction between underlying vulnerabilities, stimulation, and medication changes.[34,84]

Based on the literature and on clinical experience, postoperative hypomania is likely predominantly due to the synergistic interaction between stimulation and dopaminergic stimulation affecting similar dopaminergic-mediated regions. That mania has mood (euphoria), motivational (increased goal directed activity), cognitive (increased rate of thought processes or rapid speech), and motoric (increased motor activity) symptoms could be hypothesized to be related to stimulation affecting the limbic, cognitive, and motoric STN regions and their downstream striatal and frontal processes.[96] This behavior could be mediated by initial surgical, stimulation, and/or dopaminergic effects.

Emotional Processing

Emotional reactivity, or excessive mood-congruent emotional responses to minor triggers, is common following STN DBS surgery and was identified in 75% of STN stimulation patients.[30]

Observations of emotional reactivity, euphoria, and changes in social adjustment have led to investigations on the effect of STN stimulation on emotional processing. For instance, emotional processing during STN stimulation was studied utilizing a mood-induction paradigm of exposure to differing facial emotional expressions.[97] Consistent with the observation of increased emotional reactivity, the ON stimulation/*off* medication state was associated with enhanced emotional experience and recall of emotionally valenced immediate memory in comparison to the OFF stimulation/*off* medication state.

Nonverbal information processing was investigated in two studies using an emotional facial expression recognition paradigm.[98] Stimulation was associated with a decline in anger recognition and a decline in sadness and anger recognition was found ON stimulation compared to preoperative baseline.[99] Subjects were unable to recognize this impairment. Interactions between the medial–limbic STN and the anterior cingulate and nondopaminergic mechanisms were implicated. In both studies, the recognition of positive emotional facial expression was not impaired.

These studies suggest that the experience, recall, and expression of emotion may be increased following STN stimulation; however, the recognition of negative emotional facial expressions and, as a corollary, the appropriateness of response to these expressions may be impaired. These observations were suggested to have a potential impact in social relationships that require the ability to process such nonverbal cues. The relationship between this impairment and the states of euphoria or emotional reactivity is not known. Regions commonly implicated in emotional processing include the amygdala, medial prefrontal cortex, and orbitofrontal cortex, which have indirect connections to the medial limbic STN.

Affective dysregulation or disorders of emotional expression such as pathological crying or mood-incongruent crying associated with pseudobulbar palsy has been described following STN stimulation.[100] Similar to pathological affect observed in multiple neurological disorders, the symptoms responded rapidly to agents with serotonin reuptake inhibitor properties.[101] Okun and colleagues[100] speculated on several mechanisms of action including inhibition of STN output resulting in an affective release phenomenon, activation of the medial limbic STN or the connections within the zona incerta and medial forebrain bundle to limbic circuits, and activation involving centers regulating facial expression in the brainstem, hypothalamus, or thalamus. The resolution with a serotonin reuptake inhibitor was suggested by the authors to affect the serotonergic dorsal raphe projections potentially involved in the integration of bucco–oral–facial activity. That these symptoms are infrequent suggests that electrode placement may be playing a role.

Response Inhibition

Impairments in response inhibition following STN stimulation have been recently demonstrated by abnormalities in the interference arm of the Stroop task.[21,22] This observation could explain the behavioral symptoms of disinhibition,[24] emotional reactivity,[30] and potentially of the emotional and cognitive domains of hypomanic symptoms, which may reflect impaired inhibitory processes in the early postoperative period. For instance, hypomania may be due to excessive dopamine stimulation or STN stimulation, resulting in downstream impairments of medial frontal and inhibitory functioning in vulnerable individuals.[102] The disinhibition of underlying vulnerabilities including that of premorbid mood disorders or personality traits may also help explain the observation of the range of psychiatric symptoms (such as dysphoria and hypomania) following STN DBS.

Hedonistic Homeostatic Dysregulation or Levodopa Abuse

Excessive (or inappropriate) levodopa use in the postoperative period for its subjective euphorigenic effect rather than its motor effect has been reported as case reports. Three patients have been described with a preoperative history of levodopa abuse who required limitations on the postoperative dose of levodopa.[18,30] However, recently the postoperative outcomes of two patients with preoperative histories of severe levodopa abuse or dopamine dysregulation syndrome were reported following STN stimulation.[103] One patient had postoperative transient alcohol abuse symptoms but the outcomes of the two patients were otherwise unremarkable. The patients were characterized by a younger age of PD onset, shorter duration of PD, and high motivation to cease self-medication. The dose of levodopa was dramatically reduced immediately after surgery. The replacement of the pulsatile administration of high doses of levodopa with continuous stimulation was hypothesized to play a stabilizing role in decreasing the addictive behaviors. Decreasing the pulsatile administration of levodopa may decrease the experience of negative emotional states and decrease the abnormal sensitization of motivational symptoms associated with the meso–striato–limbic system.[102] A study investigating cognitive measures in postoperative PD patients *off* medications did not demonstrate any group differences in a gambling task or reward-learning paradigm either ON or OFF STN stimulation. This outcome suggests that STN stimulation per se does not worsen these cognitive measures, which may be implicated in substance use disorders; however, as preoperative measures were not obtained, changes with respect to the preoperative state were not reported. Given the differences in postoperative outcomes between the case reports,[18,30] caution should be exercised with these patients pending further studies of predictive outcome factors.

Obsessive–Compulsive Symptoms

Obsessive–compulsive disorder symptoms were documented to improve in case reports of PD patients with STN stimulation localized in the anteromedial STN and zona incerta.[104,105] Obsessive–compulsive symptom scores were reported to improve in patients following STN DBS.[15] However, the potentially confounding variable of depression was not examined. Furthermore, whether the prevalence of comorbid obsessive–compulsive symptoms is elevated in PD is not clear.[106–109]

Apathy

Apathy is a common postoperative symptoms in the long term and has been reported to occur between 12% and 25% in 3 to 5 years after STN stimulation surgery.[18,26]

Apathy is defined as decreased responses to internal and external stimulation. In the general PD population, apathy has been reported between 16.5% and 42%.[1,110] Apathy, understood as a distinct clinical syndrome, also has overlaps with depression, hedonic tone, personality traits, and cognitive function. In the general PD population, apathy has been associated with cognitive dysfunction, particularly executive dysfunction, rather than depression.[110] Apathy in neuropsychiatric disorders and in PD has been reported to respond to dopaminergic medications implicating an underlying dopaminergic etiology.[111,112]

The limbic cortico–striato–thalamo–cortical (CSTC) loop projecting to the anterior cingulate has been implicated and bilateral lesions to the anterior cingulate or globus pallidus are reported to be associated with symptoms of apathy.[112] However, a study comparing apathy states both ON and OFF stimulation found an improvement in group scores of self-reported apathy with ON stimulation.[113] The patients with improvements in apathy had a shorter disease duration and less severe parkinsonism compared to those without improvements. However, conclusions from the study are limited by the lack of preoperative assessment of apathy, limitations due to the self-report nature of the Apathy Scale, and limitations of the use of such a scale to assess transient acute states induced by changes in stimulation.

Similarly, transient apathy early in the postoperative period is commonly part of the dopaminergic or psychostimulant withdrawal syndrome[114,115] and responds to increasing levodopa. Levodopa administration and acute STN stimulation have similar subjective effects.[96] Apathy can also occur in the context of postoperative depression.

In contrast, more permanent symptoms of apathy late in the postoperative period may be more likely related to underlying frontal dysexecutive symptoms[18,26] related to the neurodegenerative process of PD. STN stimulation appears to act on motor regions mediated by dopaminergic systems but has a more variable effect on the limbic regions mediated by dopamine.[26] Apathy associated with cognitive deficits may also be mediated by nondopaminergic or neurodegenerative etiologies.

Visual Hallucinations

New-onset visual hallucinations (VHs) were described following STN DBS responding to decreases in levodopa; recurrence of hallucinations 3 years later was time-locked with stimulation of an electrode within the zona incerta.[116] The recurrent VH responded to decreases in stimulation and to clozapine. Proposed etiologies included stimulation affecting the medial limbic STN, the ventral tegmental area (VTA) projections, or serotonergic fibers projecting to the frontal cortex. The cortico–striato–thalamo–cortical loop involving area TE of the inferotemporal cortex has also been implicated in VH.[117] However, connections to the STN have not yet been demonstrated. Indeed, late-onset hallucinations appear to be more likely to be associated with the underlying PD process potentially interacting with increases in dopaminergic medications given its association in patients with cognitive deficits[18] and may reflect underlying progression of nondopaminergic pathology.

The role of preoperative symptoms remains to be clarified. A survey of patients presenting for STN stimulation revealed a preoperative history of hallucinations or delusions in 35% of patients.[84] The decrease in medications following STN stimulation presumably decreases the stimulation of dopaminergic receptors outside of motor pathways and in theory should decrease postoperative psychotic symptoms. However, hallucinations may have nondopaminergic etiologies including serotonin and acetylcholine and furthermore may be associated with cognitive decline, aspects of which are not modifiable with stimulation. As such, whether patients with a history of preoperative psychotic symptoms, which may be a marker for cognitive decline, are at greater risk of postoperative neurobehavioral symptoms is not known.

Anxiety

Generalized anxiety disorder (GAD) was diagnosed retrospectively in 18 of 24 patients with PD (75%) following STN DBS in one study, 17 of whom had a preoperative history of GAD. Ten patients (42%) had a specific fear that the stimulator would suddenly fail.[34] The extent to which these symptoms overlap with those of other comorbid psychiatric disorders is not known. However, overall group anxiety rating scores have been reported in some studies to improve significantly on anxiety measurements,[23,28] although specificity of the symptoms was not reported.

Dementia and Cognition

Dementia meeting DSM criteria was observed in only 3 patients (7%) in an uncontrolled 5-year outcome study of 42 of 49 original patients prospectively studied following STN DBS.[18] That this figure is lower than dementia in the general PD population may reflect selection bias since patients with severe cognitive deficits are excluded from DBS. Although the evolution of dementia has not been compared in DBS and unoperated PD groups, other cognitive changes have been studied more extensively (see prior section on cognitive outcomes).

The pathophysiology of cognitive changes after DBS remains largely a matter of speculation. One might argue that an anatomical basis for cognitive changes with STN stimulation is plausible given that the STN has been observed to have more widespread connections with basal ganglia and cortical areas than once thought, and that the segregated cortico–basal ganglionic limbic, associative, and motor circuits may communicate via open elements within these circuits.[88,118–120] Furthermore, it is a simple matter to argue that current spread from segregated motor circuits to adjacent limbic and associate circuits entrain cortical changes downstream that would be expected to cause cognitive changes. Indeed, functional imaging studies suggest that STN DBS is associated with metabolic alterations in cortical areas extending beyond motor and supplementary motor regions, and specifically those areas that are part of the associative and limbic circuits.[121,122] For example, PET activation studies have demonstrated that STN and GPi stimulation results in increased activation in the supplementary motor area (SMA), dorsolateral prefrontal cortex (DLPFC), and anterior cingulate during random joystick movements.[123] Inferences regarding the potential pathophysiology of cognitive changes observed following DBS can be drawn by combining findings from the functional imaging and stimulation literatures. Jahanshahi and colleagues[22] demonstrated that acute stimulation of the STN resulted in improvements in several executive function tasks. These data, in combination with the PET findings, suggest that DBS might "release the brake" in PD and result in improvements in aspects of executive function presumably related to increased activation of DLPFC and other frontal regions. Conversely, Jahanshahi and colleagues[22] found that DBS in the STN can also result in increased difficulty on cognitive tasks that require behavioral changes in response to novel contexts.[124] These latter findings might be driven via the indirect CSTC motor circuit, whereas the facilitatory effect on DLPFC function might reflect greater involvement of the direct CSTC motor circuit.

A few studies have provided additional insight into the pathophysiology of verbal fluency changes, though the studies' results appear to be vexingly contradictory. On the one hand, a functional neuroimaging study found that stimulation reduced verbal fluency, and that stimulation-related metabolic changes (inferior frontal and temporal) were correlated with verbal fluency performance differences during and without stimulation.[125] On the other hand, clinical studies comparing verbal fluency with and without stimulation after surgery have generally failed to find differences,[13,49] even though declines are common between presurgical baseline and postoperative assessment. In addition, a 3-year follow-up study observed a decline in fluency between preoperative baseline and 1 year, but no further decline between the first and third years,[26] suggesting that the change is unlikely to be due to disease progression. How stimulation, changes in medication, and microlesion effects might interact to produce verbal fluency changes remains to be determined. More detailed theoretically driven studies are needed to tease out the underlying neurophysiological processes involved in cognitive changes following DBS.

PREOPERATIVE AND POSTOPERATIVE MANAGEMENT OF NEUROBEHAVIORAL SYMPTOMS

Treatment algorithms for the preoperative assessment and postoperative management of neurobehavioral symptoms associated with stimulation for PD are presented in Tables 4 and 5, respectively. The algorithms are most relevant for STN stimulation given the potential interactions between medication changes and stimulation. The algorithms are based on expert opinion given the limited published literature on this topic.

CONCLUSIONS

A common evolution of cognitive or psychiatric symptoms appears to emerge following STN stimulation. In the short term following surgery, symptoms may be more frequent due to significant changes in dopaminergic medications, the effects of a life-changing event, and potentially stimulation-related effects. However, over the long term, with chronic stimulation replacing the pulsatile effects of dopaminergic medications, fewer but qualitatively different symptoms emerge. As patients are followed beyond a decade, dealing with the effects of natural disease progression, increasing dopaminergic medications, progressive cognitive decline, and a differ-

TABLE 4. *Potential areas for preoperative psychiatric assessment for deep brain stimulation for Parkinson's disease*

Depression: current (see also preoperative supplement)	Moderate 1. Decision based on individual patient factors 2. Consider antidepressant prophylaxis Severe 1. Refer to psychiatry 2. Surgery when depression treated 3. Antidepressant prophylaxis 4. Ensure antidepressants and benzodiazepines continued postoperatively 5. Psychoeducation for potential relapse 6. Close postoperative follow-up with adequate postoperative psychiatric management and support 7. Gradual postoperative medication reduction 8. Patients with nonmodifiable high suicide risk should be contraindicated from surgery Treatment-refractory severe depression: contraindicated from surgery
Depression: past history	Mild: single episode, rapid improvement with antidepressants or psychotherapy 1. Proceed to surgery Moderate–severe: hospitalization, suicidal ideation, electroconvulsive therapy 1. Refer to psychiatry for optimization of treatment 2. Psychoeducation for potential relapse 3. Ensure adequate postoperative psychiatric management and support 4. Ensure antidepressants and benzodiazepines continued postoperatively 5. Close postoperative follow-up 6. Gradual postoperative medication reduction
Hypomania/mania	Primary bipolar disorder 1. Adequately controlled: decision based on individual patient factors and adequacy of postoperative psychiatric management and support 2. Severe treatment refractory: contraindicated from surgery Medication-induced hypomania/mania Past history 1. Psychoeducation of patient and family for potential relapse 2. Close postoperative follow-up (e.g., contact with patient or family at least once every 2 weeks for the first 3 postoperative months) Current 1. Decrease or discontinue associated medication or decrease overall dopaminergic medication dose 2. Psychoeducation of patient and family for potential relapse 3. Proceed to surgery 4. Close postoperative follow-up
Suicidal ideation	Referral to psychiatry for assessment of severity of ideation, need for management, and appropriateness for surgery
Hallucinations/psychosis	1. Assessment for cognitive deficits 2. Mild (good insight, infrequent, does not affect behavior): consider atypical antipsychotic (clozapine/quetiapine) prophylaxis; decision based on individual patient factors 3. Moderate to severe (limited insight, frequent, or affects behavior): decision dependent on factors such as cognitive status, degree of association with dopaminergic medications (or expected improvement with decreasing dopaminergic medications), response to atypical antipsychotics (clozapine/quetiapine), patient supports, and access to postoperative neurobehavioral management 4. Primary severe psychotic disorder: contraindicated from surgery
Medication-related pathological gambling or hypersexuality	1. Assess potential relationship with medication (i.e., temporal association with medication and trial of decreasing medications) 2. Decrease or discontinue implicated medications 3. If preoperative changes in medications not tolerated or behaviors persist, may proceed cautiously with surgery with informed consent on potential risk of persisting behavioral symptoms; decision dependent on factors such as cognitive status, likely association with dopaminergic medications, patient supports, capacity for behavioral controls, and access to postoperative neurobehavioral management

Algorithms are most relevant for subthalamic stimulation given potential interactions between stimulation and medications.

ing set of psychosocial concerns or disappointments will create another set of unique challenges.

Information is beginning to emerge on potential differences between STN and GPi stimulation. However, at present the evidence is inconclusive. Some studies suggest that adverse neuropsychiatric events may be more common in the STN compared to GPi patients. Alternatively, some neuropsychiatric symptoms may be more

TABLE 5. *Postoperative management for psychiatric symptoms following deep brain stimulation for Parkinson's disease*

Depression	Early 1. Increase levodopa 2. Antidepressants ± psychotherapy if not responsive or partially responsive 3. Consider trial or restart/dose increase of dopamine agonist with mood-elevating properties (e.g., pramipexole) 4. Evaluation for suicidal ideation 5. Consider psychiatric referral Late 1. Trial of increase levodopa 2. Antidepressants and/or psychotherapy if not responsive or partially responsive 3. Consider trial of dopamine agonist with mood-elevating properties 4. Evaluation for suicidal ideation 5. Assess for primary apathy or cognitive deficits 6. Consider psychiatric referral Suicidal ideation: refer to psychiatry (see section on suicidal ideation) Treatment-refractory depression: optimization of pharmacological management with adequate dosing and duration of treatment, switching of antidepressant classes, and combination and augmentation strategies; augmentation with atypical antipsychotics is not recommended; safety of the use of electroconvulsive therapy in patients with implanted stimulators is not known, although a case report has been published describing the safety and efficacy of electroconvulsive therapy utilized in the treatment of depression in a PD patient following DBS surgery[125]
Hypomania/mania	1. Assess for suicidal ideation, risk-taking behaviors (driving, finances, excessive spending, sexual behaviors): concurrent referral to psychiatry if risk-taking behaviors present for capacity and safety assessments, potential hospitalization, treatment 2. Assess for necessity for treatment Mild: time-limited, none of the above behaviors, responsive to interventions 1. No treatment required 2. Consider decreasing dopaminergic medications or decreasing stimulation Persistent or moderate to severe 1. Decrease dopaminergic medications or decrease stimulation 2. Discontinue antidepressants 3. Clozapine and/or mood stabilizer (carbamezapine, valproic acid)
Apathy	Early 1. Increase levodopa 2. Assess for depression (including dysthymia, subsyndromal or minor depression) 3. Antidepressant if depression present Late 1. Trial of increasing levodopa 2. Assess for depression (including dysthymia, subsyndromal or minor depression) 3. Antidepressant if present or trial of antidepressant if uncertain 4. Assess for cognitive status a. Cholinesterase inhibitor if dementia present b. Caregiver psychoeducation on apathy symptoms c. Multidisciplinary approach for dementia management
Suicidal ideation	1. Referral to psychiatry (note that the management of comorbid psychiatric symptoms is affected by dopaminergic withdrawal symptoms and the presence of stimulation; see appropriate sections for management) 2. Assessment for postoperative depression, hypomania/mania, psychotic symptoms with management as outlined in previous sections 3. Standard psychiatric management of suicidal ideation
Hallucinations/psychosis	1. Adjustment of antiparkinsonian medications 2. Trial of decreasing stimulation parameters 3. Atypical antipsychotics if needed: clozapine or quetiapine 4. Assessment for cognitive deficits: cholinesterase inhibitors if dementia present
Pathological gambling/hypersexuality	1. Decrease or discontinue any implicated dopaminergic medication (e.g., dopamine agonist) and/or decrease total dopaminergic medication dose 2. Rule out medication- or stimulation-related hypomania/mania (see management of postoperative hypomania/mania) 3. Trial of decreasing stimulation 4. Consider atypical antipsychotics (clozapine or quetiapine) 5. Multidisciplinary addiction management

Algorithms are most relevant for subthalamic stimulation given potential interactions between stimulation and medications.

likely to be improved by STN stimulation since it affords a greater reduction or elimination of dopaminergic medications and STN stimulation itself may play a role in improving certain symptoms (e.g., obsessive–compulsive symptoms). Thus, pending the outcomes of larger well-documented randomized controlled studies, preoperative neuropsychiatric comorbidity may 1 day play a role in target selection.

The postoperative cognitive and psychiatric states following stimulation for PD are poorly understood and understudied. Patients with severe PD who undergo DBS, particularly in the STN, provide a unique opportunity to study potential biological and psychosocial variables underlying several cognitive and psychiatric symptoms prospectively. Such studies can provide further insight not only into symptoms associated with PD, but also into drug withdrawal mechanisms and potentially mood, addiction, and behavioral disorders unrelated to PD. The range of cognitive and psychiatric symptoms observed in PD patients following DBS and the paucity of available literature provides a fertile ground for further pathophysiological and clinical studies.

Stimulation for advanced PD is effective and safe for the vast majority of well-selected patients. The majority of the observed psychiatric symptoms is transient and manageable and ideally, if appropriately understood and managed, preventable. Studies with appropriate control groups with advanced PD on high doses of medications would place these observations into further context. This article is intended as a companion to the preoperative and postoperative issues papers in this supplement on DBS for PD. Further information on cognitive and behavioral clinical issues can be found elsewhere in this issue.

Acknowledgments: We gratefully acknowledge the assistance of Dr. Jean Saint-Cyr and Dr. Jerome Yelnik in their comments on the anatomical table.

REFERENCES

1. Aarsland D, Larsen JP, Lim NG, et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1999;67:492–496.
2. Zgaljardic DJ, Borod JC, Foldi NS, Mattis P. A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. Cogn Behav Neurol 2003;16: 193–210.
3. Evans AH, Lees AJ. Dopamine dysregulation syndrome in Parkinson's disease. Curr Opin Neurol 2004;17:393–398.
4. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001;345:956–963.
5. Volkmann J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 2001;56:548–551.
6. Anderson VC, Burchiel KJ, Hogarth P, et al., Pallidal versus subthalamic deep brain stimulation in Parkinson's disease. Arch Neurol 2005;62:554–560
7. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al., Bilateral deep brain stimulation in Parkinson's disease: a multicenter study with 4 years followup. Brain 2005;128;2240–2249.
8. Volkmann J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 2001;56:548–551.
9. Krack P, Fraix V, Mendes A, Benabid AL, Pollak P. Postoperative management of subthalamic nucleus stimulation for Parkinson's disease. Mov Disord 2002;17(Suppl. 3):S188–S197.
10. Fields JA, Tröster AI. Cognitive outcomes after deep brain stimulation for Parkinson's disease: a review of initial studies and recommendations for future research. Brain Cogn 2000;42:268–293.
11. Woods SP, Fields JA, Tröster AI. Neuropsychological sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a critical review. Neuropsychol Rev 2002;12:111–126.
12. Moretti R, Torre P, Antonello RM, et al. Neuropsychological changes after subthalamic nucleus stimulation: a 12 month follow-up in nine patients with Parkinson's disease. Parkinsonism Relat Disord 2003;10:73–79.
13. Morrison CE, Borod JC, Perrine K, et al. Neuropsychological functioning following bilateral subthalamic nucleus stimulation in Parkinson's disease. Arch Clin Neuropsychol 2004;19:165–181.
14. Gironell A, Kulisevsky J, Rami L, Fortuny N, Garcia-Sanchez C, Pascual-Sedano B. Effects of pallidotomy and bilateral subthalamic stimulation on cognitive function in Parkinson disease: a controlled comparative study. J Neurol 2003;250:917–923.
15. Alegret M, Junque C, Valldeoriola F, et al. Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. Arch Neurol 2001;58:1223–1227.
16. Ardouin C, Pillon B, Peiffer E, et al. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 1999;46:217–223.
17. Burchiel KJ, Anderson VC, Favre J, Hammerstad JP. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. Neurosurgery 1999;45:1375–1382.
18. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925–1934.
19. Perozzo P, Rizzone M, Bergamasco B, et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: comparison of pre- and postoperative neuropsychological evaluation. J Neurol Sci 2001;192:9–15.
20. Pillon B, Ardouin C, Damier P, et al. Neuropsychological changes between "OFF" and "ON" STN or GPi stimulation in Parkinson's disease. Neurology 2000;55:411–418.
21. Witt K, Pulkowski U, Herzog J, et al. Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. Arch Neurol 2004; 61:697–700.
22. Jahanshahi M, Ardouin CM, Brown RG, et al. The impact of deep brain stimulation on executive function in Parkinson's disease. Brain 2000;123(Pt. 6):1142–1154.
23. Daniele A, Albanese A, Contarino MF, et al. Cognitive and behavioural effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74:175–182.
24. Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimula-

tion of the subthalamic nucleus in Parkinson's disease. Brain 2000;123(Pt. 10):2091–2108.
25. Berney A, Vingerhoets F, Perrin A, et al. Effect on mood of subthalamic DBS for Parkinson's disease: a consecutive series of 24 patients. Neurology 2002;59:1427–1429.
26. Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:834–839.
27. Moro E, Scerrati M, Romito LM, Roselli R, Tonali P, Albanese A. Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 1999;53:85–90.
28. Dujardin K, Defebvre L, Krystkowiak P, Blond S, Destee A. Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. J Neurol 2001;248:603–611.
29. Trepanier LL, Kumar R, Lozano AM, Lang AE, Saint-Cyr JA. Neuropsychological outcome of GPi pallidotomy and GPi or STN deep brain stimulation in Parkinson's disease. Brain Cogn 2000; 42:324–347.
30. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002;72:701–707.
31. Hariz MI, Johansson F, Shamsgovara P, Johansson E, Hariz GM, Fagerlund M. Bilateral subthalamic nucleus stimulation in a parkinsonian patient with preoperative deficits in speech and cognition: persistent improvement in mobility but increased dependency—a case study. Mov Disord 2000;15:136–139.
32. Hershey T, Revilla FJ, Wernle A, Gibson PS, Dowling JL, Perlmutter JS. Stimulation of STN impairs aspects of cognitive control in PD. Neurology 2004;62:1110–1114.
33. Molinuevo JL, Valldeoriola F, Tolosa E, et al. Levodopa withdrawal after bilateral subthalamic nucleus stimulation in advanced Parkinson disease. Arch Neurol 2000;57:983–988.
34. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002;72:701–707.
35. Iansek R, Rosenfeld JV, Huxham FE. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Med J Aust 2002;177:142–146.
36. Tavella A, Bergamasco B, Bosticco E, et al. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: long-term follow-up. Neurol Sci 2002;23(Suppl. 2):S111–S112.
37. Vesper J, Klostermann F, Stockhammer F, Funk T, Brock M. Results of chronic subthalamic nucleus stimulation for Parkinson's disease: a 1-year follow-up study. Surg Neurol 2002;57:306–311.
38. Herzog J, Volkmann J, Krack P, et al. Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. Mov Disord 2003;18:1332–1337.
39. Landi A, Parolin M, Piolti R, et al. Deep brain stimulation for the treatment of Parkinson's disease: the experience of the neurosurgical department in Monza. Neurol Sci 2003;24(Suppl. 1):S43–S44.
40. Tamma F, Rampini P, Egidi M, et al. Deep brain stimulation for Parkinson's disease: the experience of the Policlinico–San Paolo Group in Milan. Neurol Sci 2003;24(Suppl. 1):S41–S42.
41. Romito LM, Raja M, Daniele A, et al. Transient mania with hypersexuality after surgery for high frequency stimulation of the subthalamic nucleus in Parkinson's disease. Mov Disord 2002; 17:1371–1374.
42. Daniele A, Albanese A, Contarino MF, et al. Cognitive and behavioural effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74:175–182.
43. Doshi PK, Chhaya N, Bhatt MH. Depression leading to attempted suicide after bilateral subthalamic nucleus stimulation for Parkinson's disease. Mov Disord 2002;17:1084–1085.
44. Burkhard PR, Vingerhoets FJ, Berney A, et al. Suicide after successful deep brain stimulation for movement disorders. Neurology 2004;63:2170–2172.
45. Voon V, Moro E, Saint-Cyr JA, Lozano AM, Lang AE. Psychiatric symptoms following surgery for Parkinson's disease with an emphasis on subthalamic stimulation. In: Anderson KE, Weiner WJ, Lang AE, editors. Advances in neurology, behavioral neurology of movement disorders, 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2005. p 147.
46. Rodriguez-Oroz MC, Gorospe A, Guridi J, et al. Bilateral deep brain stimulation of the subthalamic nucleus in Parkinson's disease. Neurology 2000;55(Suppl. 6):S45–S51.
47. Martinez-Martin P, Valldeoriola F, Tolosa E, et al. Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. Mov Disord 2002;17:372–377.
48. Ostergaard K, Sunde N, Dupont E. Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson's disease and motor fluctuations. Mov Disord 2002;17:693–700.
49. Pillon B, Ardouin C, Damier P, et al. Neuropsychological changes between "OFF" and "ON" STN or GPi stimulation in Parkinson's disease. Neurology 2000;55:411–418.
50. Dujardin K, Defebvre L, Krystkowiak P, Blond S, Destee A. Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. J Neurol 2001;248:603–611.
51. Baron MS, Vitek JL, Bakay RA, et al. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann Neurol 1996;40:355–366.
52. Bezerra ML, Martinez JV, Nasser JA. Transient acute depression induced by high-frequency deep-brain stimulation. N Engl J Med 1999;341:1003.
53. Vitek JL, Bakay RA, Freeman A, et al. Randomized trial of pallidotomy versus medical therapy for Parkinson's disease. Ann Neurol 2003;53:558–569.
54. Fields JA, Tröster AI, Wilkinson SB, Pahwa R, Koller WC. Cognitive outcome following staged bilateral pallidal stimulation for the treatment of Parkinson's disease. Clin Neurol Neurosurg 1999;101:182–188.
55. Vingerhoets G, van der Linden C, Lannoo E, et al. Cognitive outcome after unilateral pallidal stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry 1999;66:297–304.
56. Tröster AI, Fields JA, Wilkinson SB, et al. Unilateral pallidal stimulation for Parkinson's disease: neurobehavioral functioning before and 3 months after electrode implantation. Neurology 1997;49:1078–1083.
57. Volkmann J, Allert N, Voges J, Sturm V, Schnitzler A, Freund HJ. Long-term results of bilateral pallidal stimulation in Parkinson's disease. Ann Neurol 2004;55:871–875.
58. Tröster AI, Woods SP, Fields JA, Hanisch C, Beatty WW. Declines in switching underlie verbal fluency changes after unilateral pallidal surgery in Parkinson's disease. Brain Cogn 2002;50: 207–217.
59. Dujardin K, Krystkowiak P, Defebvre L, Blond S, Destee A. A case of severe dysexecutive syndrome consecutive to chronic bilateral pallidal stimulation. Neuropsychologia 2000;38:1305–1315.
60. Ardouin C, Pillon B, Peiffer E, et al. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 1999;46:217–223.
61. Higginson C, Fields J, Tröster A. Which symptoms of anxiety diminish after surgical interventions for Parkinson disease? Neuropsychiatry Neuropsychol Behav Neurol 2001;14:117–121.
62. Miyawaki E, Perlmutter JS, Tröster AI, Videen TO, Koller WC. The behavioral complications of pallidal stimulation: a case report. Brain Cogn 2000;42:417–434.

63. Roane DM, Yu M, Feinberg TE, Rogers JD. Hypersexuality after pallidal surgery in Parkinson disease. Neuropsychiatry Neuropsychol Behav Neurol 2002;15:247–251.
64. Krause M, Fogel W, Heck A, et al. Deep brain stimulation for the treatment of Parkinson's disease: subthalamic nucleus versus globus pallidus internus. J Neurol Neurosurg Psychiatry 2001;70:464–470.
65. Hugdahl K, Wester K. Neurocognitive correlates of stereotactic thalamotomy and thalamic stimulation in Parkinsonian patients. Brain Cogn 2000;42:231–252.
66. Woods SP, Fields JA, Lyons KE, et al. Neuropsychological and quality of life changes following unilateral thalamic deep brain stimulation in Parkinson's disease: a one-year follow-up. Acta Neurochir 2001;143:1273–1277.
67. Tröster AI, Wilkinson SB, Fields JA, et al. Chronic electrical stimulation of the left ventrointermediate (Vim) thalamic nucleus for the treatment of pharmcotherapy-resistant Parkinson's disease: a differential impact on access to semantic and episodic memory? Brain Cogn 1998;38:125–149.
68. Schuurman PR, Bruins J, Merkus MP, Bosch DA, Speelman JD. A comparison of neuropsychological effects of thalamotomy and thalamic stimulation. Neurology 2002;59:1232–1239.
69. Woods SP, Conover E, Carey CL, Parsons TD, Tröster AI. Statistical power of studies examining the cognitive effects of subthalamic nucleus deep brain stimulation in Parkinson's disease. Clin Neuropsychol 2006;20:27–38.
70. Alegret M, Vendrell P, Junque C, et al. Effects of unilateral posteroventral pallidotomy on "on–off" cognitive fluctuations in Parkinson's disease. Neuropsychologia 2000;38:628–633.
71. Green J, Barnhart H. The impact of lesion laterality on neuropsychological change following posterior pallidotomy: a review of current findings. Brain Cogn 2000;42:379–398.
72. York MK, Levin HS, Grossman RG, Hamilton WJ. Neuropsychological outcome following unilateral pallidotomy. Brain 1999; 122(Pt. 12):2209–2220.
73. Sawrie SM, Chelune GJ, Naugle RI, Luders HO. Empirical methods for assessing meaningful neuropsychological change following epilepsy surgery. J Int Neuropsychol Soc 1996;2:556–564.
74. Schmand B, de Bie RM, Koning-Haanstra M, de Smet JS, Speelman JD, van Zomeren AH. Unilateral pallidotomy in PD: a controlled study of cognitive and behavioral effects—the Netherlands Pallidotomy Study (NEPAS) group. Neurology 2000;54: 1058–1064.
75. Burn DJ, Tröster AI. Neuropsychiatric complications of medical and surgical therapies for Parkinson's disease. J Geriatr Psychiatry Neurol 2004;17:172–180.
76. Francel P, Ryder K, Wetmore J, et al. Deep brain stimulation for Parkinson's disease: association between stimulation parameters and cognitive performance. Stereotact Funct Neurosurg 2004;82: 191–193.
77. Okun MS, Green J, Saben R, Gross R, Foote KD, Vitek JL. Mood changes with deep brain stimulation of STN and GPi: results of a pilot study. J Neurol Neurosurg Psychiatry 2003;74:1584–1586.
78. Bejjani BP, Damier P, Arnulf I, et al. Transient acute depression induced by high-frequency deep-brain stimulation. N Engl J Med 1999;340:1476–1480.
79. Brown RG. Behavioural disorders, Parkinson's disease, and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002;72:689.
80. Agid Y, Arnulf I, Bejjani P, et al. Parkinson's disease is a neuropsychiatric disorder. Adv Neurol 2003;91:365–370.
81. Krack P, Ardouin C, Funkiewiez A, et al. What is the influence of STN stimulation on the limbic loop? In: Kultas-Ilinsky K II, editor. Basal Ganglia and Thalamus in Health and Movement Disorders. New York: Kluwer Academic/Plenum Publishers; 2001. p 333–340.
82. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry 1992;149:443–454.
83. Dooneief G, Mirabello E, Bell K, Marder K, Stern Y, Mayeux R. An estimate of the incidence of depression in idiopathic Parkinson's disease. Arch Neurol 1992;49:305–307.
84. Voon V, Saint-Cyr JA, Lozano AM, Moro E, Poon Y, Lang AE. Psychiatric symptoms in Parkinson's patients presenting for deep brain stimulation. J Neurosurg 2005;103:246–251.
85. Giovannoni G, O'Sullivan JD, Turner K, Manson AJ, Lees AJ. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry 2000;68:423–428.
86. Rektorova I, Rektor I, Bares M, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol 2003;10: 399–406.
87. Yelnik J. Functional anatomy of the basal ganglia. Mov Disord 2002;17(Suppl. 3):S15–S21.
88. Parent A, Hazrati LN. Functional anatomy of the basal ganglia: II, the place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Brain Res Rev 1995;20:128–154.
89. Stefurak T, Mikulis D, Mayberg H, et al. Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. Mov Disord 2003;18:1508–1516.
90. Kumar R, Lozano AM, Sime E, Halket E, Lang AE. Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. Neurology 1999;53:561–566.
91. Derry PA, Wiebe S. Psychological adjustment to success and to failure following epilepsy surgery. Can J Neurol Sci 2000; 27(Suppl. 1):S116–S120.
92. Krack P, Kumar R, Ardouin C, et al. Mirthful laughter induced by subthalamic nucleus stimulation. Mov Disord 2001;16:867–875.
93. Olbrisch ME, Levenson JL. Psychosocial assessment of organ transplant candidates: current status of methodological and philosophical issues. Psychosomatics 1995;36:236–243.
94. Herzog J, Reiff J, Krack P, et al. Manic episode with psychotic symptoms induced by subthalamic nucleus stimulation in a patient with Parkinson's disease. Mov Disord 2003;18:1382–1384.
95. Kulisevsky J, Berthier ML, Gironell A, Pascual-Sedano B, Molet J, Pares P. Mania following deep brain stimulation for Parkinson's disease. Neurology 2002;59:1421–1424.
96. Funkiewiez A, Ardouin C, Krack P, et al. Acute psychotropic effects of bilateral subthalamic nucleus stimulation and levodopa in Parkinson's disease. Mov Disord 2003;18:524–530.
97. Schneider F, Habel U, Volkmann J, et al. Deep brain stimulation of the subthalamic nucleus enhances emotional processing in Parkinson disease. Arch Gen Psychiatry 2003;60:296–302.
98. Schroeder U, Kuehler A, Hennenlotter A, et al. Facial expression recognition and subthalamic nucleus stimulation. J Neurol Neurosurg Psychiatry 2004;75:648–650.
99. Dujardin K, Blairy S, Defebvre L, et al. Subthalamic nucleus stimulation induces deficits in decoding emotional facial expressions in Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:202–208.
100. Okun MS, Raju DV, Walter BL, et al. Pseudobulbar crying induced by stimulation in the region of the subthalamic nucleus. J Neurol Neurosurg Psychiatry 2004;75:921–923.
101. Robinson RG, Parikh RM, Lipsey JR, Starkstein SE, Price TR. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. Am J Psychiatry 1993;150:286–293.
102. Lawrence AD, Evans AH, Lees AJ. Compulsive use of dopamine replacement therapy in Parkinson's disease: reward systems gone awry? Lancet Neurol 2003;2:595–604.
103. Witjas TBC, Henry JM, Delfini M, et al. Addiction in Parkinson's disease: impact of subthalamic nucleus deep brain stimulation. Mov Disord 2005;20:1052–1055.
104. Mallet L, Mesnage V, Houeto JL, et al. Compulsions, Parkinson's disease, and stimulation. Lancet 2002;360:1302–1304.

105. Fontaine D, Mattei V, Borg M, et al. Effect of subthalamic nucleus stimulation on obsessive–compulsive disorder in a patient with Parkinson disease: case report. J Neurosurg 2004;100: 1084–1086.
106. Alegret M, Junque C, Valldeoriola F, Vendrell P, Marti MJ, Tolosa E. Obsessive–compulsive symptoms in Parkinson's disease. J Neurol Neurosurg Psychiatry 2001;70:394–396.
107. Maia AF, Pinto AS, Barbosa ER, Menezes PR, Miguel EC. Obsessive–compulsive symptoms, obsessive–compulsive disorder, and related disorders in Parkinson's disease. J Neuropsychiatry Clin Neurosci 2003;15:371–374.
108. Muller N, Putz A, Kathmann N, Lehle R, Gunther W, Straube A. Characteristics of obsessive–compulsive symptoms in Tourette's syndrome, obsessive–compulsive disorder, and Parkinson's disease. Psychiatry Res 1997;70:105–114.
109. Sharma P, Gupta N. Obsessive–compulsive phenomenon and Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;72: 420–421.
110. Pluck GC, Brown RG. Apathy in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;73:636–642.
111. Chatterjee A, Fahn S. Methylphenidate treats apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 2002;14:461–462.
112. Marin RS, Fogel BS, Hawkins J, Duffy J, Krupp B. Apathy: a treatable syndrome. J Neuropsychiatry Clin Neurosci 1995;7:23–30.
113. Czernecki V, Pillon B, Houeto JL, et al. Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? J Neurol Neurosurg Psychiatry 2005;76:775–779.
114. Krack P, Pollak P, Limousin P, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 1998;121(Pt. 3):451–457.
115. Kalechstein AD, Newton TF, Leavengood AH. Apathy syndrome in cocaine dependence. Psychiatry Res 2002;109:97–100.
116. Diederich NJ, Alesch F, Goetz CG. Visual hallucinations induced by deep brain stimulation in Parkinson's disease. Clin Neuropharmacol 2000;23:287–289.
117. Middleton FA, Strick PL. The temporal lobe is a target of output from the basal ganglia. Proc Natl Acad Sci U S A 1996;93:8683–8687.
118. Parent A, Levesque M, Parent M. A re-evaluation of the current model of the basal ganglia. Parkinsonism Relat Disord 2001;7: 193–198.
119. Hamani C, Saint-Cyr JA, Fraser J, Kaplitt M, Lozano AM. The subthalamic nucleus in the context of movement disorders. Brain 2004;127(Pt. 1):4–20.
120. Joel D, Weiner I. The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia–thalamocortical circuitry. Brain Res Brain Res Rev 1997;23:62–78.
121. Hilker R, Voges J, Weisenbach S, et al. Subthalamic nucleus stimulation restores glucose metabolism in associative and limbic cortices and in cerebellum: evidence from a FDG-PET study in advanced Parkinson's disease. J Cereb Blood Flow Metab 2004; 24:7–16.
122. Schroeder U, Kuehler A, Lange KW, et al. Subthalamic nucleus stimulation affects a frontotemporal network: a PET study. Ann Neurol 2003;54:445–450.
123. Limousin P, Greene J, Pollak P, et al. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Ann Neurol 1997;42:283–291.
124. Marsden CD, Obeso JA. The function of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain 1994;117:877–897.
125. Chou KL, Hurtig HI, Jaggi JL, et al. Electroconvulsive therapy for depression in a Parkinson's disease patient with bilateral subthalamic nucleus deep brain stimulators. Parkinsonism Relat Disord 2005;11:403–406.
126. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998;339:1105–1111.
127. Lopiano L, Rizzone M, Bergamasco B, et al. Daytime sleepiness improvement following bilateral chronic electrical stimulation of the subthalamic nucleus in Parkinson's disease. Eur Neurol 2001; 46:49–50.
128. Fukuda M, Ghilardi MF, Carbon M, et al. Pallidal stimulation for parkinsonism: improved brain activation during sequence learning. Ann Neurol 2002;52:144–152.
129. Tröster AI, Wilkinson SB, Fields JA, Miyawaki K, Koller WC. Chronic electrical stimulation of the left ventrointermediate (Vim) thalamic nucleus for the treatment of pharmacotherapy-resistant Parkinson's disease: a differential impact on access to semantic and episodic memory? Brain Cogn 1998;38:125–149.
130. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–381.
131. Groenewegen HJ, Berendse HW. Connections of the subthalamic nucleus with ventral striatopallidal parts of the basal ganglia in the rat. J Comp Neurol 1990;294:607–622.
132. Saint-Cyr JA, Hoque T, Pereira LC, et al. Localization of clinically effective stimulating electrodes in the human subthalamic nucleus on magnetic resonance imaging. J Neurosurg 2002;97: 1152–1166.
133. Voges J, Volkmann J, Allert N, et al. Bilateral high-frequency stimulation in the subthalamic nucleus for the treatment of Parkinson disease: correlation of therapeutic effect with anatomical electrode position. J Neurosurg 2002;96:269–279.
134. Yelnik J, Damier P, Demeret S, et al. Localization of stimulating electrodes in patients with Parkinson disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. J Neurosurg 2003;99:89–99.
135. Cossette M, Levesque M, Parent A. Extrastriatal dopaminergic innervation of human basal ganglia. Neurosci Res 1999;34:51–54.
136. Sato F, Parent M, Levesque M, Parent A. Axonal branching pattern of neurons of the subthalamic nucleus in primates. J Comp Neurol 2000;424:142–152.
137. Schroeder U, Kuehler A, Haslinger B, et al. Subthalamic nucleus stimulation affects striato–anterior cingulate cortex circuit in a response conflict task: a PET study. Brain 2002;125(Pt. 9):1995–2004.
138. Koob GF, Nestler EJ. The neurobiology of drug addiction. In: Salloway S, Malloy P, Cummings JL, editors. The Neuropsychiatry of Limbic and Subcortical Disorders. Washington, DC: American Psychiatric Press; 1997. p 179.
139. Mayberg HS, Liotti M, Brannan SK, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry 1999;156:675–682.
140. Freedman LJ, Insel TR, Smith Y. Subcortical projections of area 25 (subgenual cortex) of the macaque monkey. J Comp Neurol 2000;421:172–188.
141. Mitrofanis J. Some certainty for the "zone of uncertainty"? exploring the function of the zona incerta. Neuroscience 2005;130: 1–15.
142. Mitrofanis J, Mikuletic L. Organisation of the cortical projection to the zona incerta of the thalamus. J Comp Neurol 1999;412: 173–185.
143. Heise CE, Mitrofanis J. Evidence for a glutamatergic projection from the zona incerta to the basal ganglia of rats. J Comp Neurol 2004;468:482–495.
144. Reardon F, Mitrofanis J. Organisation of the amygdalo–thalamic pathways in rats. Anat Embryol (Berl) 2000;201:75–84.
145. Orieux G, Francois C, Feger J, et al. Metabolic activity of excitatory parafascicular and pedunculopontine inputs to the sub-

thalamic nucleus in a rat model of Parkinson's disease. Neuroscience 2000;97:79–88.
146. Keating GL, Walker SC, Winn P. An examination of the effects of bilateral excitotoxic lesions of the pedunculopontine tegmental nucleus on responding to sucrose reward. Behav Brain Res 2002; 134:217–228.
147. Winn P. Frontal syndrome as a consequence of lesions in the pedunculopontine tegmental nucleus: a short theoretical review. Brain Res Bull 1998;47:551–563.
148. Ashby P, Kim YJ, Kumar R, Lang AE, Lozano AM. Neurophysiological effects of stimulation through electrodes in the human subthalamic nucleus. Brain 1999;122(Pt. 10):1919–1931.
149. Bergman H, Wichmann T, Delong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990;249:1436–1438.
150. Bergman H, Wichmann T, Karmon B, Delong MR. The primate subthalamic nucleus: II, neuronal activity in the MPTP model of parkinsonism. J Neurophysiol 1994;72:507–520.
151. Hutchison WD, Allan RJ, Opitz H, et al. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann Neurol 1998;44:622–628.
152. Levy R, Dostrovsky JO, Lang AE, et al. Effects of apomorphine on subthalamic nuclues and globus pallidus internus neurons in patients with Parkinson's disease. J Neurophysiol 2001;86:249–260.
153. Krack P, Pollak P, Limousin P, et al. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease. Lancet 1997; 350:1675.
154. Krack P, Pollak P, Limousin P, Benazzouz A, Deuschl G, Benabid AL. From *off*-period dystonia to peak-dose chorea: the clinical spectrum of varying subthalamic nucleus activity. Brain 1999;122(Pt. 6):1133–1146.
155. Rogers D, Lees AJ, Smith E, et al. Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness: an experimental study. Brain 1987;110:761–776.
156. Mayeux R, Stern Y, Sano M, et al. Clinical and biochemical correlates of bradyphrenia in Parkinson's disease. Neurology 1987;37:1130–1134.
157. Gotham AM, Brown RG, Marsden CD. "Frontal" cognitive function in patients with Parkinson's disease "*on*" and "*off*" levodopa. Brain 1988;111:299–321.
158. Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. J Neurol 1997;244:2–8.
159. Maricle RA, Nutt JG, Valentine RJ, Carter JH. Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: a double-blind, placebo-controlled study. Neurology 1995;45:1757–1760.
160. Gotham AM, Brown RG, Marsden CD. Depression in Parkinson's disease: a quantitative and qualitative analysis. J Neurol Neurosurg Psychiatry 1986;49:381–389.
161. Riley DE, Lang AE. The spectrum of levodopa-related fluctuations in Parkinson's disease. Neurology 1993;43:1459–1464.